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Angular gyrus connectivity at alpha and beta oscillations is reduced during tonic pain – Differential effect of eye state

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ABSTRACT

The angular gyrus (AG) is a common hub in the pain networks. The role of the AG during pain perception, however, is still unclear. This crossover study examined the effect of tonic pain on resting state functional connectivity (rsFC) of the AG under eyes closed (EC) and eyes open (EO). It included two sessions (placebo/pain) separated by 24 hours. Pain was induced using topical capsaicin (or placebo as control) on the right forearm. Electroencephalographic rsFC assessed by Granger causality was acquired from 28 healthy participants (14 women) before (baseline) and 1-hour following the application of placebo/capsaicin. Subjects were randomly assigned and balanced to groups of recording sequence (EC-EO, EO-EC). Decreased rsFC at alpha-1 and beta, but not alpha-2, oscillations was found during pain compared to baseline during EC only. For alpha-1, EC-EO group showed a pain-induced decrease only among connections between the right AG and each of the posterior cingulate cortex (PCC, $P = 0.002$), medial prefrontal cortex (mPFC, $P = 0.005$), and the left AG ($P = 0.023$). For beta rsFC, the EC-EO group showed a bilateral decrease in rsFC spanning the connections between the right AG and mPFC ($P = 0.015$) and between the left AG and each of PCC ($P = 0.004$) and mPFC ($P = 0.026$). In contrast, the EO-EC group showed an increase in beta rsFC only among connections between the left AG and each of PCC ($P = 0.012$) and mPFC ($P = 0.036$). No significant change in the AG rsFC was found during EO. These results provide insight into the involvement of the AG in pain perception and reveal methodological considerations when assessing rsFC during EO and EC.

1. Introduction

Whether viewed from a dynamic connectome (Kucyi and Davis, 2015) or a matrix (Garcia-Larrea and Peyron, 2013) perspective, pain is a complex experience comprising sensory, cognitive and emotional aspects. Pain results from the coordinated communication between several networks comprising the pain matrix or connectome including the cingulo-opercular, salience/ventral attention, and default mode network (DMN) networks (Garcia-Larrea and Bastuji, 2018; Garcia-Larrea and Peyron, 2013; Kucyi and Davis, 2017, 2015). The angular gyrus (AG, BA 39) is identified as a common hub connecting the aforementioned pain networks (Igelström and Graziano, 2017; Ramanan et al., 2018) and shown to be affected in chronic pain (Giesecke et al., 2004; Gupta et al., 2019; Lo Buono et al., 2017). Due to the cross-modal connections, the AG is involved in higher-order brain functioning, integrating bottom-up multisensory information and top-down cognitive predictions (Seghier, 2013). As the AG is a major hub in the networks implicated in pain perception, exploring how this area processes pain would be interesting.

A few studies show an involvement of the AG during tonic pain processing (Kong et al., 2010, 2006; Wiech et al., 2005). However, these studies have some methodological issues. For example, Kong et al. (2006) and Wiech et al. (2005), report a pain-related change in the AG activity during tasks requiring cognitive processing with no control group (e.g. only pain or no pain groups). The lack of control group renders it difficult to pinpoint the effect of pain on the AG activity. A task-free resting state functional connectivity (rsFC) assessing temporal correlations between the AG and brain areas involving in pain perception (Barkhof et al., 2014; Friston et al., 1993) would shed more light on the role of AG during pain processing.

The medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) are shown to have strong connections with the AG (Igelstrom et al., 2015; Igelström and Graziano, 2017; Kong et al., 2010; Kucyi et al., 2014; Tanaka and Kirino, 2019) and play major roles in pain

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perception (Garcia-Larrea and Peyron, 2013; Kong et al., 2010; Kucyi et al., 2014; Kucyi and Davis, 2015). Connectivity between these three areas (major hubs within the DMN) is shown to be positively correlated with the activity of alpha and beta bands (Bowman et al., 2017; Mantini et al., 2007; Neuner et al., 2014; Samogin et al., 2019; Tang et al., 2017) – two brain rhythms recognized for their role in pain processing (Kim and Davis, 2021). EEG, MEG, and intracranial recordings have revealed alpha/beta decreased power in response to tonic pain (Furman et al., 2020; Giehl et al., 2014; Nickel et al., 2017; Nir et al., 2012; Schulz et al., 2015), that increases during chronic pain (Kisler et al., 2020).

Resting state functional connectivity findings on pain rely on models employing brief stimulation (e.g. seconds or few minutes). However, understanding the transition from acute to persistent pain requires models capable of inducing pain over a longer duration to better model chronic pain conditions (Kim and Davis, 2021). These tonic pain models, albeit still brief in comparison to persistent pain, can provide insight into changes associated with tonic pain before developing into more persistent states. Moreover, there is evidence of a differential cortical processing (including in rsFC) between EC and EO occuring throughout the life span (Barry et al., 2009; Barry and De Blasio, 2017) and existing in otherwise healthy blind individuals (Hüfner et al., 2009).

The primary aim of this study was to examine the effects of 1-hour capsaicin-induced pain on EEG rsFC within and between the bilateral AG and PCC and mPFC at alpha and beta oscillations under EC and EO states. Compared to both pain-free state at baseline and placebo conditions, it was hypothesized that alpha and beta rsFC (1) would decrease in the capsaicin condition, with (2) different connections exhibiting a decrease in rsFC during EC compared to EO.

2. Methods

2.1. Subjects

Twenty-eight healthy right-handed subjects (14 women, age 25.1 ± 4 years, mean ± SD) participated in the study and were recruited online and through flyers posted at Aalborg University. Handedness was assessed using Edinburgh Handedness Inventory (Oldfield, 1971). Participants reported no neurological or psychiatric disorders, no current or chronic pain, and no significant medical disorders. The study was conducted according to the Helsinki Declaration and approved by the local ethics committee (N-20190057). Signed informed consent was obtained from the participants before the experiment.

2.2. Study protocol

This crossover study included two sessions (placebo/pain) separated by 24 hours. To control for the possible effect of eye sequence on rsFC when recording EEG, subjects were randomly assigned and balanced to one of two groups (50% women in each group): EC-EO group and EO-EC group. EEG signals were recorded in the EC-EO group for 5 min during EC followed by 5 min during EO. In the same way, EEG signals were recorded in the EO-EC group for 5 min during EO followed by 5 min during EC. The same eye sequence for each group was maintained for placebo and capsaicin sessions (Fig. 1). In each group, pain was induced by a topical application of a placebo patch in one session and an 8% capsaicin patch in the second session on the right forearm. Given that pain and residual effects can last for days after capsaicin patch removal (Lo Vecchio et al., 2018), the placebo session preceded the capsaicin session. Each session consisted of a series of baseline measures including questionnaires, EEG recordings, and Quantitative Sensory Testing (QST), followed by 1-hour patch application (placebo or capsaicin). Immediately following the removal of the patch, EEG recordings and QST measures were re-assessed. QST measures included thermal and mechanical pain sensitivity assessment, but are not presented in this study. Data collection took place at Aalborg University in Denmark between February 2020 to July 2020.

2.3. Tonic pain model

Cutaneous pain was induced using a (5x10 cm) 8% topical capsaicin patch (transdermal patch, 'Qutenza', Astellas) on the volar part of the dominant right forearm (5 cm from the wrist) of each participant. For the placebo condition, a vehicle patch (Demo patch, Astellas) was applied to the same location and comprises the same formulation except for capsaicin. The application of capsaicin and vehicle patches was performed according to the manufacturer's instructions using nitrile gloves. The patch (capsaicin or placebo) was covered with two layers of medical tape (Fixomull stretch, BSN).

Pain intensity was assessed on a numerical rating scale (NRS) from 0 "no pain" to 10 "the worst imaginable pain". Throughout the one-hour patch application, participants were asked to report their pain NRS ratings every 5 min. Three pain parameters were then calculated: average pain intensity across all the 5-minute NRS reports, current pain intensity as the pain NRS level reported at the end of one-hour patch application, and the peak pain intensity as the highest pain NRS score reported.

2.4. Questionnaires

Questionnaires were used to assess pain-related behavior such as vigilance and catastrophizing, as well as fatigue, sleep quality, and negative mood as they are shown to influence both subjective pain reports and rsFC scores (Alshelh et al., 2018; Baliki and Apkarian, 2015).

Pain Vigilance and Awareness Questionnaire (PVAQ). This

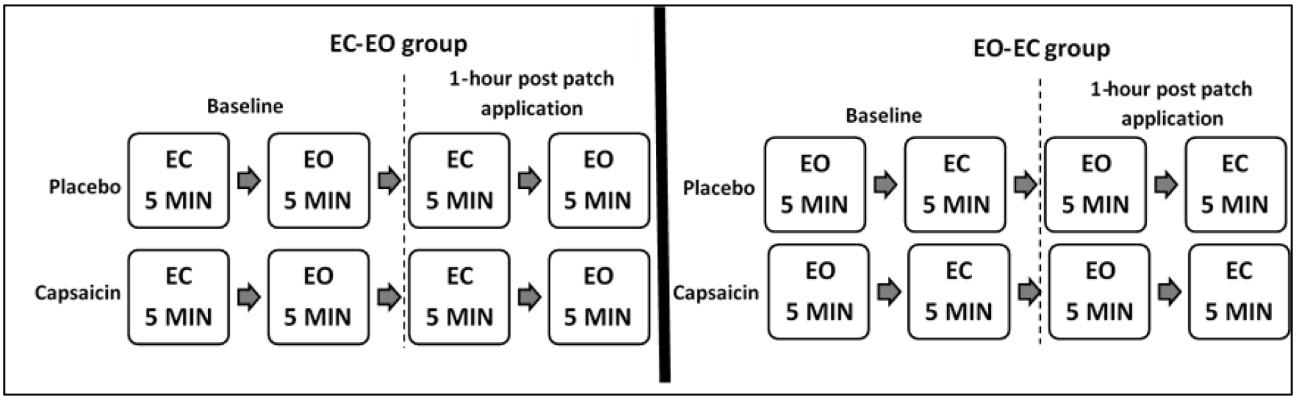

Fig. 1. Electroencephalographic (EEG) recording and randomization of eye sequence. Depending on the eye sequence, subjects were randomly and balanced assigned to two groups: eyes-closed-eyes-open (EC-EO) group (n = 14) and eyes-closed-eyes-open (EO-EC) group (n = 14). EEG signals were recorded for 5 min for each sub-condition. The first session was always placebo, and then after 24 hours it was followed by the capsaicin session.

questionnaire was used to assess preoccupation and attention to one's pain in the past two weeks (McCracken, 1997). It comprises 16 items rated between 0 = "never" and 5 = "always", with a maximum score of 80. Higher scores indicate higher vigilance and preoccupation with pain.

Pain Catastrophizing Scale (PCS). This questionnaire consists of 13 items rated 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 assesses three domains of catastrophizing: rumination, magnification, and helplessness. Subjects indicate the degree to which they have specific thoughts and feelings when experiencing pain over the last three months. Higher scores reflect a higher degree of pain catastrophizing.

Pittsburgh Sleep Quality Index (PSQI). This questionnaire assesses sleep quality and sleep patterns by addressing seven areas: 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). Subjects rate each of these seven areas of sleep on a scale from 0 = "no difficulty" to 3 = "severe difficulty," with a maximum score of 21. Higher scores indicate poor sleep quality.

Modified Fatigue Impact Scale (MFIS). The MFIS is a self-report instrument designed to evaluate the extent to which fatigue affects overall perceived function over the last 4-week time interval (Fisk et al., 1994). It includes three subscales: cognitive functioning (9 items), physical functioning (10 items), and psychosocial functioning (2 items). Each item is rated on a scale from 0 = "no problem" to 4 = "extreme problem", with a maximum score of 120. Higher scores reflect higher levels of fatigue.

Positive and Negative Affect Scale (PANAS). This self-report scale consisted of 20 descriptions used to independently assess two categories of emotions: negative and positive (10 items each) (Watson et al., 1988). Subjects indicate to what extent they feel a specific emotion the past week. The emotions are rated between 1 = "very slightly or not at all" to 5 = "Extremely," with a maximum of 50 for each emotion category. Higher scores reflect more intense emotions in both the negative and positive categories.

Beck Depression Inventory (BDI-II). The BDI evaluates the severity of depressive mood states such as hopelessness, guilt, fatigue, and other physical symptoms over the last month (Richter et al., 1998). It consists of 21 questions, rated between 0 = "no symptom impact" and 3 = "maximum symptom impact" with a maximum score of 63. Higher scores indicate severe depressive symptoms.

2.5. EEG acquisition

EEG recordings during the pain and placebo conditions for each participant took place at the same time of the day, either 9 am or 1 pm. Participants were seated in a comfortable chair in a light- and sound-attenuated room and were instructed during EC and EO states to relax, stay awake, and refrain from any movement. Specifically for EO, participants were instructed to fixate on a cross positioned about 70 cm from where they were seated. For each session (placebo or capsaicin), EEG signals were recorded at two time-points: Baseline and 1 h-following patch application. For each of these two time-points, EEG signals were collected during EC (5 min, Fig. 1) and EO (5 min, Fig. 1).

EEG data were recorded using an EEG cap consisting of 64 electrodes (g.GAMMA cap2). The cap was applied according to 10–5 system with Cz positioned on the vertex of the head. An additional EEG electrode (Fp1) was mounted above the left eye to monitor eye movement. The ground electrode in the cap was positioned in the middle of the distance between the eyebrows. EEG signals were amplified (50000×) and sampled at 1200 Hz (g.HIamp biosignal amplifier) with the electrode impedances kept below 5 kΩ.

2.6. EEG processing

EEG data were processed and analyzed using Brain Electrical Source Analysis (BESA Research 7.1, GmbH, Gräfelfing, Germany). Data were down-sampled offline to 500 Hz and high-pass filtered at 0.53 Hz and low-pass filtered at 175 Hz, with a notch filter of 50 Hz. Each 5-min EEG recordings were segmented into 2-s epochs. The epochs were screened through visual inspection, and evident artifacts were rejected manually. Then these epochs were screened for eye movement using the automatic artifact correction in BESA. This method has the advantage of separating eye-movement-related artifacts without distorting brain signals of interest. It is based on transforming EEG data into a predefined source montage (a combination of BR29 and EOG-HVB source montages). The BR29 (Brain 29) source montage includes 29 regional sources distributed in the entire brain. The EOG-HVB source montage, on the other hand, consists of 3 spatial components that represent eye blinks (B-EOG), as well as vertical (V-EOG) and horizontal eye movements (H-EOG). Waveforms associated with blink and vertical eye movement are combined as one component (VB-EOG), which then, along with the (H-EOG) are correlated with the original data to detect eye-movement-related artifacts. The epochs were then scanned in BESA to exclude epochs that have artifacts not related to eye movement.

To examine rsFC of the connections between the AG and each of PCC and mPFC, EEG data were transformed from sensor (electrode) space to source space using pre-defined source montages for resting state networks in the BESA Research software. Source analysis moves away from the scalp to the brain through transforming continuous EEG to a specific set of brain regions to enhance the signals arising from these regions (Michel and Brunet, 2019; Scherg et al., 2019). This approach has the advantage of reducing the effect of volume conduction and field spread caused by scalp electrodes (Scherg et al., 2019). The pre-defined source montages are constructed for the 81 electrodes of standard 10–10 electrode system. Therefore, recorded data is interpolated onto the standard 81 electrodes to match the position and number of electrodes. After that, the source waveforms are computed using spatial filters based on a 4-shell ellipsoidal head model (Scherg et al., 2019).

Resting state montages implemented in BESA rely on source solutions, for which regional sources were placed at the locations of the brain areas of interest determined by Montreal Neurological Institution (BESA Research 7.1, GmbH). When brain regions are represented with bilateral sources that are not perfectly symmetrical, these sources were symmetrized favouring the less superficial source. In order to increase the sensitivity of the sources of interest, additional noise sources were identified and added to each resting state network. As the AG, PCC, and mPFC are parts of the DMN, a resting state source montage for the DMN was used. The source locations for the resting state network were derived from the DMN system identified by Power et al. (2011). The artifact-scanned and accepted epochs in each sub-condition were then selected for connectivity analysis.

2.7. Connectivity analysis

Source connectivity analysis uncovers the functional connectivity between brain areas by reducing the effects of volume conduction problem that arises when analyzing the data in the electrode space. Connectivity between the pre-defined sources (bilateral AG, PCC, and mPFC) was assessed using BESA connectivity 1.0 (MEGIS Software GmbH).

Data were first transformed to the time–frequency domain using time–frequency analysis, specifically, the complex demodulation method. Complex demodulation is a technique that describes the amplitude and phase of a given frequency component of a time series as functions of time, providing a uniform frequency resolution across the analysis bandwidth (Hao et al., 1992). Granger causality was computed in the frequency domain (Geweke, 1982) employing a non-parametric spectral factorization approach (Dhamala et al., 2008) at alpha-1 (8–10 Hz), alpha-2 (11–13) and beta (14–30 Hz) bands.

EEG research identifies two frequency ranges within the alpha band: the lower component (alpha-1: 8–10 Hz) and the upper component

(alpha-2: 11–13 Hz) with different reactivity and topographical features (Klimesch et al., 2006, 1998a, 1998b; Lopez da Silva, 1999; Perry et al., 2010; Pfurtscheller et al., 2000). The two bands may be associated with different mechanisms, as supported by studies on spatiovisual attention (Lobier et al., 2018), alertness and expectancy (Klimesch et al., 1998a), cognitive control (Hanslmayr et al., 2005; Zoefel et al., 2011), verbal and visual imagery (Cremades and Pease, 2007; Petsche et al., 1997), mood, and neural activity associated with listening and composing music (Petsche et al., 1997). Investigating the alpha band from a split-band perspective may provide more insight into the brain rhythms of pain. rsFC at alpha-1, alpha-2, and beta oscillations was calculated at each of five connections (right AG-PCC, right AG-mPFC, left AG-PCC, left AG-mPFC, and right AG-left AG) as the average of rsFC scores for all the artifact-free epochs in each sub-condition.

2.8. Statistics

Data were analyzed using SPSS software, version 26. All data are shown as the mean and standard error of the mean (SEM). Statistical significance was set at $P < 0.05$ unless stated otherwise. For normality, all variables were tested for kurtosis and skewness by assessing their corresponding z scores, and data were considered normal when z scores did not exceed ± 1.96 (Field, 2018). Five separate mixed model analysis of variance (ANOVA) were performed to assess rsFC at five pairs: (1) right AG-PCC, (2) right AG-mPFC, (3) left AG-PCC, (4) left AG-mPFC, and (5) right AG-left AG. For each ANOVA, the within-subject factors were time (baseline, 1-h), condition (placebo, capsaicin), and eye state (closed, open), and the between-subjects factor was group [EC-EO, EO-EC]. To control for potential error resulting from multiple ANOVAs (5 pairs), the P-value from the ANOVAs was Bonferroni corrected to $P < 0.01$ (i.e. 0.05/5) for accepting significant main effects or interactions. Where appropriate, post-hoc analysis was performed using Bonferroni-corrected multiple comparison tests. The association between pain intensity NRS scores and rsFC was examined using Pearson correlation analyses. Only rsFC pairs that exhibit a significant change in response to capsaicin application were considered for correlation. To compensate for multiple correlation analyses, significance levels were Bonferroni-corrected based on the number of correlations performed. To examine whether the groups were similar in baseline characteristics (i.e. age and questionnaires measures) and pain NRS ratings, one-way ANOVAs were conducted . If the two groups differ in any of the characteristics variables, these variables will be listed as covariates, and analysis of covariance (ANCOVA) will be performed to control for their effects.

3. Results

Data from all participants were included in the analysis (dataset: Alhajri et al., 2021).

3.1. Baseline characteristics

There was a significant difference between EC-EO and EO-EC groups in sleep ($F(1,26) = 6.17$, $P = 0.020$), depression ($F(1,26) = 7.48$, $P = 0.011$), and negative affect ($F(1,26) = 4.74$, $P = 0.039$). EO-EC group reported poorer sleep quality, higher depression scores, and more intense negative affect than the EC-EO group (Table 1). The scores on these three scales were within the normal range for both groups. There was no significant difference between the two groups in other baseline characteristics.

Table 1
Baseline characteristics (Mean ± SEM) in (EC-EO) and (EO-EC) groups.

	EC-EO group	EO-EC group	F (1,26)	P-value
Age (years)	24.36 ± 0.95	25.93 ± 1.16	1.10	0.305
Sleep (PSQI)	**3.86 ± 0.63**	**5.93 ± 0.55**	**6.17**	**0.020**
Depression (BDI-II)	**2.93 ± 0.55**	**7.07 ± 1.41**	**7.48**	**0.011**
Fatigue (MFIS)	22.36 ± 3.46	26.50 ± 3.32	0.74	0.396
Catastrophizing (PCS) Rumination	6.57 ± 1.16	6.00 ± 1.22	0.11	0.737
Catastrophizing (PCS) Magnification	3.07 ± 0.32	4.07 ± 0.65	1.89	0.180
Catastrophizing (PCS) Helplessness	6.71 ± 0.99	7.21 ± 1.41	0.08	0.774
Vigilance (PVAQ)	39.07 ± 3.27	42.07 ± 2.99	0.46	0.504
Positive Affect (PANAS)	26.50 ± 1.4	29.64 ± 2.2	1.45	0.240
Negative Affect (PNAS)	**12.14 ± 0.6**	**15.00 ± 1.2**	**4.74**	**0.039**

F and P-value are from the one-way ANOVAs. Pittsburgh Sleep Quality Index (PSQI). Beck Depression Inventory (BDI-II). Modified Fatigue Impact Scale (MFIS). Pain Catastrophizing Scale (PCS). Pain Vigilance and Awareness Questionnaire (PVAQ). Positive and Negative Affect Scale (PANAS).

3.2. Capsaicin-induced pain

Current pain NRS scores for EC-EO and EO-EC groups were 7.8 ± 0.5 and 7.0 ± 0.6, respectively, following capsaicin, which were higher than 0 ± 0 and 0.2 ± 0.2 after placebo [ANOVA: ($F(1,26) = 319.13$, $P < 0.001$]. The average pain NRS scores after capsaicin for both groups (5.0 ± 0.4 and 5.0 ± 0.4) were higher than placebo (0.0 ± 0.0 and 0.2 ± 0.2) [ANOVA: ($F(1,26) = 305.81$, $P < 0.001$]. Finally, the capsaicin peak pain NRS scores (8.0 ± 0.5 and 7.5 ± 0.5) were higher than placebo (0.1 ± 0.1 and 0.3 ± 0.2; ANOVA: $F(1,26) = 377.23$, $P < 0.001$). There was no significant difference between the two groups in any of the three pain ratings: Average pain (ANOVA: $F(1,26) = 0.004$, $P = 0.953$), current pain (ANOVA: $F(1,26) = 0.92$, $P = 0.347$), and peak pain (ANOVA: $F(1,26) = 0.54$, $P = 0.471$).

3.3. AG connectivity at alpha-1 oscillations

3.3.1. Baseline AG connectivity at alpha-1 oscillations

The ANOVAs revealed that of the five examined rsFC connections (right AG-PCC, right AG-mPFC, left AG-PCC, left AG-mPFC, and right AG-left AG), two showed higher alpha-1 rsFC during EC compared to EO due to a main effect of eye state (Fig. 2A-B; right AG-PCC: $F(1,26) = 12.70$, $P = 0.001$, $\eta^2 = 0.33$; right AG-mPFC: $F(1,26) = 7.85$, $P = 0.009$, $\eta^2 = 0.23$), with the third and fourth connections approaching significance (Fig. 2C-D; left AG-PCC: $F(1,26) = 7.83$, $P = 0.01$, $\eta^2 = 0.23$; left AG-mPFC: $F(1,26) = 5.81$, $P = 0.023$, $\eta^2 = 0.18$).There were no other significant main effects or interactions, indicating that there was no significant differences between the groups (i.e. EC-EO, EO-EC) or conditions (i.e. placebo, capsaicin) at baseline (Table 2).

3.3.2. AG connectivity at alpha-1 oscillations with ***eyes closed*** during capsaicin-induced pain

As the groups differed in sleep, negative affect, and depression scores, these variables were added as covariates in the ANCOVA.

Right AG-PCC & right AG-mPFC connections: The ANCOVAs revealed a significant positive relationship between negative affect (i.e. covariate) and alpha-1 rsFC at the right AG-mPFC (Table 3; $F(1,23) = 8.74$, $P = 0.007$, $\eta^2 = 0.27$). There was also a condition × time × group interaction for the right AG-PCC (Table 3; $F(1,23) = 11.02$, $P = 0.003$, $\eta^2 = 0.32$) and right AG-mPFC ($F(1,23) = 17.08$, $P < 0.001$, $\eta^2 = 0.43$). Interestingly, eye sequence appears to influence alpha-1 rsFC at these two connections. Post hoc analysis revealed that in EC-EO group, alpha-1 rsFC was lower after 1-hour capsaicin-induced pain compared to baseline (right AG-PCC: $P = 0.002$, $d = 0.97$, Fig. 3A; right AG-mPFC: $P = 0.005$, $d = 0.83$, Fig. 3B). Surprisingly, the EO-EC group showed a

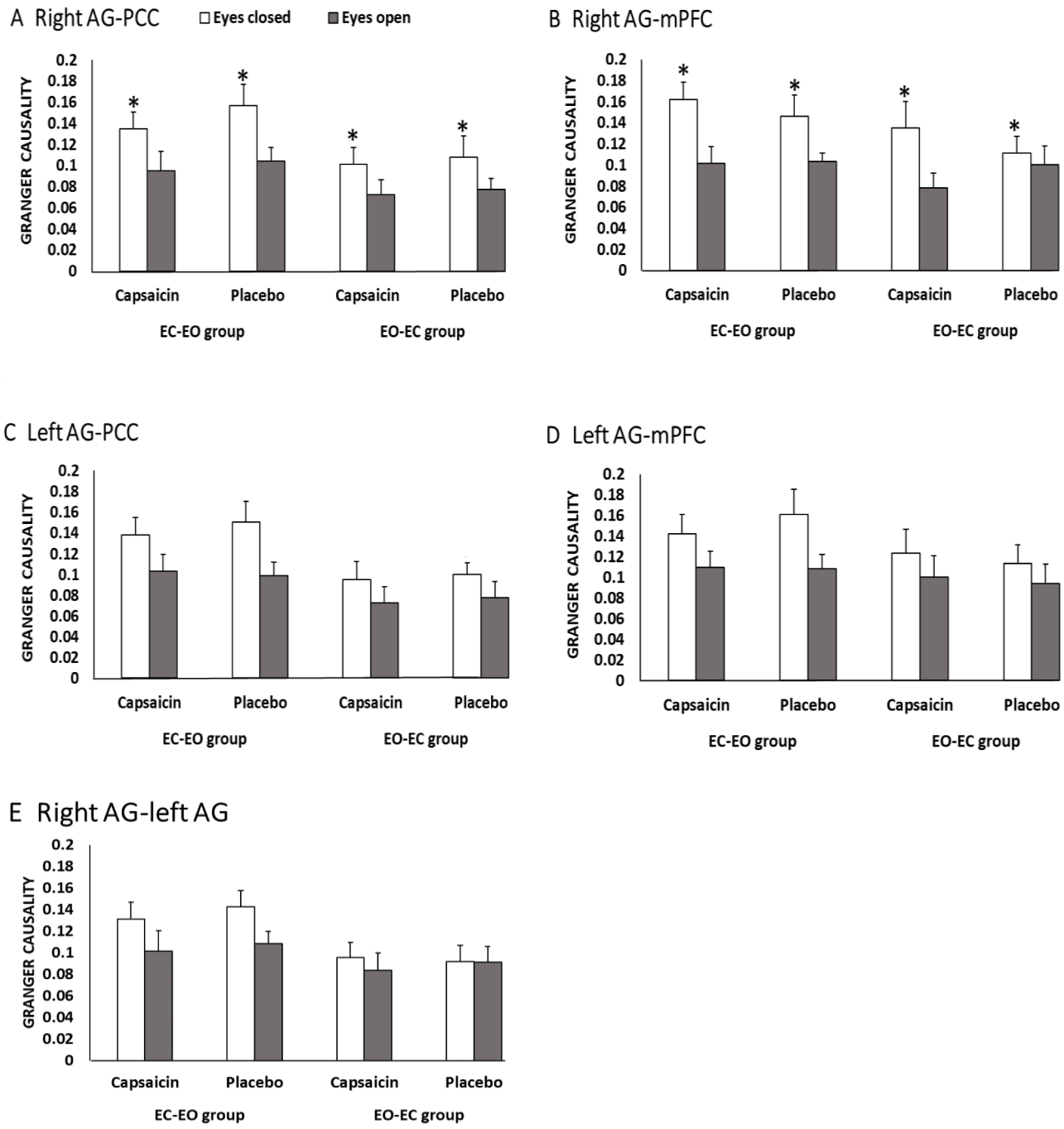

Fig. 2. Mean (+SEM, n = 14) Granger causality reflecting alpha-1 resting state functional connectivity (rsFC) between eyes closed (white bars) and eyes open (solid bars) states at **baseline**, in eyes-closed-eyes-open (EC-EO) and eyes-open-eyes-closed (EO-EC) groups at five connections (**A**: right AG-PCC; **B**: right AG-mPFC; **C**: left AG-PCC; **D**: left AG-mPFC, **E**: right AG-left AG). Significantly higher compared with eyes open (*, $P < 0.05$) illustrated on both groups and both conditions as there was a significant main effect of eye state with no other significant main effects or interactions.

non-significant increase in alpha-1 rsFC after capsaicin-induced pain compared with baseline at both connections (right AG-PCC: $P = 0.067$, $d = 0.53$; right AG-mPFC: $P = 0.399$, $d = 0.24$).

For the placebo condition, there was no significant change in alpha-1 rsFC after 1-hour placebo application compared with baseline at these connections for the EC-EO group (right AG-PCC: $P = 0.994$, $d = 0$; right AG-mPFC: $P = 0.074$, $d = 0.49$), or EO-EC group (right AG-PCC: $P = 0.102$, $d = 0.46$; right AG-mPFC: $P = 0.101$, $d = 0.45$).

Left AG-PCC & left AG-mPFC connections: The ANCOVAs revealed no significant time main effect or interactions at these two connections during EC (Table 3).

Right AG-left AG connection: The ANCOVA showed a condition × time × group interaction for the right AG-left AG connection (Table 3; $F(1,23) = 8.59$, $P = 0.008$, $\eta^2 = 0.27$). Post hoc analysis revealed that in EC-EO group, alpha-1 rsFC was lower after 1-hour capsaicin-induced pain compared to baseline (right AG-left AG: $P = 0.023$, $d = 0.65$, Fig. 3E). Surprisingly, the EO-EC group showed a non-significant increase in alpha-1 rsFC after capsaicin-induced pain compared with baseline (right AG-left AG: $P = 0.267$, $d = 0.31$).

For the placebo condition, there was no significant change in alpha-1 rsFC after 1-hour placebo application compared with baseline at this connection for the EC-EO group (right AG-left AG: $P = 0.313$, $d = 0.26$),

Table 2
ANOVA findings on **baseline** alpha-1 resting state functional connectivity (rsFC) under eyes closed and eyes open states, in two groups (eyes-closed-eyes-open sequence(EC-EO, n = 14) and eyes-open-eyes-closed sequence (EO-EC, n = 14)) at five connections (right AG-PCC; right AG-mPFC; left AG-PCC; left AG-mPFC; right AG-left AG). F-values and P-values are from the mixed models ANOVA (significance accepted at 0.01, Bonferroni corrected due to multiple ANOVAs).

Connection	Main effects			Interactions			
	group	condition	eye	Condition × group	eye × group	condition × eye	condition × eye × group
right AG-PCC	F(1,26) = 4.87 P = 0.036	F(1,26) = 1.03 P = 0.319	F(1,26) = 12.70 P = 0.001	F(1,26) = 0.201 P = 0.658	F(1,26) = 0.611 P = 0.442	F(1,26) = 0.164 P = 0.689	F(1,26) = 0.082 P = 0.777
right AG-mPFC	F(1,26) = 1.47 P = 0.235	F(1,26) = 0 P = 0.985	F(1,26) = 7.851 **P = 0.009**	F(1,26) = 0.310 P = 0.583	F(1,26) = 2.544 P = 0.123	F(1,26) = 6.21, P = 0.019	F(1,26) = 2.60 P = 0.119
left AG-PCC	F(1,26) = 6.70 P = 0.016	F(1,26) = 0.557 P = 0.462	F(1,26) = 7.83 P = 0.01	F(1,26) = 0.564 P = 0.459	F(1,26) = 4.36 P = 0.047	F(1,26) = 0.673 P = 0.419	F(1,26) = 1.93, P = 0.117
left AG-mPFC	F(1,26) = 3.55 P = 0.071	F(1,26) = 0.019 P = 0.891	F(1,26) = 5.81 P = 0.023	F(1,26) = 1.43 P = 0.243	F(1,26) = 2.12 P = 0.157	F(1,26) = 0.019 P = 0.892	F(1,26) = 1.24 P = 0.275
right AG-left AG	F(1,26) = 6.19 P = 0.020	F(1,26) = 0.252 P = 0.620	F(1,26) = 2.64 P = 0.116	F(1,26) = 0.118 P = 0.734	F(1,26) = 1.15 P = 0.293	F(1,26) = 0.047 P = 0.830	F(1,26) = 0.252 P = 0.620

or EO-EC group (right AG-left AG: P = 0.11, d = 0.43).

3.3.3. AG connectivity at alpha-1 oscillations with **eyes open** during capsaicin-induced pain

The ANCOVAs revealed no significant time main effect or interactions at the five examined connections during EO (Table 4).

3.3.4. Correlation between AG connectivity at alpha-1 and capsaicin-induced pain during EC

During EC, there was a significant negative correlation between current pain NRS scores and alpha-1 rsFC at the right AG-PCC (r = -0.68, P = 0.007) and the right AG-left AG (r = -0.69, P = 0.007), which was moderate but not significant at the right AG-mPFC (r = -0.35, P = 0.220).

3.4. AG connectivity at alpha-2 oscillations during capsaicin-induced pain (see supplementary materials)

At baseline, of the five examined connections (right AG-PCC, right AG-mPFC, left AG-PCC, left AG-mPFC, right AG-left AG), only left AG-PCC showed higher alpha-2 rsFC during EC compared to EO due to a main effect of eye state (Fig. S1C). For capsaicin-induced pain, unlike alpha-1, the ANCOVAs showed no significant change in alpha-2 rsFC after 1-hour capsaicin application compared to baseline during EC (Table S2) or EO (Table S3) for both groups.

3.5. AG connectivity at beta oscillations during capsaicin-induced pain (see Supplementary materials)

At baseline, of the five examined connections (right AG-PCC, right AG-mPFC, left AG-PCC, left AG-mPFC, and right AG-left AG), only left AG-PCC showed higher beta rsFC during EC compared to EO due to a main effect of eye state (Fig. S4C). There was a bilateral change in beta rsFC after 1-hour capsaicin application compared to baseline during EC only for capsaicin-induced pain. Specifically, the EC-EO group showed a decrease in rsFC at all connections except right AG-PCC (Fig. S5A) and right AG-left AG (Fig. S5E). In contrast, EO-EC exhibited an increase at the left connections (left AG-PCC, Fig. S5C; left AG-mPFC, Fig. S5D). Similar to alpha-1 and alpha-2 oscillations, the ANCOVAs showed no significant change in beta rsFC after 1-hour capsaicin application compared to baseline during EO (Table S6).

4. Discussion

This study examined the effect of 1-hour capsaicin-induced pain on rsFC within the AG as well as the connections between the AG and each of the PCC and mPFC at alpha and beta oscillations during eyes-closed and eyes-open states. Overall, capsaicin-induced pain was associated with a decrease in rsFC during EC only, at alpha-1 and beta oscillations, with no significant change at alpha-2 oscillations. This study highlights the importance of eye-state at baseline and eye sequence when assessing rsFC during tonic pain.

4.1. Baseline connectivity

At baseline, alpha-1 rsFC at the connections from the bilateral AG to the PCC and mPFC was lower during EO than EC, which is in line with previous studies (Barry et al., 2009; Barry and De Blasio, 2017; Jao et al., 2013; Tan et al., 2013; Xu et al., 2014). The AG, PCC, and mPFC may play a regulatory role monitoring the environment and maintaining the balance between internal and external attention (Gusnard et al., 2001; Leech and Sharp, 2014; Seghier, 2013). Closing the eyes tends to shift the attention internally causing high connectivity between these brain areas thought to mediate introspective processes (Raichle, 2015; Xu et al., 2014). During EO, the attention is usually shifted externally decreasing connectivity to facilitate visual perception by blocking introspective processes that would otherwise interfere with visual processing (Jao et al., 2013; Tan et al., 2013; Xu et al., 2014). Interestingly, for alpha-2 and beta, EC connectivity was higher than EO for one connection only. Notably, alpha-1, but not alpha-2, activity is shown to reflect alertness and attentional demands (Klimesch et al., 1998a). As the difference between the two eye-states mainly reflects a difference in interoceptive vs. exteroceptive processes (Xu et al., 2014), it is not surprising that the most prominent difference between the two eye-states occurred at alpha-1 oscillations.

4.2. AG connectivity and capsaicin-induced pain during eyes closed

After controlling for the effect of sleep, depression, and negative affect, the capsaicin-induced pain decreased AG connectivity during EC only. At alpha-1, this decrease occurred at the connection between right and left AG and involved only the right connections to PCC and mPFC, compared to a bilateral decrease at beta, with no significant changes at alpha-2. This finding is consistent with other pain studies showing decreased alpha/beta power (Nickel et al., 2017; Nir et al., 2012; Schulz et al., 2015) and reduced AG activity (Kong et al., 2010) during tonic pain. The lack of change in rsFC at alpha-2 oscillations was expected as the distinctive activity of upper and lower alpha oscillations is reported in both pain (Nir et al., 2012) and non-pain studies (Hanslmayr et al., 2005; Klimesch et al., 1998a; Lobier et al., 2018; Zoefel et al., 2011). For example, consistent with our results, Nir et al. (2012) found that alpha-1, but not alpha-2, power is a stable measure of subjective pain intensity and that resting state alpha-1 power may explain inherent individual differences in tonic pain sensitivity. Further, a review by Klimesch et al. (2006) showed that alpha-2 rhythms is more involved during semantic memory processing than processing of perceptual stimuli including pain. This suggests that alpha-1, as opposed to alpha-2, oscillations are more involved in pain perception, which could be due to the role of

Table 3
ANCOVA findings comparing alpha-1 resting state functional connectivity (rsFC) between baseline and after 1-hour (time) capsaicin and placebo application (cond.: condition) under **eyes closed**, in two groups (eyes-closed-eyes-open sequence (EC-EO, n = 14) and eyes-open-eyes-closed sequence (EO-EC, n = 14) at five connections (right AG-PCC; right AG-mPFC; left AG-PCC; left AG-mPFC, right AG-left AG). F-values and P-values are from the mixed models ANCOVA (significance accepted at 0.01, Bonferroni corrected due to multiple ANCOVAs). Covariates are sleep, BDI scores: depression, and NA: Negative affect.

Connect-ion	Main effects						Interactions											
	group	sleep	BDI	NA	Cond.	Time	Cond. × sleep	Cond. × BDI	Cond. × NA	Cond. × group	Time × sleep	Time × BDI	Time × NA	Time × group	Cond. × time	Cond. × time × sleep	Cond. × time × BDI	Cond. × time × NA	Cond. × time × group
Right AG-PCC	F(1,23) = 7.67 P = 0.011	F(1,23)= 6.08 P = 0.022	F(1,23) = 1.69 P = 0.206	F(1,23) = 6.36 P = 0.019	F(1,23) = 0.002 P = 0.966	F(1,23) = 0.169 P = 0.685	F(1,23) = 1.49 P = 0.235	F(1,23) = 0.118 P = 0.734	F(1,23) = 1.24 P = 0.227	F(1,23) = 4.15 P = 0.053	F(1,23) = 0.499 P = 0.487	F(1,23) = 0.256 P = 0.611	F(1,23) = 1.14 P = 0.298	F(1,23) = 0.311 P = 0.582	F(1,23) = 5.35 P = 0.030	F(1,23) = 0.846 P = 0.367	F(1,23) = 2.02 P = 0.168	F(1,23) = 4.89 P = 0.037	F(1,23) = 11.02 **P = 0.003**
Right AG-mPFC	F(1,23) = 6.37 P = 0.019	F(1,23) = 4.21 P = 0.052	F(1,23) = 1.10 P = 0.305	F(1,23) = 8.74 **P = 0.007**	F(1,23) = 0.006 P = 0.940	F(1,23) = 1.48 P = 0.236	F(1,23) = 0.989 P = 0.768	F(1,23) = 0.935 P = 0.344	F(1,23) = 0.032 P = 0.861	F(1,23) = 3.93 P = 0.059	F(1,23) = 4.75 P = 0.040	F(1,23) = 0.321 P = 0.567	F(1,23) = 0.004 P = 0.949	F(1,23) = 0.133 P = 0.719	F(1,23) = 11.08 **P = 0.003**	F(1,23) = 0.112 P = 0.741	F(1,23) = 1.74 P = 0.200	F(1,23) = 5.50 P = 0.028	F(1,23) = 17.08 **P < 0.001**
Left AG-PCC	F(1,23) = 4.22 P = 0.052	F(1,23) = 0.092 P = 0.756	F(1,23) = 0.00 P = 0.994	F(1,23) = 0.284 P = 0.599	F(1,23) = 0.401 P = 0.533	F(1,23) = 0.063 P = 0.805	F(1,23) = 0.220 P = 0.644	F(1,23) = 2.93 P = 0.100	F(1,23) = 1.12 P = 0.301	F(1,23) = 4.71 P = 0.041	F(1,23) = 0.041 P = 0.842	F(1,23) = 0.720 P = 0.405	F(1,23) = 1.07 P = 0.312	F(1,23) = 2.61 P = 0.120	F(1,23) = 6.62 P = 0.017	F(1,23) = 1.38 P = 0.251	F(1,23) = 5.51 P = 0.028	F(1,23) = 6.19 P = 0.021	F(1,23) = 1.76 P = 0.197
Left AG-mPFC	F(1,23) = 6.47 P = 0.018	F(1,23) = 2.09 P = 0.162	F(1,23) = 0.353 P = 0.558	F(1,23) = 3.40 P = 0.078	F(1,23) = 1.19 P = 0.286	F(1,23) = 1.97 P = 0.174	F(1,23) = 0.756 P = 0.391	F(1,23) = 1.08 P = 0.310	F(1,23) = 0.072 P = 0.790	F(1,23) = 2.41 P = 0.134	F(1,23) = 0.259 P = 0.616	F(1,23) = 0.034 P = 0.854	F(1,23) = 3.40 P = 0.078	F(1,23) = 0.099 P = 0.756	F(1,23) = 5.32 P = 0.030	F(1,23) = 0.322 P = 0.576	F(1,23) = 0.465 P = 0.502	F(1,23) = 5.39 P = 0.029	F(1,23) = 3.20 P = 0.087
Right AG-left AG	F(1,23)= 8.71 P = 0.007	F(1,23)= 2.50 P = 0.127	F(1,23)= 0.559 P = 0.462	F(1,23)= 2.84 P = 0.105	F(1,23) = 2.15 P = 0.156	F(1,23) = 0.315 P = 0.559	F(1,23) = 0.412 P = 0.527	F(1,23) = 0.109 P = 0.744	F(1,23) = 5.05 P = 0.035	F(1,23) = 8.12 **P = 0.009**	F(1,23) = 0.116 P = 0.736	F(1,23) = 0.322 P = 0.576	F(1,23) = 0.181 P = 0.675	F(1,23) = 0.001 P = 0.979	F(1,23) = 2.41 P = 0.134	F(1,23) = 0.466 P = 0.502	F(1,23) = 0.002 P = 0.961	F(1,23) = 4.71 P = 0.040	F(1,23) = 8.59 **P = 0.008**

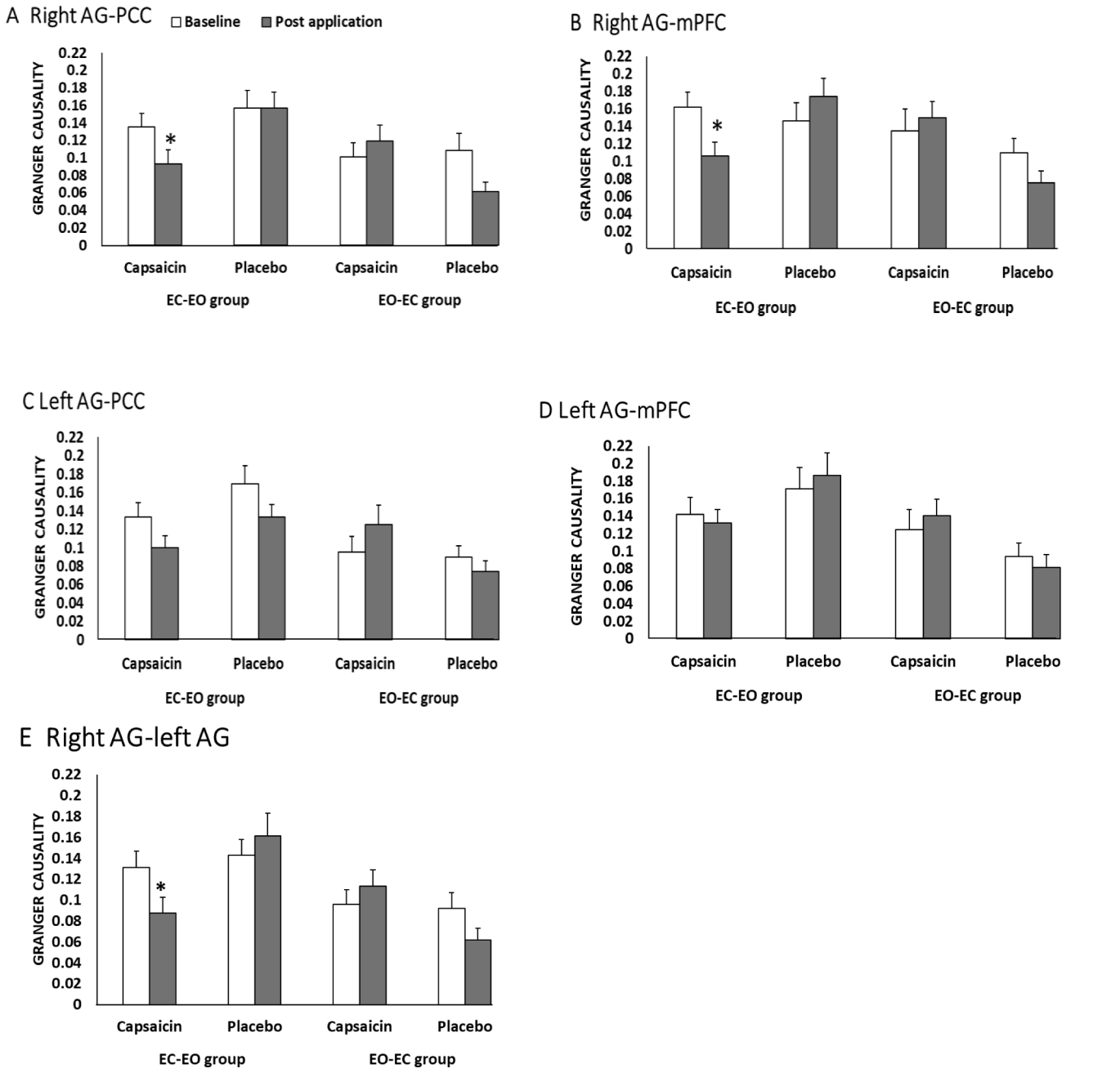

Fig. 3. Mean (+SEM, n = 14) Granger causality reflecting alpha-1 resting state functional connectivity (rsFC) between baseline (white bars) and after 1-hour (solid bars) capsaicin or placebo application under **eyes closed**, in eyes-closed-eyes-open (EC-EO) and eyes-open-eyes-closed (EO-EC) groups at five connections (**A**: right AG-PCC; **B**: right AG-mPFC; **C**: left AG-PCC; **D**: left AG-mPFC; **E**: right AG-left AG). Significantly lower compared with baseline (*, $P < 0.05$).

alpha-1 in attentional and motor processes (Klimesch et al., 1998b; Pfurtscheller et al., 2000). These processes would facilitate a conscious response to painful stimuli. Notably, due to the wide-spread functional and structural connections, the AG receives and integrates inputs from different modalities (likely including the occipital and somatosensory cortices) necessary for executing this conscious response (Igelstrom et al., 2015; Igelström and Graziano, 2017).

4.3. Functional significance of decreased AG connectivity

The present data provide evidence for the involvement of the AG in pain perception in the absence of any experimental task. The AG exhibit high rsFC with PCC and mPFC (Igelström and Graziano, 2017; Kong et al., 2010; Kucyi et al., 2014; Tanaka and Kirino, 2019) that decreases to shift attention from internal to external processing essential for responding to contextual demands and hence healthy cognitive functioning (Anticevic et al., 2012; Laird et al., 2009; Smith et al., 2009).

4.3.1. Decreased right AG connectivity at alpha-1 oscillations

Decreased connectivity at alpha-1 while experiencing tonic pain may serve as an adaptive mechanism for focusing attention (Palva et al., 2005). This explanation lends support from the involvement of the AG, PCC, and mPFC in attention regulation (Bowman et al., 2017; Gusnard et al., 2001; Leech and Sharp, 2014; Seghier, 2013), and the link between alpha-1 and attentional processes (Klimesch et al., 1998b; Pfurtscheller et al., 2000). This attention-related decrease may explain

Table 4
ANCOVA findings comparing alpha-1 resting state functional connectivity (rsFC) between baseline and after 1-hour (time) capsaicin and placebo application (cond.: condition) under **eyes open**, in two groups (eyes-closed-eyes-open sequence (EC-EO, n = 14) and eyes-open-eyes-closed sequence (EO-EC, n = 14) at five connections (right AG-PCC; right AG-mPFC; left AG-PCC; left AG-mPFC; right AG-left AG). F-values and P-values are from the mixed models ANCOVA (significance accepted at 0.01, Bonferroni corrected due to multiple ANCOVAs). Covariates are sleep, BDI scores: depression, and NA: Negative affect.

Connection	Main effects						Interactions													
	group	sleep	BDI	NA	Cond.	Time	Cond. × sleep	Cond. × BDI	Cond. × NA	Cond. × group	Time × sleep	Time × BDI	Time × NA	Time × group	Cond. × time	Cond. × time × sleep	Cond. × time × BDI	Cond. × time × NA	Cond. × time × group
Right AG-PCC	F(1,23) = 1.26 P = 0.273	F(1,23) = 1.11 P = 0.302	F(1,23) = 1.17 P = 0.290	F(1,23) = 2.16 P = 0.155	F(1,23) = 0.00 P = 0.985	F(1,23) = 0.021 P = 0.887	F(1,23) = 0.887 P = 0.356	F(1,23) = 1.73 P = 0.202	F(1,23) = 0.215 P = 0.647	F(1,23) = 0.000 P = 0.988	F(1,23) = 1.46 P = 0.239	F(1,23) = 1.74 P = 0.200	F(1,23) = 0.479 P = 0.496	F(1,23) = 1.72 P = 0.202	F(1,23) = 0.525 P = 0.476	F(1,23) = 1.83 P = 0.190	F(1,23) = 0.181 P = 0.675	F(1,23) = 3.19 P = 0.087	F(1,23) = 0.256 P = 0.618
Right AG-mPFC	F(1,23) = 0.003 P = 0.956	F(1,23) = 1.25 P = 0.276	F(1,23) = 0.624 P = 0.438	F(1,23) = 3.82 P = 0.063	F(1,23) = 0.356 P = 0.556	F(1,23) = 0.098 P = 0.757	F(1,23) = 0.570 P = 0.458	F(1,23) = 0.000 P = 0.990	F(1,23) = 0.118 P = 0.734	F(1,23) = 1.60 P = 0.219	F(1,23) = 3.02 P = 0.096	F(1,23) = 3.58 P = 0.071	F(1,23) = 0.500 P = 0.487	F(1,23) = 0.296 P = 0.592	F(1,23) = 0.012 P = 0.915	F(1,23) = 0.002 P = 0.969	F(1,23) = 0.864 P = 0.362	F(1,23) = 0.016 P = 0.902	F(1,23) = 0.170 P = 0.648
Left AG-PCC	F(1,23) = 1.41 P = 0.247	F(1,23) = 0.077 P = 0.783	F(1,23) = 0.356 P = 0.557	F(1,23) = 2.66 P = 0.116	F(1,23) = 0.201 P = 0.658	F(1,23) = 2.37 P = 0.138	F(1,23) = 0.367 P = 0.550	F(1,23) = 0.336 P = 0.568	F(1,23) = 1.37 P = 0.254	F(1,23) = 0.344 P = 0.563	F(1,23) = 1.74 P = 0.200	F(1,23) = 5.76 P = 0.025	F(1,23) = 1.18 P = 0.288	F(1,23) = 0.044 P = 0.836	F(1,23) = 0.074 P = 0.788	F(1,23) = 0.011 P = 0.917	F(1,23) = 1.66 P = 0.211	F(1,23) = 0.222 P = 0.642	F(1,23) = 2.39 P = 0.136
Left AG-mPFC	F(1,23) = 0.876 P = 0.359	F(1,23) = 0.309 P = 0.584	F(1,23) = 0.161 P = 0.692	F(1,23) = 2.65 P = 0.117	F(1,23) = 3.39 P = 0.079	F(1,23) = 3.87 P = 0.061	F(1,23) = 0.744 P = 0.397	F(1,23) = 0.051 P = 0.823	F(1,23) = 9.60 P = 0.005	F(1,23) = 1.87 P = 0.185	F(1,23) = 1.31 P = 0.256	F(1,23) = 2.64 P = 0.118	F(1,23) = 2.58 P = 0.122	F(1,23) = 0.074 P = 0.787	F(1,23) = 0.299 P = 0.590	F(1,23) = 0.102 P = 0.753	F(1,23) = 1.83 P = 0.189	F(1,23) = 0.002 P = 0.969	F(1,23) = 0.835 P = 0.370
Right AG-left AG	F(1,23) = 0.629 P = 0.436	F(1,23) = 0.138 P = 0.714	F(1,23) = 0.666 P = 0.423	F(1,23) = 1.20 P = 0.284	F(1,23) = 0.368 P = 0.550	F(1,23) = 0.378 P = 0.545	F(1,23) = 0.002 P = 0.968	F(1,23) = 0.071 P = 0.793	F(1,23) = 1.01 P = 0.326	F(1,23) = 0.00 P = 0.994	F(1,23) = 2.70 P = 0.114	F(1,23) = 4.31 P = 0.049	F(1,23) = 0.611 P = 0.442	F(1,23) = 0.825 P = 0.373	F(1,23) = 0.174 P = 0.680	F(1,23) = 2.14 P = 0.157	F(1,23) = 1.30 P = 0.266	F(1,23) = 1.74 P = 0.200	F(1,23) = 0.031 P = 0.861

the right hemispheric dominance at alpha-1 oscillations among connections with PCC and mPFC reported here. Neuroimaging studies provide evidence that the right AG is involved in attentional processes and the left AG is linked to memory and language (Igelström and Graziano, 2017; Seghier, 2013) as well as executive control processing (Kucyi et al., 2012). Kucyi et al. (2012), for example, show that both left and right temporal, parietal junction (including the AG) exhibit connections with the salience/ventral attention network, but the connections with the right sub-division are stronger. However, the present study revealed a robust decrease in connectivity between the right and left AG, suggesting that the communication between the two hemispheres (within the AG) is essential for focused attention during tonic pain.

4.3.2. *Decreased AG connectivity at beta oscillations*

Another possible purpose for shifting attention externally is related to the decreased connectivity at beta oscillations, which is to withdraw or avoid further injury (Baliki and Apkarian, 2015). This lends support from the proposed link between decreased beta activity and movement anticipation and planning (Engel and Fries, 2010; Zaepffel et al., 2013). This possible motoric protective response is further supported by reports on increased beta activity in the primary motor cortex during tonic pain (Martel et al., 2017), which may serve as a preparation for withdrawal or avoidance (Stančák et al., 2007).

This proposed neuroplastic adaptive mechanism is supported by increased connectivity shown by chronic pain patients (Kucyi et al., 2014; Lo Buono et al., 2017; Zhang et al., 2016). The increased connectivity exhibited by chronic pain patients may reflect enhanced focus on internal thoughts related to pain and the failure to disengage from the negative loop of their thoughts and feelings. This increased connectivity, as opposed to the decreased connectivity, during tonic pain, may be subject to underlying maladaptive mechanisms contributing to persistent pain.

4.3.3. *Correlation between the AG connectivity and capsaicin-induced pain during eyes closed*

This study showed that the rsFC at the right AG-PCC and right AG-left AG, but not right AG-mPFC, showed a significant correlation with subjective pain ratings. This is in line with previous research showing that self-rated pain intensity during chronic pain was primarily correlated with PCC activity (Lee et al., 2018). PCC is the sub-region of the cingulum, where the evaluation of sensory events is encoded to maintain relevant processes such as attention and memory (Vogt and Thomaschke, 2007). As self-rated pain intensity is mainly a subjective evaluation of a sensory experience (i.e. nociceptive), the stronger correlation between self-rated pain intensity and PCC connectivity in the present study is not surprising.

4.4. *The effect of eye sequence on AG connectivity during tonic pain under eyes closed*

Surprisingly, the eye sequence was crucial for the decrease in rsFC, but only during EC. Unlike the EC-EO group, the EO-EC group exhibited increased AG connectivity (significant at beta but non-significant at alpha). It is noteworthy that the eyes-closed state in the EO-EC group was recorded five minutes after the capsaicin patch was removed. Some participants indicated that the subjective pain intensity level during EC for EO-EC group was lower compared to that reported immediately after patch removal (i.e. in EC-EO group). The lower pain level may have allowed the subjects to engage in self-referential thoughts as a distraction, attenuating the pain-related connectivity decrease (Kucyi et al., 2013). Unfortunately, we did not report the subjective pain intensity five minutes following the patch removal. A previous study showed that the pain NRS score during a 1-h capsaicin application had a peak of 6 ± 3 which declined to 5 ± 2 after 1 h of patch removal (Landmann et al., 2016). Whether 5 min after patch removal could alter capsaicin

concentration (and hence pain perception) remains unknown, but it cannot be excluded affecting EC recordings in the EO-EC group.

Another explanation for the increase in connectivity among the EO-EC group could be differences in sleep quality and/or depression and negative affect scores as compared to EC-EO group. Depression and sleep deprivation are associated with disrupted rsFC (De Havas et al., 2012; Sheline et al., 2009). Nevertheless, after controlling for the effects of these factors, the same results were obtained, indicating that the observed increase in the AG connectivity during EC in the EO-EC group is less attributable to sleep quality and or more intense negative mood, and more likely related to pain level.

4.5. AG connectivity and capsaicin-induced pain during eyes open

Interestingly, after controlling for the effects of sleep, depression, and negative affect, there was no significant change in rsFC in response to one-hour capsaicin application during eyes open at alpha or beta oscillations for both groups. This suggests that the observed non-significant reduction in rsFC during EO (Fig. 4) is less likely to be pain-related and more likely to be related to sleep quality and/or negative mood. This implies that slight disturbances in sleep quality/and or negative mood could influence the interpretations of rsFC changes during pain, which is not entirely surprising given the complex relationship between negative mood and pain perception (Baliki and Apkarian, 2015). Future pain studies on rsFC should attempt to control

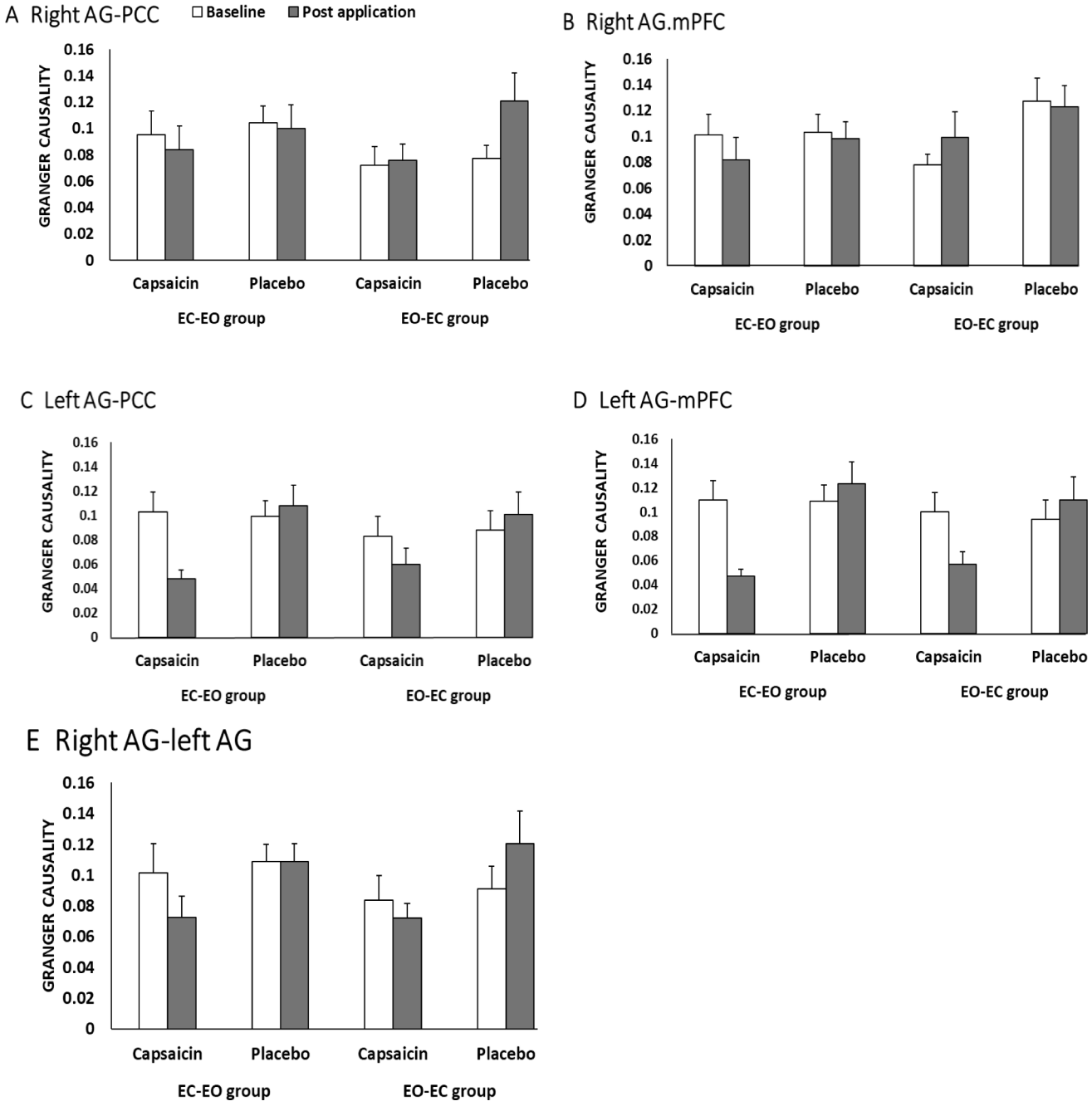

Fig. 4. Mean (+SEM, n = 14) Granger causality reflecting alpha-1 resting state functional connectivity between baseline (white bars) and after 1-hour (solid bars) capsaicin or placebo application under **eyes open**, in eyes-closed-eyes-open (EC-EO) and eyes-open-eyes-closed (EO-EC) groups at five connections (**A**: right AG-PCC; **B**: right AG-mPFC; **C**: left AG-PCC; **D**: left AG-mPFC; **E**: right AG-left AG).

for sleep quality and/or negative mood even if their values are within the normal range.

Nevertheless, the effect of pain on rsFC during eyes open cannot be excluded. It could be that the already decreased connectivity at baseline due to visual processing and enhanced attention shadows a pain-related decrease during EO. To avoid attention as a possible confound during EO, EC state with its higher connectivity may be a better baseline to detect a change in EEG-based rsFC. Particularly when this change, as in a painful context, is expected to be a decrease. A review paper discussing the challenges facing EEG-based rsFC recommended using EC, as opposed to EO, as a baseline state when assessing rsFC due to its stability over sessions and its robust topographical effect (van Diessen et al., 2015).

4.6. Limitations

Volume conduction and field spread are inherent confounds of connectivity analysis (van Diessen et al., 2015). Granger causality was used as a measure of rsFC, and this connectivity measure is sensitive to volume conduction. However, we used a source montage, which is shown to reduce the effect of volume conduction and field spread resulting from examining connectivity at the electrode level (Scherg et al., 2019). Further, no significant changes were found in the control condition at any connection during both eye-states. These arguments indicate that the changes in rsFC reported here reflect physiological (i.e. pain-induced) rather than artifact-generated changes. Nevertheless, the control condition cannot control for all potential confounds such as attentional focus (body centered vs. object centered), and salience (Eccleston and Crombez, 1999; Legrain et al., 2011). Salience and attention are inherent aspects of the pain experience, whose influence cannot be discarded entirely (Eccleston and Crombez, 1999; Legrain et al., 2011). Finally, the interpretations of the non-significant results may be limited by the low sample size, so employing a larger sample size would provide a better picture of the differences in pain-related changes in rsFC between EC and EO.

4.7. Conclusion

This study shows changes in rsFC in alpha and beta during EC, providing insights into the correlates of longer-lasting painful stimulation among the AG connections that may involve or precipitate persistent pain states. Additionally, resting state connectivity may be influenced by slight disturbances in mood and/or quality of sleep, which makes it critical to control for their effects when assessing rsFC during pain-related changes. Further, this study reveals two methodological considerations that may have an implication for settings employing rsFC as a method for assessing pain-related processes. First, EC baseline may allow a reliable detection of pain-related changes. Second, when examining rsFC during both eye-states, eye sequence could be critical, especially during EC.

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CRediT authorship contribution statement

Najah Alhajri: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Shellie Ann Boudreau:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Thomas Graven-Nielsen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102907.

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