Probing and Modulating Changes in Default Mode Network Connectivity Associated with Short- and Long-Term Experimental Pain

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PROBING AND MODULATING CHANGES IN DEFAULT MODE NETWORK CONNECTIVITY ASSOCIATED WITH SHORT- AND LONG-TERM EXPERIMENTAL PAIN

BY
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DENMARK

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by

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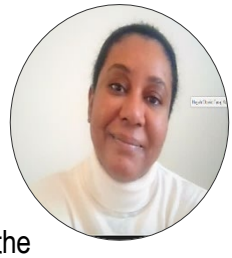

Najah Al Hajri received a BA degree in psychology from Concordia University, Canada, where she was awarded the *Governor-General Medal*, dating back to 1873, bestowed upon the highest-ranking student graduating with a bachelor's degree from a Canadian university, as well as the *J.W. Bridges Medal for Psychology*; awarded to the most outstanding student in psychology. After finishing her bachelor's in 2012, Najah worked as a research assistant in different labs, from personality and social psychology to behavioral neuroscience. In 2015, she actualized her passion for science by moving to Vancouver, where she received her master's degree in rehabilitation sciences (brain research) from the University of British Colombia in 2017. During her master's period, she was involved in different collaborative projects targeting interventions for people with traumatic brain injury.

In 2019, Najah started her PhD training under the supervision of Professor Thomas Graven-Nielsen, at the Center for Neuroplasticity and Pain, Aalborg University. During the PhD period, she has been involved in various dissemination activities within the Pain and Motor Systems Plasticity group and through presenting posters at IASP (virtually) and EFIC pain conferences.

ENGLISH SUMMARY

Chronic pain is a leading global cause of disability, affecting about 30% of the human population. However, the neuroplastic mechanisms underlying the transition to chronic pain are still unclear. Experimental prolonged pain models, albeit unable to capture the complexity of chronic pain conditions, can provide a unique reversible manifestation of pain-driven changes providing better insights into the transition to more persistent pain states. Unfortunately, most experimental pain studies rely on short-term models (seconds to minutes) that can uncover pain effects in the very early stages but fall short in modeling chronic pain.

The brain consists of highly connected, constantly reorganizing networks, and hence employing measures that reflect the network nature of the brain would be a proper approach to examining brain responses. One of these measures that have been shown to reflect experience-dependent neuroplasticity is resting-state functional connectivity (rsFC), which assesses the temporal correlations between brain regions and networks. The default mode network (DMN), consisting of the angular gyrus (AG), medial prefrontal cortex (mPFC), and posterior cingulate cortex (PCC), is one of the most researched brain network that plays a crucial role in cognition and consciousness. The DMN is a major network in the dynamic pain connectome that is altered during both acute and chronic pain, suggesting that alterations in this network may be a part of the neuroplastic mechanisms underlying the transition from acute to chronic pain. Overall, there is a lack of electroencephalographic (EEG) research targeting the effect of pain on rsFC in general and the DMN in particular.

This work aimed to understand the neuroplastic mechanisms underlying the transition from tonic (one hour) to prolonged (24 hours) pain as reflected in changes in EEG-based DMN rsFC at lower alpha and beta oscillations. Pain was evoked using a capsaicin patch applied to the right forearm. Unlike other connections within the DMN, the AG connections during pain are largely understudied; hence Paper I established the effect of tonic pain on AG connections within the DMN during eyes closed (EC) and eyes open (EO) in two groups of participants (EC-EO, EO-EC groups) divided based on the eye sequence during EEG acquisition. Paper II examined changes in DMN connectivity between one hour and 24 hours of pain and whether these changes are resistant to changes in pain intensity. Paper III determined

whether pain-free DMN connectivity could contribute to individual differences in subjective pain intensity.

Paper I demonstrated that one hour of capsaicin-induced pain reduced AG connectivity at lower alpha but exclusively during EC in EC-EO group. At beta, during EC, the results showed decreased lAG and rAG connectivity in EC-EO group and increased lAG connectivity in EO-EC group. No significant change in connectivity was observed during EO at both lower alpha and beta oscillations for both groups. Paper II showed the same decrease following one hour of pain among the rAG, mPFC (lower alpha and beta) and PCC (beta) connections that persisted 24 hours later (except for mPFC-lAG), despite the reduction in pain intensity between one and 24 hours. Cooling or heating the capsaicin patch did not alter the decreased connectivity significantly following 24 hours. Paper III revealed that pain-free DMN connectivity, especially the connectivity between mPFC and lAG (mPFC-lAG), can predict the variation in subjective pain intensity beyond the contribution of emotional and pain-specific psychological factors assessed at baseline.

These findings indicate that tonic and prolonged pain are associated with robust decreased DMN connectivity occurring in continuous loops between regions linked to attentional and emotional processing. As pain progresses, these loops grow resistant to pain relief or exacerbation. This resistance to changes in pain intensity may signify a shift to emotional/attentional processing, possibly contributing to more persistent pain conditions. Additionally, pain-free DMN connectivity can identify individuals susceptible to enhanced pain perception. Further, findings from this work show that when assessing the effect of pain on DMN connectivity using EEG, two issues should be considered: (1) the EC state may be a more appropriate baseline, and (2) when both eye-states are examined, the order of eye-states during EEG acquisition might be crucial.

The generalizability of these results is, however, limited by the small sample size and lack of a control group for salience. Nonetheless, this work has elucidated the role of the DMN in pain processing, highlighting possible emotional/attentional processes encoded in the DMN that may be involved in the transition to more persistent pain states. Identifying these processes at the early stages of pain may help address these processes before they contribute to this transition. This work has also established pain-free DMN connectivity (at lower alpha) based on EEG measures as a potential screening tool for pain-related vulnerability, which could be efficiently utilized in clinical settings.

DANSK RESUME

Kroniske smerter er en førende global lidelse, der påvirker omkring 30% af den menneskelige befolkning. Imidlertid er de neuroplastiske mekanismer, der ligger til grund for overgangen fra akut til kronisk smerte, stadig uklare. Eksperimentelle langvarige smertemodeller, omend de ikke er i stand til at fange kompleksiteten af kroniske smertetilstande, kan give en unik reversibel manifestation af smertedrevne ændringer, der giver bedre indsigt i overgangen til mere vedvarende smertetilstande. Desværre tager de fleste eksperimentelle smerteundersøgelser udgangspunkt i kortsigtede modeller (sekunder til minutter), der kan afdække smerteeffekter i de meget tidlige stadier, men de kommer til kort i modellering af kronisk smerte.

Hjernen består af forbundne, konstant omorganiserende netværk, og derfor vil anvendelse af målinger, der afspejler hjernens netværksnatur, være en egnet tilgang til at undersøge hjernens reaktioner. En af disse målinger, der har vist sig at afspejle neuroplasticitet, er resting-state functional konnektivitet (rsFC), som vurderer de tidsmæssige sammenhænge mellem hjerneområder og netværk. Default mode network (DMN), der består af vinkelgyrus (AG), medial præfrontal cortex (mPFC) og posterior cingulate cortex (PCC), er et af de mest undersøgte hjernenetværk, der spiller en afgørende rolle i kognition og bevidsthed. DMN er et vigtigt netværk i den dynamiske smerteforbindelse, der ændres under både akutte og kroniske smerter, hvilket tyder på, at ændringer i dette netværk kan være en del af de neuroplastiske mekanismer, der ligger til grund for overgangen til kronisk smerte. Samlet set mangler der elektroencefalografisk (EEG) forskning rettet mod effekten af smerte på rsFC generelt og DMN i særdeleshed.

Formålet med dette forskningsarbejde er at forstå de neuroplastiske mekanismer, der ligger til grund for overgangen fra tonic (en time) til langvarig (24 timer) smerte, og som er afspejlet i ændringer i EEG-baserede DMN rsFC ved lavere alfa- og beta-svingninger. Smerter blev fremkaldt ved hjælp af et capsaicinplaster påført højre underarm. Paper I undersøger effekten af tonisk smerte på AG-forbindelser inden for DMN med lukkede øjne (EC) og med åbne øjne (EO) i to deltagergrupper (EC-EO, EO-EC-grupper) opdelt på øjensekvensen under en EEG-måling. Paper II undersøgte ændringer i konnektiviteten af DMN ved påført smerte i en time og i 24 timer, og om disse ændringer er modstandsdygtige over for ændringer i smerteintensitet. Paper III

fastslog, om smertefri DMN-konnektivitet kunne bidrage til individuelle forskelle i subjektiv smerteintensitet.

Paper I viste, at en times capsaicin-påført smerte nedsatte AG-konnektivitet ved lavere alfa, men udelukkende under EC i EC-EO-gruppen. Ved beta viste resultaterne reduceret lAG- og rAG-konnektivitet i EC-EO-gruppen og øget lAG-konnektivitet i EO-EC-gruppen. Der blev ikke observeret nogen signifikant ændring i konnektivitet under EO for begge grupper ved både lavere alfa- og beta-svingninger. Papir II viste samme udfald efter en times smerte blandt rAG, mPFC (lavere alpha og beta) and PCC (beta), der fortsatte 24 timer senere på trods af reduktionen i smerteintensitet mellem en time og 24 timer. En nedkøling eller opvarmning af capsaicin-plasteret ændrede ikke den nedsatte konnektivitet væsentligt efter 24 timer. Paper III afslørede, at smertefri DMN-konnektivitet, især forbindelsen mellem mPFC og lAG (mPFC-lAG), kan forudsige variationen i subjektiv smerteintensitet ud over bidraget fra følelsesmæssige og smertespecifikke psykologiske faktorer vurderet ved baseline.

Disse resultater indikerer, at tonic og langvarig smerte er forbundet med robust nedsat DMN-konnektivitet, der forekommer i kontinuerlige sløjfer mellem regioner forbundet med opmærksomhed og følelsesmæssig behandling. Efterhånden som smerten forværres, bliver disse sløjfer resistente over for smertelindring, hvilket kan betyde et skift til følelsesmæssig / opmærksom behandling, hvilket muligvis bidrager til mere vedvarende smertetilstande. Derudover kan smertefri DMN-konnektivitet identificere personer, der er modtagelige for forbedret smerteopfattelse. Når man vurderer effekten af smerte på DMN- konnektivitet ved hjælp af EEG, kan EC være en mere passende baseline end EO. Endelig er rækkefølgen af øjentilstandsregistrering afgørende, når begge øjentilstande undersøges.

Grundlaget for en egentlig generalisering af disse resultater er imidlertid begrænset på grund af den relative lille forføgsgruppe samt mangel på en kontrolgruppe for salience. Ikke desto mindre har dette forskningsarbejde belyst DMN's rolle i smertebehandling og fremhævet mulige følelsesmæssige / opmærksomhedsprocesser kodet i DMN, der kan være involveret i overgangen til mere vedvarende smertetilstande. Dette forskningsarbejde har samtidig etableret smertefri DMN-konnektivitet (ved lavere alfa) baseret på EEG målingeer som et potentielt screeningsværktøj for smerterelateret sårbarhed, der effektivt kan udnyttes i kliniske indstillinger.

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To my family and friends who supported me emotionally throughout this journey, many thanks. To my parents, because I owe it all to you. You are not with us anymore, but you have always been the blood in my veins, pushing me to be bigger than all the hardships life throws my way. To Rita, my Canadian-Italian friend, your precious friendship and constant emotional support have been the light guiding me through the difficult times.

This journey has been a journey of pain not only experimentally but also personally. To my beloved sister, Rahmah, who departed this world very early, leaving a black hole of sorrow in my heart, I would like to devote this work to

you because I completed it for you, to honor your love and all the sacrifices you made for me!

To my husband, Casper, your love, patience, and understanding have seen me through this journey. I love you deeply and, I can't find the words to describe the overwhelming gratitude to have your loving heart in my life!

Albeit unconventional, I would like to say thank you Aalborg for being you, the green, cozy, homey town that embraced me for three years. Places also can be kind! And thank you to everyone I crossed path with at some point during the PhD period, you might not know it, but you have helped to shape this work in one way or another!

Lastly, I would like to say thank you to the fighter in me; thank you for carrying the exhausted part of me to the end of the tunnel. We made it!

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CHAPTER 1. INTRODUCTION

1.1. EXPERIMENTAL PAIN MODELS

Chronic pain is a serious health problem affecting about 30% of the human population [146], with a detrimental impact spanning all aspects of life [50]. As such, a primary objective motivating pain studies is to understand the processes contributing to the development of chronic pain conditions. With chronic pain investigations, albeit highly insightful, it is hard to determine whether the observed changes (in brain activity or behavior) are pain-triggered or already present before the initial painful exposure. Although unable to capture the complexity of chronic pain conditions, experimental pain models can provide a unique reversible manifestation of pain-driven changes [7,32,59]. In these models, controlling for the duration, location, and intensity of painful stimuli is possible, which offers objective quantitative measures of the highly subjective pain experience [7,32,59]. Such experimental pain models, exceedingly prolonged models, can be valuable tools for understanding the cornification process of pain. Specifically, experimental models allow for tracking the progression of pain before, during, and following exposure, as well as uncovering the contribution of baseline pain-free individual characteristics to pain perception.

Neuroplasticity is an intrinsic neurophysiological process associated with a multitude of functional, structural, and chemical alterations in neuronal properties [183,190]. Neuroplastic changes associated with both chronic and experimentally induced acute pain are well-documented [26,27,33,51,114,180,187,208]. The neuroplastic mechanisms underpinning the shift from acute to chronic pain are, however, still largely unknown. Most experimental pain studies rely on short-term models (seconds to minutes) that can uncover pain effects in the very early stages but fall short in modeling chronic pain conditions. Prolonged pain models (hours or days) can offer better insights into the neuroplastic mechanisms involved in the transition to more persistent pain states [103]. One of these mechanisms may be reflected in changes in resting-state functional connectivity (rsFC).

1.2. RESTING-STATE FUNCTIONAL CONNECTIVITY AS A MEASURE OF NEUROPLASTICITY

The brain consists of highly connected networks that undergo rapid and constant reorganization [17,18] to allow for a timely response crucial for executing vital mental and physiological processes [29]. Therefore, experimental brain data are relational, requiring measures that consider the network nature of the brain [18]. Over the last few decades, rsFC has emerged as a measure of brain activity that assesses intrinsic temporal connections between and within spatially separated brain regions and networks in the absence of any experimental task [119,124]. As such, rsFC serves as a reference against which any observed brain alterations could be interpreted as a response to a given pre-defined experimental condition [119,172]. There are many advantages to using rsFC to probe brain activity. First, rsFC is a highly sensitive measure detecting brain disorders in the absence of any structural changes [13]. Moreover, as opposed to task-based connectivity, rsFC can be ideal when probing multiple neuronal networks simultaneously or examining brain changes among individuals with severe motor problems or those in a coma or vegetative state [13]. Most importantly, rsFC has been shown to reflect experience-dependent neuroplasticity [81], which makes rsFC a candidate for assessing pain neuroplasticity.

1.2.1. EEG-BASED RESTING-STATE FUNCTIONAL CONNECTIVITY

rsFC measures based on functional magnetic resonance imaging (fMRI) have been the most evaluated connectivity measures by far [35]. Although spatially sensitive, fMRI cannot capture real-time neuronal activity due to the poor temporal resolution [31,40]. In contrast, electroencephalography (EEG) is known for its high temporal resolution ranging from milliseconds to seconds [107]. Precise timing is critical for coordinating the constantly changing information flow in the brain to ensure efficient perceptual and cognitive processes and ultimately consciousness [107,214]. Thus, EEG can be ideal for assessing the activity of the rapidly changing brain [214]. However, due to the inflated noise-to-signal ratio in EEG measures as a result of volume conduction and field spread, drawing conclusions based on EEG signals can be challenging [211]. Nonetheless, a comprehensive study compared a wide range of EEG-based connectivity measures based on accuracy and specificity, and found an accuracy range of 0.98–1 and a specificity range of 0.99-1, concluding that EEG-based connectivity parameters are of comparable

accuracy to fMRI measures [210]. Additionally, resting-state networks detected by magnetoencephalography (MEG) [9] and fMRI [2,119] appear to share the same underlying neural mechanisms [100]. Further, a considerable overlap has been reported between EEG and fMRI resting networks in motor, premotor, sensory, frontal, and parietal areas, except for the temporal regions due to the significant disparity between the two methods in terms of temporal resolution [198]. Further, EEG-based connectivity has been successfully used as a tool in clinical settings. For example, EEG-derived networks help inform early epilepsy diagnosis [56] and enhance the accuracy of epilepsy surgeries [55]. As for reliability, EEG functional networks exhibit a core network structure that is stable across different states of consciousness and over several days [23,43].

1.3. THE DEFAULT MODE NETWORK (DMN)

Research has identified several resting-state networks, including the motor-sensory, visual, executive control, dorsal and ventral attention, language, and the well-known default mode network (DMN) [124]. Interestingly, 90% of the brain energy is allocated to intrinsic activity within these resting networks rather than task-induced activity [173]. Most of this 90%-energy level can be ascribed to the DMN activity [69], indicating that the “DMN baseline activity may support and maintain other activity within the brain” [97]. Because this network is easy to detect exhibiting consistent activity across subjects and time with a high test-retest reliability [13,141], the DMN is the most studied resting-state network across different imaging modalities [124,171]. The DMN comprises several brain regions, including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and bilateral angular gyrus (AG) [166], which are shown to be preferentially active at rest and in the absence of any tasks [173].

The DMN function has been described within two frameworks or hypotheses: introspection and sentinel hypotheses. The introspection hypothesis emphasizes the DMN role in self-referential thoughts, mind wandering, and internal mentation [136]. In contrast, the sentinel hypothesis stresses the involvement of the DMN in maintaining external vigilance necessary for guarding the body against any attention-demanding stimuli [83,172]. However, a more accurate account of the DMN function in cognition is a combination of these two perspectives, in which this network regulates the attention between internal and external environments to ensure the individual’s responsiveness to their surroundings [28]. Given this critical role in cognition, the DMN activity has been associated with healthy and diseased brain [4,68]. DMN deactivation

(i.e. decreased DMN activity), for example, is linked to healthy cognitive functioning, while the lack of deactivation may reflect poor cognitive performance [6,222], and, in some severe cases, cognitive/affective disorders (see Anticivic et al.[5] for review). Despite the common belief that the DMN regions respond similarly to different stimuli, recent evidence points towards a differential sensitivity within the DMN [4,116,186].

1.4. DMN CONNECTIVITY AND PAIN

The DMN is a key network in the dynamic pain connectome (DPC), which also comprises the salience network and the ascending nociceptive and descending modulation pathways [109,110]. Given the vital role the DMN plays in guiding our consciousness and responsiveness to the world, listing the DMN as a part of the DPC is not surprising. fMRI studies have demonstrated the involvement of the DMN in both acute and chronic pain conditions, suggesting that alterations in this network may be a part of the mechanisms underpinning the shift from acute to chronic pain. Specifically, fMRI findings linked acute pain to reduced DMN connectivity [3], whereas both increased [112,127,228] and decreased [3,11,39,88] DMN connectivity were reported in relation to chronic pain.

For EEG, research has shown that pain alters EEG-resting-state oscillations at various frequency ranges suggesting that changes in EEG rsFC can serve as a clinical biomarker of neuroplastic mechanisms underlying pain [76]. Given that pain is partially a cognitive experience [101], and that the DMN plays a critical role in cognition where brain response is time sensitive [29], one would expect the effects of pain on EEG-based DMN connectivity (with its high temporal resolution) to be well-documented. Unfortunately, a few recent EEG studies have examined pain-related changes in rsFC in response to both chronic pain [132,212] and experimentally induced acute pain (i.e. seconds to minutes) [77,94,126,134,149], none of which was specifically targeting the DMN. For more prolonged pain exposure (e.g. 24 hours), research on EEG-based rsFC is still lacking.

A simultaneous fMRI-EEG analysis of the brain oscillations showed that the DMN has a specific “electrophysiological signature” combining the activity of various brain oscillations, particularly at alpha and beta bands [133]. The positive association between the DMN activity and alpha and beta oscillations is further supported by fMRI-EEG [28,90,95,148,182] and MEG [206] data.

These two neuronal oscillations are found to be involved in pain processing [103]. At rest, the DMN exhibits decreased connectivity during eyes open (EO) in comparison to eyes closed (EC) [96,205,225], supporting a cortical differential processing between the two eye-states [16,92,135,221]. This differential cortical processing between the two eye states has been shown to occur across different developmental stages [14,15] and is present in otherwise healthy blind people [92]. Yet, it is still unknown whether the effect of pain on DMN rsFC differs between EC and EO.

1.5. AIM AND OBJECTIVES

The overarching purpose of this work was to understand the neuroplastic processes contributing to the transition from tonic to prolonged pain, as reflected in changes in EEG-based DMN rsFC at alpha and beta oscillations, and whether these changes are persistent to changes in pain intensity. Additionally, this work aimed to examine whether pain-free DMN connectivity could contribute to individual differences in pain perception. More specifically, the objectives were to investigate the following **(Figure 1-1)**:

I. Whether capsaicin-induced pain applied to the dominant right forearm for one hour (tonic) induces changes in AG connectivity within the DMN (Paper I). As the effect of pain on AG connectivity within the DMN is still unknown, Paper I aimed to establish this effect.
II. Whether pain-related effect on AG connectivity differs between eyes-closed and eyes-open states (Paper I).
III. How changes in DMN connectivity evolve/progress between one hour (tonic) and 24 hours (prolonged) of capsaicin-induced pain (Paper II).
IV. Whether prolonged pain-related changes in DMN connectivity are resistant to cooling (pain reduction) or heating (pain aggravation) the capsaicin patch (Paper II).
V. Whether DMN connectivity changes during pain are related to pain intensity (Paper I-II).
VI. To examine whether baseline pain-free DMN connectivity contributes to the variation in tonic pain intensity (Paper III).

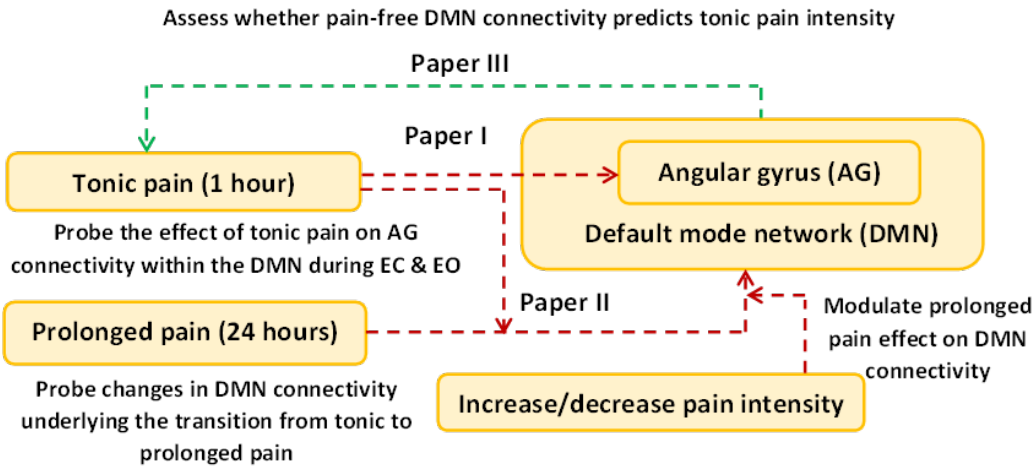

Figure 1-1. A conceptual overview of the papers included in the current PhD thesis*. Findings from Paper I were used to establish tonic pain's effect on AG connectivity, which was then examined together with other DMN regions to assess and modulate the transition to prolonged pain (Paper II). Baseline pain-free data from Studies I and II were used to determine the predictive value of pain-free DMN connectivity in relation to tonic pain intensity (Paper III).*

1.6. PAPERS ASSOCIATED WITH THE PHD THESIS

The current PhD thesis is based on two studies (I-II), which resulted in 3 papers: one published (Paper I), one accepted (Paper II), and one submitted manuscript (Paper III). Experimental designs for Studies I-II are shown in Figures 2-1 and 2-2.

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

Paper II: Alhajri, N., Boudreau, S. A., & Graven-Nielsen, T (2022). Decreased default mode network connectivity following 24 hours of capsaicin-induced pain persists during immediate pain relief and facilitation. Accepted, The journal of pain.

Paper III: Alhajri, N., Boudreau, S. A., Mouraux, A., & Graven-Nielsen, T. (Submitted). Pain-free default mode network connectivity predicts tonic experimental pain intensity beyond the contribution of negative mood and other pain-related factors.

CHAPTER 2. EXPERIMENTAL PROTOCOLS AND INDIVIDUAL CHARACTERISTICS

This chapter provides an overview of the experimental designs for Studies (I-II) as well as demographic, psychological, and pain-related sensitivity characteristics of the included participants. Figures 2-1 and 2-2 show an overview of the experimental procedures of studies (I-II).

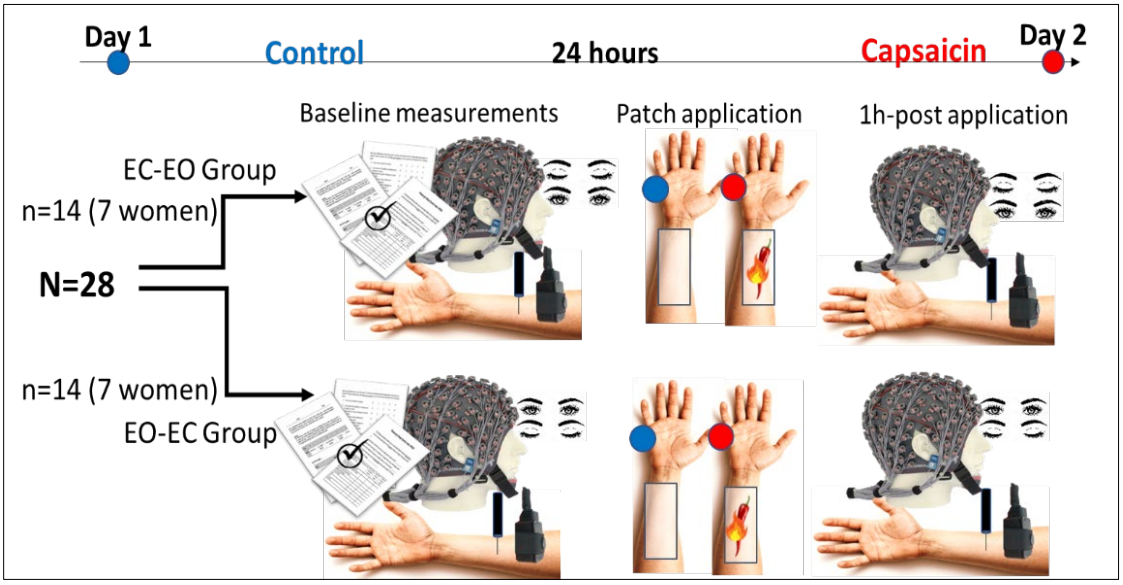

Figure 2-1. Experimental procedures for Study I. *All participants were randomly divided into two groups: Eyes-closed-eyes-open (EC-EO) or eyes-open-eyes-closed (EO-EC), based on the order of the eye-state during EEG acquisition. Participants in each group experienced the control condition and 24 hours later the capsaicin condition. Each condition comprises baseline assessments (Questionnaires, EEG measurements, pain sensitivity measures) followed by a one-hour patch application. Immediately after one hour, the patch was removed, and the EEG and pain sensitivity measurements were reassessed. Questionnaires assessed fatigue, sleep, mood, pain vigilance, and catastrophizing. EEG signals were acquired during eyes closed (5min) and eyes open (5min). Pain sensitivity measures assessed thermal and mechanical pain thresholds. Pain was evoked using a capsaicin patch (8%, 5x10 cm) on the volar part of the right dominant forearm.*

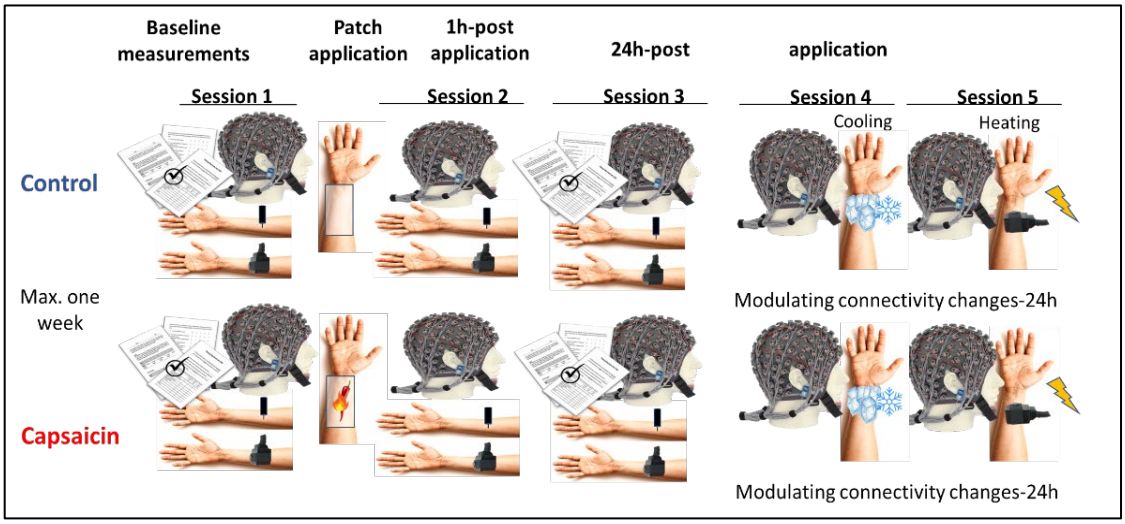

Figure 2-2. Experimental procedures for Study II*. Participants underwent five sessions for each condition: (1) baseline, (2) one hour (as in study I), (3)24 hours post patch application, (4) cooling, and (5) heating the patch following 24 hours. As Study I showed that the eyes-closed state might be a proper baseline for assessing pain-related changes in DMN connectivity, EEG signals, and hence connectivity were evaluated during the eyes-closed state.*

2.1. INCLUSION/EXCLUSION CRITERIA

Selecting the suitable experimental sample is essential for reducing the effect of potential confounding factors, which allows for accurate conclusions about the impact of capsaicin-induced pain on brain connectivity. It also ensures the safety of the included participants. Research has shown that handedness may be critical when assessing pain perception. For example, the dominant hand has been shown to be less pain sensitive than the non-dominant hand, but only for right-handed individuals [154,158,170]. As such, right-handed individuals were selected to ensure consistency and homogeneity in the current sample **(Table 2-1)**. They were also selected to ensure an easier and faster recruitment

process, as right-handedness is more common in the population than left-handedness.

Table 2-1. *Inclusion and exclusion criteria for all experimental studies.*

	Study I-II
General	Healthy right-handed men and women, aged (19-44), able to understand and speak English, no pregnancy
Capsaicin-related	No chili allergy
Pain	No present or history of chronic or current acute pain
Drug or medication	No regular medication use (including analgesic and anti-inflammatory drugs), no substance abuse.
Disorders	No present or previous neurological, musculoskeletal, or mental disorders.
EEG-related	No alcohol, caffeine, or tobacco consumption at least 6 hours prior to the trials, no hair products that may affect EEG conduction including gel and excluding hair shampoo.

2.2. DEMOGRAPHIC CHARACTERISTICS

Research has shown that demographic characteristics, including age, gender, and body mass index (BMI), can influence pain sensitivity as well as reported pain intensity. Specifically, females [41,64,74,137], older individuals [147], and those with a higher BMI [201,226] are more prone to report more pain and exhibit altered pain sensitivity than their counterparts. No statistical differences in age, weight, or height were observed between the groups (Study I) **(Table 2-2)**. In the present work, participants were relatively young (19-41years) with BMI within normal limits. Additionally, each study included an equal number of

men and women **(Table 2-2)**. The lack of any significant differences between groups suggests that it is unlikely that age, BMI, or gender contributed to the observed group differences in Study I.

Table 2-2. *Demographic characteristics of all participants.*

	Study I			**Study II**
	EC-EO group	EO-EO group	P value	
N	14	14		24
Gender	7 women	7 women	-	12 women
Age (year)	24.4±3.5	25.9±4.4	0.305	27.5±5.1
Height (cm)	173.8±2.7	172.5±2.4	0.734	170.2±8.2
Weight (Kg)	66.6±3.4	73.4±4.2	0.224	68.3±12.1

2.3. BASELINE CHARACTERISTICS INFLUENCING PAIN PERCEPTION

Several characteristics, such as sleep, mood, fatigue, pain vigilance, and catastrophizing, have been shown to impact the individual's pain experience. In the present work, these characteristics were examined using various validated questionnaires. It is noteworthy that the main objective of this work was not to examine how these factors change with pain, but rather assess their effects as potential contributors to the group differences in DMN connectivity (Paper I) or potential baseline predictors of pain intensity (Paper III).

2.3.1. PAIN VIGILANCE

Pain hypervigilance, an attentionally-biased preoccupation with pain, has been shown to predict acute postoperative pain [120] and characterize chronic pain patients [48]. Pain hypervigilance has been also linked to poor pain-related outcomes [139]. Generally, compared with other pain-specific psychological factors, such as catastrophizing, pain hypervigilance is under-investigated [57,91,121]. In the present work, pain hypervigilance was measured using the *Pain Vigilance and Awareness Questionnaire (PVAQ)*, which evaluates fixation on and attention to pain with a maximum score of 80 (higher scores reflect

greater pain vigilance) [139]. PVAQ has been validated in numerous pain and pain-free samples [138,140] and has shown good internal validity [177]. Studies evaluating pain vigilance found the average vigilance score for pain-free sample to be ***35±10.5*** [115], which is slightly lower than the group average for Study I groups ***(39.1±12.2*** and ***42.1±11.2)*** and slightly higher than the group average for Study II ***(29±13.5)*** **(Table 2-3)**.

2.3.2. PAIN CATASTROPHIZING

Pain catastrophizing, a cognitively distorted perception of pain as an unreasonably overwhelming threat, has been shown to contribute to severe postoperative pain intensity [157,159] and is considered a risk factor for chronic postsurgical pain intensity [159]. In the current work, catastrophizing was evaluated using the *Pain Catastrophizing Scale (PCS)*, which evaluates specific pain-related thoughts and feelings across three subscales: rumination, magnification, and helplessness, with greater scores indicating greater catastrophizing level [202]. PCS has a high construct validity [49,153]. A study evaluating pain catastrophizing found the average score for pain-free sample to be ***20.5±7.6*** [115], which is slightly higher than the group average reported in Study I groups ***(16.3±8.2*** and ***17.3±11.2)*** and Study II ***(13.4±7.1)*** **(Table 2-3)**, suggesting that the included sample showed relatively low catastrophizing levels.

2.3.3. MOOD

There is mounting evidence of the detrimental influence of negative mood on the individual's pain experience. For example, negative affect is associated with greater susceptibility to hyperalgesia [60] and altered pain perception [215]. Similarly, depression has been shown to exacerbate postoperative [62,161] and chronic pain [37]. To assess affect, this work employed *Negative and Positive Affect Scale (PANAS)*, which is a valid, reliable measure for assessing negative and positive emotions [38,46]. This scale evaluates negative and positive emotions rated at a maximum of 50 for each emotion group, with greater scores signifying more intense feelings. [220]. In the present work, momentary emotions (at the time of questionnaire administration) were assessed. The typical average score for momentary positive affect is ***29.7±7.9,*** which is relatively similar to the group average obtained in Study I groups ***(26.5±5.1*** and ***29.6±8.3)*** and Study II ***(26±9.4)***. For negative affect, the typical average score is ***14.8±5.4,*** which is also relatively similar to the group average

observed in Study I groups ***(12.1±2.1*** and ***15.0±4.4)*** and Study II ***(12.5±2.4)*** **(Table 2-3)**. These values indicate that the affect showed by the included participants was within the typical limits.

The Beck Depression Inventory (BDI-II) was used to evaluate depression. BDI-II is a validated inventory that has been employed as a screening device for mood disorders [20,175,200]. The BDI assesses the intensity of depressive symptoms rated at a maximum score of 63, with greater scores reflecting more intense depressive symptoms [175]. To obtain a trait measure as opposed to a state measure of negative mood (i.e. momentary affect) participants were asked to react to the questions in the BDI in a way revealing how they generally feel. Scores ranging from ***1 to 10*** are considered normal, while those ranging from ***17 to 20*** indicate borderline clinical depression. The group average for depression scores reported in both experimental studies ranged from **4.5 to 7.1 (Table 2-3)**, which is within the normal range.

2.3.4. SLEEP

Sleep impairments are associated with a higher risk for reduced tolerance during experimental pain [194] and reliably predict the onset and aggravations of chronic pain [66]. Moreover, acute experimentally induced sleep loss enhances pain sensitivity [122,195]. In this work, *Pittsburgh Sleep Quality Index (PSQI)* was used to measure sleep quality, which is a valid, reliable measure [8,144]. PSQI is rated with a maximum score of 21, with greater scores reflecting poorer sleep quality [34]. Good sleep quality is described with a score range of ***less than or equal to 6.5***, whereas poor sleep quality is defined with a score ranging from ***6.5 to 14.2*** [102]. The group average for overall sleep quality for Study I groups (***3.9*** *and* ***5.9)*** and Study II (***5.0)*** are within normal values **(Table 2-3)**.

2.3.5. FATIGUE

Fatigue and pain work hand in hand, aggravating the effects of one another [52,98]. *The Modified Fatigue Impact Scale (MFIS)*, a valid fatigue measure [1,108,184], was used to assess fatigue across three dimensions: cognitive, physical, and psychosocial functioning, rated with a maximum score of 84, with greater scores indicating elevated fatigue levels [67]. A study evaluating MFIS across healthy controls and patients with multiple sclerosis found the average fatigue value for healthy controls to be ***24.1±12*** [1]. Overall, this value is not

very far from the group average reported in Study I ***(22.4±13, 26.5±12.4),*** *but higher than that for Study II* (***16.7±13.2***), suggesting that the included participants in the current experimental studies exhibited relatively normal to low fatigue levels **(Table 2-3)**.

2.3.6. PAIN SENSITIVITY

Research has shown that high pain sensitivity might be a potential predictor of the transition to chronic pain [82,191] as well as pain-related outcomes in acute [219] and chronic pain patients [75]. For experimental settings, the association between pain sensitivity and pain perception is highly reliant on the pain modality, the examined body site, and the time of evaluation [87,178]. When assessing pain sensitivity in the present work, the focus has been on mechanical and thermal thresholds as they are most relevant to the capsaicin pain model. The main objective of this work was not to examine how pain sensitivity changes with pain. However, changes in pinprick mechanical pain sensitivity (MPT), an indicator of secondary hyperalgesia, were assessed in relation to prolonged pain (Paper II) to examine how changes in DMN connectivity may be related to the central pain mechanisms. Warmth detection (WDT) and heat pain (HPT) thresholds were assessed employing a stimulator probe (Pathway Medoc Ltd, Israel) and identified as the lowest temperature at which the probe was perceived as warm or painfully hot, respectively. Mechanical pain threshold (MPT) was evaluated using pinprick stimulators (MRC Systems GmbH, Germany).

2.3.7. DIFFERENCES BETWEEN GROUPS

Overall, the group average scores for the examined factors were within normal limits **(Table 2-3)**. There was, however, a significant difference between the groups in negative affect, sleep, and depression reports (Study I). The EO-EC group showed greater negative affect, elevated depression levels, and poorer sleep quality than EC-EO group. Sleep, negative affect, and depression scores were considered covariates when assessing group differences in DMN connectivity (Paper I) and discussed further in **Chapter 4**.

		Study I			Study II
		EC-EO group	EO-EO group	P value	
	N	14	14		24
sleep	Overall sleep quality *(PSQI)*	3.9±2.3	5.9±2.1	**0.020**	5.0±2.1
Mood	Negative affect (PANAS)	12.1±2.1	15.0±4.4	**0.039**	12.5±2.4
	Positive affect (PANAS)	26.5±5.1	29.6±8.3	0.240	26±9.4
	Depression (BDI-II)	2.9±2.1	7.1±5.3	**0.011**	4.5±3.5
Catastrophizing	Rumination (PCS)	6.6±4.3	6.0±4.6	0.737	5.3±3.1
	Magnification (PCS)	3.1±1.2	4.1±2.4	0.180	3.6±2.3
	Helplessness (PCS)	6.7±3.7	7.2±5.3	0.774	4.5±3.3
	Total catastrophizing (PCS)	16.3±8.2	17.3±11.2	0.790	13.4±7.1
Vigilance	Vigilance (PVAQ)	39.1±12.2	42.1±11.2	0.504	29±13.5
Fatigue	Total Fatigue score (MFIS)	22.4±13	26.5±12.4	0.396	16.7±13.2
Pain sensitivity	Warmth detection threshold (WDT) (°C)	33.8±0.6	34.4±1	0.077	34.4±0.7
	Heat pain threshold (HPT) (°C)	40.3±3.2	41.5±3.1	0.376	41.1±3.6
	Mechanical pain threshold (MPT) (g)	2.8±1.7	2.3±0.9	0.769	2.3±0.5

Table 2-3. Baseline characteristics of participants M±SD.

CHAPTER 3. PROVOKING PAIN-INDUCED CHANGES IN DMN CONNECTIVITY

This chapter provides an overview of the experimental pain model as well as the related pain intensity measures and parameters used in Studies I-II.

3.1. CAPSAICIN AS AN EXPERIMENTAL PAIN MODEL

Capsaicin is a well-established experimental pain model, primarily administered topically using capsaicin cream [22,93,156] or patches [80,118,129]. The capsaicin pain model has also been used orally [42], via intradermal or intramuscular injections [123,223], or in combination with heat [168,169]. Capsaicin is used as a pain model because it can induce central sensitization and the related processes of hyperalgesia and allodynia, critical characteristics in chronic pain conditions [152]. However, modes of capsaicin application are not equally practical. For example, capsaicin intradermal injections are associated with extreme pain, whereas capsaicin cream requires constant reapplication to sustain the pain perception [152]. In contrast, capsaicin patches offer a non-invasive approach that can yield long-lasting, stable, and reproducible effects [152]. As such, the current work adopted the capsaicin patch as the administration mode of capsaicin (Studies I-II). Specifically, pain was evoked using a capsaicin patch (5x10, 8%) on the volar part of the dominant right forearm applied about 5 cm from the wrist. This patch was used safely in an earlier study [118].

Interestingly, capsaicin application can lead to both sensitization and desensitization depending on the dose and application duration [99,117,193]. In this work, an 8% capsaicin patch was applied for one hour (Study I) and 24 hours (Study II). Previous pain studies using 8% capsaicin reported that following 24 hours, participants reported moderate pain ratings, suggesting that capsaicin-induced pain is a valid model for assessing prolonged pain [80,118].

3.2. PAIN INTENSITY SCALES AND PARAMETERS

The numerical rating scale (NRS) was employed to measure pain intensity in Studies I-II. The NRS is a validated, well-documented, and widely used scale to assess perceived pain intensity in both experimental and clinical settings [24,89]. The NRS is rated on a scale from 0 representing no pain, to 10

signifying the worst imaginable pain. Traditionally, pain intensity in both experimental and clinical settings is assessed using the visual analogue scale (VAS). Research has shown that the VAS and NRS scores are highly correlated (r=0.94), and the NRS can be used as a substitute for VAS in clinically acute pain settings [24]. Interestingly, some studies favored using NRS over VAS due to less variability or measurement error [58], greater compliance rates, responsiveness, applicability, and usability [89]. Considering these findings, the NRS was chosen as an intensity measure in the current PhD studies.

In the current experimental studies, three pain intensity NRS parameters were reported: average, current, and peak pain. NRS pain intensity score was reported every five minutes throughout the one hour (Study I-II) and every hour throughout the 24 hours (Study II) of capsaicin-induced pain. The average of the five-minute or one-hour reports constituted average pain. The current pain was reported at the end of one hour (Study I-II) or 24 hours (Study II). Peak pain represented the highest pain level reported throughout one hour (Study I-II) or 24 hours (Study II).

There was no significant difference in average pain following one hour between Study I (5.1±1.5) and Study II (4.3±1.8) (M±SD). Interestingly, the current and peak NRS pain scores following one hour of capsaicin-induced pain for Study I (Current; 7.4±2.2, Peak; 7.8±1.9) were slightly higher than Study II (Current; 5.9±2, Peak; 6.5±2.1). The peak pain was almost within the range obtained by an earlier study that employed the same capsaicin patch (i.e. 5x10cm, 8%) for one hour and reported a peak intensity of 6±3 [118]. Overall, these findings suggest that the capsaicin model used in the current work is consistent regarding the perceived pain perception following one hour. For the 24-hour application, no study to date used a 5x10cm 8% capsaicin patch for that duration.

3.3. PAIN INTENSITY FINDINGS

No difference in NRS pain intensity scores was observed between EC-EO and EO-EC groups in any of the examined pain parameters: current, average, and peak **(Figure 3-1; Paper I)**.

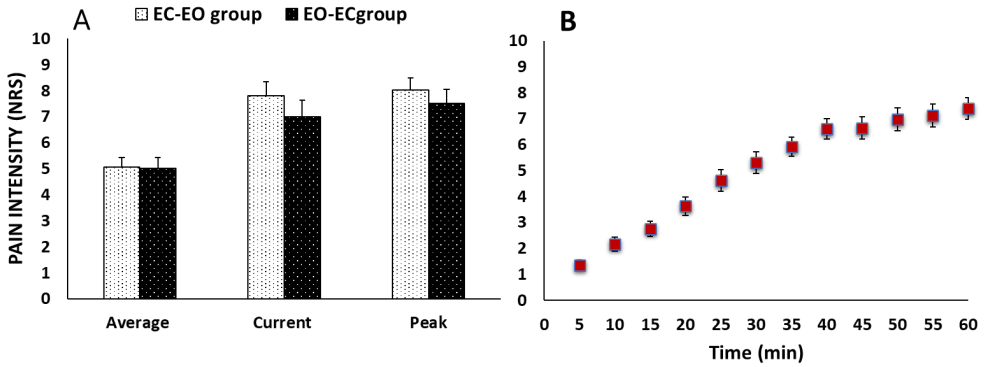

***Figure 3-1**. **Pain intensity ratings following one hour of capsaicin-induced pain. (A)** Comparing NRS pain intensity ratings (M±SEM) between EC-EO and EO-EC groups across average, current, and peak pain parameters. **(B)** Pain progression throughout the one-hour of capsaicin-induced pain.*

Between one and 24 hours, NRS pain intensity was reduced for current pain, but enhanced for both average and peak pain **(Figure 3-2, A; Paper II)**. For the pain progression, capsaicin-induced pain peaked around two hours from the initial capsaicin application at about 7±2 and fluctuated with an overall decrease to about 4±2 following 24 *hours* ***(Figure 3-2, B; Paper II).***

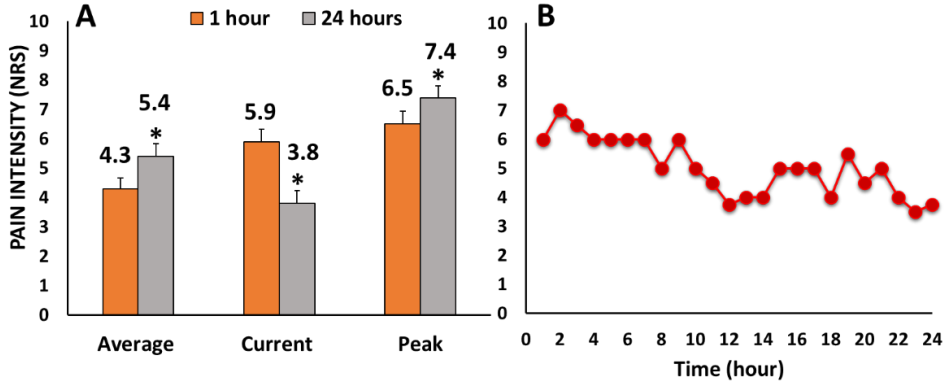

***Figure 3-2. Pain intensity ratings following one and 24 hours of capsaicin-induced pain**. **(A)** Comparing NRS pain intensity ratings (M±SEM) between one and 24 hours across average, current, and peak pain parameters. **(B)** Pain progression throughout 24 hours of capsaicin-induced pain.*

Cooling and heating the patch following 24 hours decreased and increased the perceived pain intensity, respectively **(Figure 3-3; Paper II).**

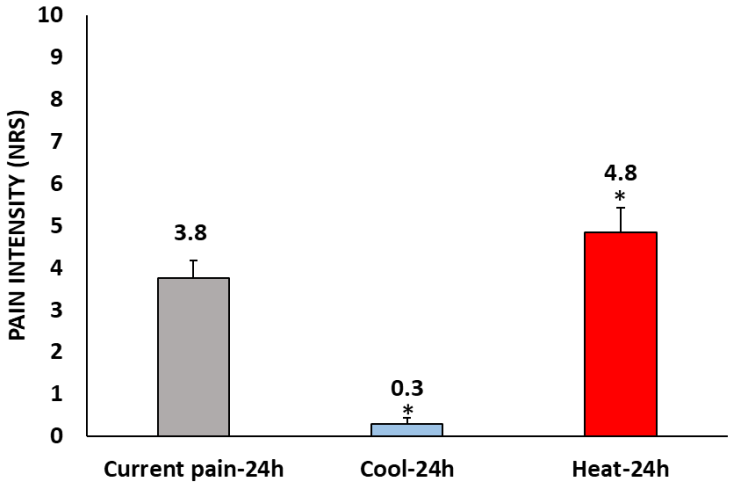

Figure 3-3. Pain relief and exacerbation *following 24 hours of capsaicin-induced pain obtained through cooling and heating the capsaicin patch, respectively (M±SEM).*

CHAPTER 4. PROBING AND MODULATING PAIN-INDUCED CHANGES IN DMN CONNECTIVITY

This chapter provides a discussion of the main findings as covered in Papers I-II.

4.1. LOWER ALPHA AND PAIN PROCESSING

Two components of the well-researched alpha frequency range (8-13Hz) are described in EEG research: lower alpha (8-10Hz) and upper alpha (11-13Hz) with distinct reactivity patterns [104–106,131,162,164]. There is evidence that the activity of these two frequency ranges may reflect distinct processes, as shown by studies on alertness and expectancy [105], verbal and visual imagery [47,163], spatiovisual attention [130], cognitive control [84,229], mood, composing and listening to music [163]. As such, examining alpha oscillations through a split-band approach may shed more light on the effect of pain on DMN connectivity.

4.2. SHORT-TERM (TONIC) PAIN

Connections between the mPFC and PCC are the most examined DMN connections both in pain and non-pain studies. In contrast, AG, another DMN region [167], and its connections with the mPFC and PCC are under-investigated. Before examining the DMN, the aim was to first establish the effects of tonic pain on AG connections within the DMN (with mPFC, PCC) (Paper I). An overview of Study I design is provided in **Figure 2-1** in chapter 2. In the current work, connectivity was measured using Granger causality, a well-established and widely used connectivity measure that takes into account the direction of information flowing between EEG signals [211]. If a previous value of Y can predict a prospect value of X, it is concluded that Y Granger-causes X [78]. Five connections were investigated in Paper I: rAG-mPFC, rAG-PCC, lAG-mPFC, lAG-PCC, and rAG-lAG at lower alpha (8-10 Hz), upper alpha (11-13Hz), and beta (14-30Hz) oscillations.

As the two groups (Study I) differed significantly in sleep, negative affect, and depression **(Table 2-3,** Chapter 2), we controlled for the effects of these factors. After controlling for these effects, there were significant changes in AG connectivity at lower alpha **(Figure 4-1; Paper I)** and beta but not upper alpha

oscillations (**Supplementary materials; Paper I)**. The non-significant change at upper alpha is consistent with previous findings showing that lower alpha (8-10 Hz) may be more related to pain perception than upper alpha (11-13Hz) oscillations [104,150]. At lower alpha, during EC, one hour of capsaicin-induced pain resulted in decreased connectivity between AG and each of mPFC and PCC, but only among the right connections *(rAG-PCC, rAG-mPFC, and rAG-lAG)* for the EC-EO group, with no significant change for EO-EC group **(Figure 4-1; Paper I)**. For beta oscillations, during EC, the EC-EO group showed significant decrease across all the investigated connections (except rAG-PCC), with the EO-EC group exhibiting a surprising increase in lAG connectivity with mPFC and PCC *(lAG- mPFC, lAG-PCC)* **(Supplementary materials; Paper I)**. Interestingly, no significant change in connectivity during EO for both groups at both oscillations was reported **(Figure 4-1,** and **Supplementary materials; Paper I).**

The AG, PCC, and mPFC [28,83,125,185] as well as lower alpha [105,164] are involved in attentional processing. The AG, PCC, and mPFC are regions of the DMN whose deactivation (i.e. decreased connectivity) is shown to reflect an attentional shift to the surrounding environment necessary for responding to demanding stimuli ensuring efficient cognitive performance [4,116,197]. During tonic pain, this decrease at lower alpha may function as an underlying mechanism for directing attention [155] to detect potential further injury. As this connectivity reduction is possibly attention-related, the right hemispheric dominance at lower alpha oscillations reported here is not surprising. Research has shown that compared to the left temporal parietal junction (TPJ) (including the lAG), the right TPJ (including the rAG) maintains stronger connections with the salience/ventral attention network [111]. Additionally, there is mounting evidence of the robust association between the activity of the right posterior parietal cortex, including the rAG, and attention reorientation and regulation [21,44,53,128,181,185,188]. As the reduction in connectivity during tonic pain may be of protective significance, the connectivity decrease at beta oscillations may signal a possible motor-related activation [61,227] to facilitate this protective function through potential withdrawal or avoidance reaction [199].

One surprising finding from Paper I is the increase in connectivity during EC (nonsignificant at lower alpha but significant at beta) in the EO-EC group. This increased connectivity could be due to the delay in recording the EC state after patch removal.

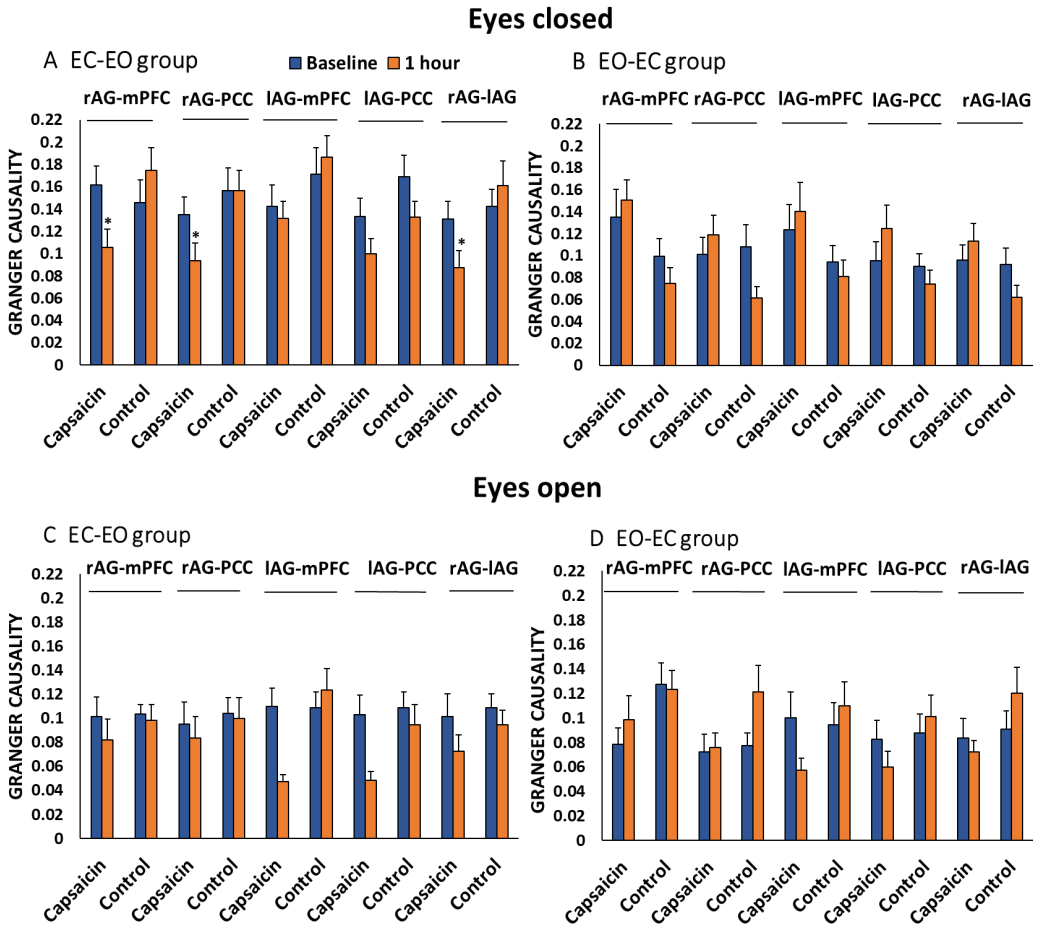

Figure 4-1. Angular gyrus connectivity following one hour of capsaicin-induced pain *(M±SEM).* ***(A)*** *Compared to baseline, rsFC between angular gyrus (AG) and each of medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and left AG (lAG) was decreased following one hour of capsaicin-induced pain. This reduction was exclusively among the right connections during eyes closed (EC) for the eyes-closed-eyes-open sequence (EC-EO) group.* ***(B)*** *No significant change in AG connectivity was shown during EC for the eyes-open-eyes-closed sequence (EO-EC) group. No significant change in AG connectivity was shown during eyes open (EO) for both* ***(C)*** *EC-EO and* ***(D)*** *EO-EC groups.*

Specifically, EEG signals during EC for the EO-EC group were acquired five minutes after the capsaicin patch was removed. This delay might have introduced a possible decrease in pain intensity (as reported by some participants), possibly weakening the connectivity decrease during EC for the EO-EC group. It is not unlikely that decreased pain intensity due to patch removal could shift the attention away from pain, mitigating the pain-related connectivity decrease [113]. A previous study using the same patch (i.e. 5x10 cm 8% capsaicin) revealed that NRS pain scores during one hour of capsaicin-induced pain peaked at 6±3, which decreased to 5±2 one hour after patch removal [118]. Unfortunately, the possible connection between pain relief and the increase in connectivity exhibited by EO-EC group remains speculative as subjective pain intensity ratings five minutes after the patch removal were not collected. In summary, the current findings show that the eye order could influence DMN connectivity when examining both eye-states, especially during EC.

Another unexpected finding is the absence of pain-related changes during EO for both groups. After controlling for negative mood and sleep quality effects, the observed decreased connectivity during EO **(Figure 4-1; Paper I)** was non-significant, suggesting that this observed reduction in connectivity might be associated with sleep quality and/or negative mood. As both groups showed average sleep and mood scores within normal limits, the lack of effect during EO suggests that mild disruptions in sleep quality/and or negative mood during pain investigations could impact DMN connectivity, especially during EO.

If sleep and mood have such an impact that could interfere with the pain effect, why was this impact evident only during EO? The answer could be related to the connectivity basal differences between the two eye-states. Compared to EC, the already reduced baseline connectivity during EO (because of visual processing and heightened attention) might have overshadowed the expected pain-related decrease. Assuming that pain has the same effect during each eye-state, the higher connectivity during EC might have allowed for a more observable change. As such, the higher connectivity during EC may make EC a more appropriate baseline for detecting pain-related changes in DMN connectivity. This conclusion agrees with a review paper demonstrating that when evaluating EEG-derived connectivity measures, the EC state is a better baseline than EO state because of its consistency across sessions and potent topographical effect [211].

4.3. THE TRANSITION FROM TONIC TO PROLONGED PAIN

After establishing the effects of pain on AG, connectivity from and to each region within the DMN (i.e. mPFC, PCC, bilateral AG) was examined resulting in ten connections: (1) mPFC-PCC, (2) mPFC-rAG, (3) mPFC-lAG, (4) PCC-mPFC, (5) PCC-rAG, (6) PCC-lAG, (7) rAG-PCC, (8) rAG-mPFC, (9) lAG-PCC, (10) lAG-mPFC (Study II). An overview of Study II design is shown in **Figure 2-2** in chapter 2**.** Given the relevance of lower alpha to pain perception, Study II focused on the lower alpha range (8-10 Hz) and beta (14-30 Hz). Following one hour of capsaicin-induced pain, a similar decrease in DMN connectivity as that observed in Study I was reported, which did not change significantly 24 hours later. Specifically, at lower alpha, this decrease included connections from the *rAG (to mPFC, PCC)* (as in Study I) and the *mPFC (to PCC, rAG, lAG)* with no observed significant difference among connections projecting from the lAG or PCC **(Figure 4-2; Paper II)**. For beta oscillations, this decrease was among connections from rAG, mPFC (as in lower alpha) as well as from PCC *to (rAG and lAG),* with no significant change in connections from lAG **(Supplementary materials; Paper II)**. Despite the decrease in current pain intensity from one hour to 24 hours **(Figure 3-2;** Chapter 3**)**, no significant difference in connectivity was observed at both lower alpha and beta oscillations, except for mPFC-lAG, which went back to baseline following 24 hours **(Figure 4-2,** and **Supplementary materials; Paper II)**.

One of the interesting findings of Study II is that the decrease in connectivity following one hour and 24 hours was bilateral (i.e. occurred in loops) involving mPFC and rAG at lower alpha and beta oscillations and PCC and rAG at beta oscillations. In Study I-II, connectivity was measured using Granger causality, which considers the direction of neural communication [78,211] between DMN regions. Examining directionality could provide further evidence for the functional heterogeneity and differential sensitivity of the DMN proposed recently [4,116,186]. Study II revealed a decrease in connectivity among projections from mPFC to rAG as well as from rAG to mPFC, indicating that the information between mPFC and rAG flows in a continuous loop. Given the involvement of mPFC and rAG in emotional [63,196,224] and attentional [21,44,53,128,181,185,188] processing, respectively, this continuous loop may signify an interaction between attention and emotions in pain processing.

Another continuous loop occurred between rAG and PCC at beta oscillations. Due to the PCC involvement in attention, learning and memory, this DMN

region is considered a "change detection region" [125,160]. Given the involvement of rAG in attention regulation, the communication between the rAG and PCC during pain may indicate augmented attention, which may represent a cognitive change. This cognitive change is encoded by the PCC, which through reduced beta activity enables a motor response [73,142,145,189,218] necessary for withdrawal or avoidance [143].

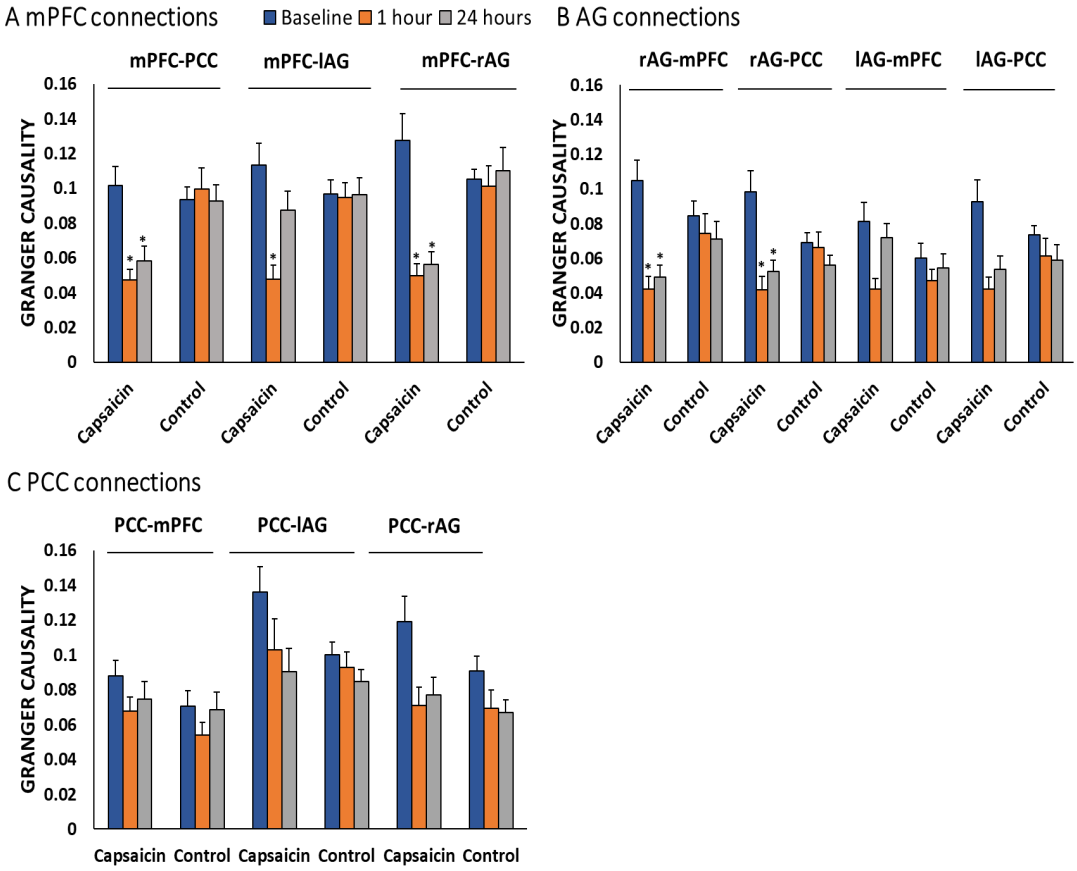

Figure 4-2. DMN connectivity changes following one and 24 hours of capsaicin-induced pain *(M±SEM).* ***(A)*** *Compared to baseline, rsFC decreased following one hour among the connections projecting from the medial prefrontal cortex (mPFC) and* ***(B)*** *right angular gyrus, but not left angular gyrus (lAG) or* ***(C)*** *posterior cingulate cortex (PCC). This decrease in connectivity was sustained 24 hours later except for the connectivity form mPFC to lAG.*

This connectivity reduction was not significantly different 24 hours later across the connections affected by pain except mPFC-lAG **(Figure 4-2; Paper II),** which suggests a differential sensitivity within the DMN.

Overall, this decrease persisted 24 hours later **(Figure 4-2; Paper II)** despite the significant reduction in current pain intensity **(Figure 3-2;** Chapter 3**).** As decreased DMN connectivity is possibly attention-related, the persistent decrease in DMN connectivity between one hour and 24 hours (despite the reduction in current pain intensity) indicates that 24 hours of pain may be associated with an attentional/emotional shift in pain processing. This possible attentional/emotional shift is supported by the significant correlation between pain intensity and DMN connectivity following one hour but not 24 hours **(Figure 5-1;** Chapter 5**).**

Chronic pain investigations have also reported this lack of significant correlation between pain intensity and DMN connectivity [209]. Interestingly, DMN connectivity changes in chronic pain are closely related to pain annoyance and interference but not the intensity of the pain [209], which suggests that chronic pain can contribute to a disruption in the brain organization that could impact emotional and cognitive processing beyond the utter feeling of pain [10]. As such, the current results suggest a possible emotional/attentional shift in pain processing during prolonged pain that may be subject to that present during persistent pain conditions.

In summary, the decrease in DMN connectivity following one hour may serve a protective function against further injury by regulating attention. This protective mechanism is triggered by the presence of pain, hence the strong association between current pain intensity and the decreased DMN connectivity following one hour. Given the decrease in current pain intensity following 24 hours, the maintained decrease in DMN connectivity following 24 hours may not hold the same protective significance, and it might not be entirely triggered by pain intensity. Instead, this decrease may be attentionally and emotionally driven, hence the lack of correlation between current pain intensity and decreased DMN connectivity following 24 hours.

4.4. MODULATING PAIN-RELATED DMN CONNECTIVITY CHANGES FOLLOWING PROLONGED PAIN

To further examine the premise that changes following prolonged pain would be, as in chronic pain conditions, independent of changes in pain intensity, these changes were modulated through pain relief or pain facilitation by way of cooling and heating the capsaicin patch, respectively **(Figure 2-2; Paper II).** Cooling or heating the primary site of the capsaicin patch following 24 hours did not significantly change the observed connectivity reduction following prolonged pain (24 hours) among the connections that exhibited decreased connectivity **(Figure 4-3; paper II)**. This finding provides further evidence of a possible emotional shift in pain processing following 24 hours that is independent of the presence of pain or lack thereof.

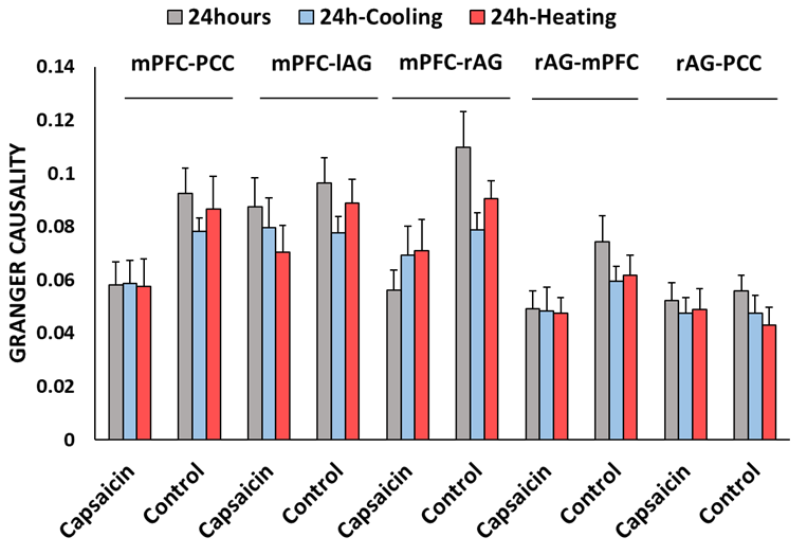

Figure 4-3. Modulating changes in DMN connectivity following 24 hours of capsaicin-induced pain *(M±SEM). Cooling or heating the capsaicin patch following 24 hours of capsaicin-induced pain did not significantly change connectivity among the already reduced connections.*

CHAPTER 5. DMN CONNECTIVITY AND PAIN INTENSITY RATINGS

This chapter covers the relationship between pain intensity ratings and both pain-free baseline and pain-related DMN connectivity. Specifically, it aims to answer whether DMN connectivity changes during pain are related to pain intensity, and whether preexisting DMN connectivity patterns can contribute to a differential pain experience.

5.1. PAIN-INDUCED DECREASE IN DMN CONNECTIVITY AND PAIN INTENSITY RATINGS

The present work showed that connections projecting from the rAG and mPFC exhibited a significant reduction following one hour and 24 hours of capsaicin-induced pain at lower alpha oscillations. Spearman's correlation analyses were employed to evaluate whether this reduction in connectivity was reflected in pain intensity ratings. Overall, a greater reduction in connectivity following capsaicin-induced pain was associated with greater pain intensity following one hour, but not following 24 hours **(Figure 5-1, Paper I-II).** mPFC and rAG activity may reflect emotional [63,196,224] and attentional [21,44,53,128,181,185,188] regulation. As such, the decreased connectivity during pain may signify a shift to externally focused processing apprehending the environment for a potential threat to avoid further harm. The greater pain intensity may enhance this focused apprehension (reflected in the greater decrease in DMN connectivity). Interestingly, the association between this possible apprehension (i.e. decreased DMN connectivity) and pain intensity was evident following one hour, but not following 24 hours. In other words, the decrease in DMN connectivity following 24 hours was present regardless of how much pain was reported by the participants indicating a possible shift to emotionally/attentionally driven pain processing that is independent of pain intensity as discussed in **Chapter 4.**

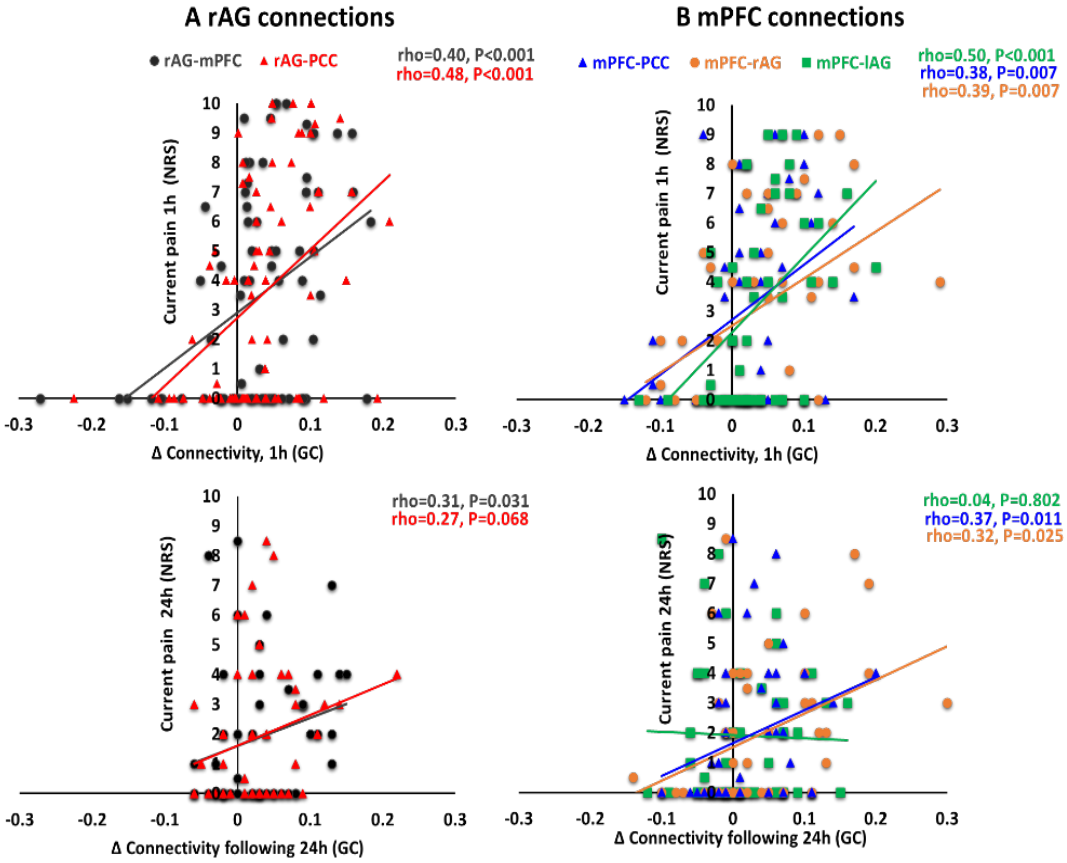

Figure 5-1 Correlation between NRS pain intensity scores and decreased DMN connectivity. *Spearman's correlation between current pain intensity following one hour (Paper I & II) and 24 hours (Paper II) and the decrease in lower alpha (8-10Hz) connectivity between baseline and one hour and 24 hours reports for capsaicin and control conditions at DMN connections that showed significant decrease in response to capsaicin application.* ***(A)*** *connections from rAG (rAG-PCC, rAG-mPFC).* ***(B)*** *connections from mPFC (mPFC-PCC, mPFC-rAG, mPFC-lAG). The significance level was Bonferroni-corrected to 0.005 due to multiple correlations. (NRS: numerical rating scale; rAG: right angular gyrus; lAG: left angular gyrus; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex).*

5.2. PAIN-FREE DMN CONNECTIVITY AND SUBSEQUENT PAIN INTENSITY RATINGS

As capsaicin-induced pain elicits reductions in DMN connectivity, which are correlated with subjective pain intensity (Paper I-II), Paper III addressed the question as to whether pain-free DMN connectivity can explain individual differences in subjective pain intensity following tonic pain (i.e. one hour). In addition to reflecting pain neuroplasticity [3,39,77,88,126,134,149,212], rsFC has been shown to predict pain intensity as well as the transition to chronic pain. Using a longitudinal approach, Baliki and colleagues, for example, have demonstrated that in contrast to healthy participants and recovering back pain (BP) patients, BP patients who developed a chronic state showed initial greater functional connectivity between the nucleus accumbens and prefrontal cortex [12]. Additionally, weak connectivity between the anterior insular cortex and the periaqueductal gray has been shown to characterize individuals whor are more likely to feel pain [165]. These investigations suggest that rsFC may be a potential biomarker for explaining individual differences in pain perception. As a resting-state network, the DMN is easy to identify, showing reliable connectivity patterns that can be measured with high test-retest reproducibility [13,141]. These connectivity patterns have been shown to be altered during acute, prolonged (as in the current work), and chronic pain. The high reliability of DMN connectivity and the involvement of this network in different phases of pain qualifies pain-free DMN connectivity as a potential biomarker of pain-related vulnerability.

5.3. FACTORS INFLUENCING PAIN PERCEPTION

To assess whether DMN connectivity can predict pain intensity, it is crucial to consider the complexity of the pain experience, which is influenced by several sensory, emotional, and cognitive factors such as mood, catastrophizing, vigilance, sleep, and fatigue. As these factors have been shown to contribute to pain perception **(Chapter 2)**, the question remains as to whether DMN connectivity offers an additional predictive value beyond the contribution of these factors. An overview of the factors that could influence pain perception, the questionnaires used to assess them, and their relationship with pain intensity/perception were discussed in **Chapter 2**.

5.4. FINDINGS ON PAIN INTENSITY PREDICTORS

Fifteen factors were examined in Paper III to assess their predictive value in relation to NRS peak pain intensity. Overall, Paper III offers a comprehensive predictive model assessing both objective (DMN connectivity) and subjective measures, including demographic, psychological, emotional, and psychophysical factors. This model explains 66% of the variance in NRS peak pain intensity following one hour of capsaicin-induced pain. Specifically, ***four*** factors contributed to the variation in NRS peak pain intensity: negative affect, helplessness, depression, and an additional predictive value by mPFC-lAG connectivity.

5.4.1. FACTORS THAT PREDICTED PAIN INTENSITY

While higher depression scores contributed to less severe peak pain intensity following one hour of capsaicin-induced pain, greater baseline negative affect and helplessness values predicted greater peak pain intensity.

Negative affect & depression. Interestingly, this work revealed that negative mood does not necessarily contribute to pain exacerbation. Negative affect and depression are both negative mood measures, yet they showed opposite relationships with peak pain intensity. These opposing associations could be attributed to the pain modality. Research has shown that depression aggravates pain perception during interoceptive (e.g. ischemic) pain, but it is associated with less severe pain during exteroceptive (e.g. cutaneous) pain [207]. This differential effect of pain modality on the pain-depression relationship may be due to the greater emotional valence of interoceptive pain as interoceptive pain is more likely to involve deep structures such as muscles and joints [207]. It is crucial, however, to emphasize that none of the included participants in Studies I-II were clinically depressed. Yet, obtaining similar results for the cutaneous pain-depression relationship among healthy individuals and clinically depressed patients is interesting.

Pain catastrophizing. There is mounting evidence supporting the role of pain catastrophizing in exacerbating pain-related outcomes [157,159,203]. However, the unique contribution of catastrophizing sub-measures (i.e. rumination, magnification, helplessness) to pain perception is not as well-documented. Of these subscales, this work revealed helplessness to be the only predictor of peak pain intensity. This finding agrees with previous research

on chronic pain patients [45,204,213], but not on acutely induced experimental pain (e.g. for 20 minutes)[3], where rumination seems to have a more pronounced impact. This finding suggests that long-lasting pain models can offer a better estimation of phycological changes characterizing chronic pain patients than short-lasting models.

5.4.2. FACTORS THAT DID NOT PREDICT PAIN INTENSITY

Sex, age, sleep, fatigue, positive affect, vigilance, thermal and mechanical thresholds did not predict peak pain intensity following one hour of capsaicin-induced pain.

Sex and age. The lack of significant association between pain intensity and sex and age is in contrast with previous research [41,64,74,137,147]. The relationship between sex and pain perception is complex and has been shown to be influenced by pain modality (e.g. thermal vs. electrical) and the measure assessing it (e.g. threshold vs. tolerance) [64,147,176]. For example, the effect of sex is small in thermal pain [176], which is consistent with the current findings assuming that capsaicin-indued pain is a thermal model. The absence of association between pain intensity and age in this work could be due to the homogenous age group (19-36 years), with only one participant of 41 years. It is noteworthy that the age-related differences in pain intensity were primarily reported among individuals of 40 years or older compared to younger adults [178].

Sleep and fatigue. Paper III revealed no significant predictive value of sleep quality or fatigue levels in relation to peak pain intensity. The lack of correlation between sleep and peak pain intensity could be because, overall, participants included in this work did not report severe sleep loss **(Chapter 2).** Perhaps more pronounced deficits in sleep would be more likely to contribute to enhanced perceived pain intensity. Additionally, the reported effect of sleep on pain perception is mainly discussed in relation to pain sensitivity [122,194]. Interestingly, pain sensitivity and pain intensity are not always correlated [79] as discussed below under the pain sensitivity section.

The effect of fatigue on pain intensity during experimentally induced pain is not well-documented. For chronic pain, research has shown that fatigue level among chronic pain patients is independent of reductions in pain perception

[98], which is consistent with the lack of significant association between fatigue and pain intensity reported in Paper III.

Vigilance. Similarly, PVAQ-vigilance did not show any significant association with peak pain intensity. This finding supports previous studies showing that when general and pain-specific psychological factors contributing to both acute [91,120] and chronic [121] postoperative pain were assessed simultaneously, pain vigilance is a potent predictor of pain disability but not pain intensity. This could be because the PVAQ focuses mainly on preoccupation with pain. Preoccupation with pain is a behavioral tendency that leads to avoidance, regardless how much pain is being experienced. This avoidance limits the individual's engagement in daily activities in fear of pain exacerbation and eventually leads to perceived disability and interference. It is not surprising, therefore, that pain-related avoidance (resulting from preoccupation with pain) is associated with greater reports of disability and interference [216,217], but not necessarily greater reports of pain intensity.

Positive affect. Unlike negative affect, positive affect did not seem to significantly predict peak pain intensity, which is not surprising, knowing that these two affect states are independent of one another in both painful [65] and nonpainful [36,220] settings. This difference in influence between positive and negative affect may be partially related to evolutionary factors. "Survival requires urgent attention to possible bad outcomes, but it is less urgent with regard to good ones" [19]. Overall, compared to positive emotions, negative emotions have a more profound persistent effect and undergo thorough processing in the brain, which renders negative emotions more resistant to disconfirmation [19,30]. The substantial lingering impact of negative emotions may offer a survival advantage by creating a powerful avoidance of certain situations that may be threatening to survival. For pain, linking more intense negative feelings to more intense pain would promote survival by facilitating the individual's avoidance of potential painful triggers.

The lack of significant relationship between positive affect and pain intensity reported in this work is, however, at odd with previous work showing that induced positive affect is linked to less severe experimentally induced pain [85]. This disagreement may be explained in light of the difference between spontaneous basal positive affect versus deliberately evoked positive affect. Studies supporting the mitigating effect of positive emotion on pain perception assessed this effect through active manipulation of pictures [174], music [192],

and thoughts [86]. In contrast, Paper III investigated the influence of positive affect at baseline without active induction of emotion, which may not yield the same emotional valence triggered by actively induced emotions. More research is needed to examine whether there is a difference between spontaneous and deliberately evoked positive affect in predicting pain intensity.

Pain sensitivity. Surprisingly, Paper III showed no correlation between peak pain intensity and pain sensitivity as measured by thermal and mechanical thresholds. This finding is consistent with previous work showing that static pain sensitivity as evaluated by single thermal suprathreshold stimuli does not predict experimentally-induced muscle pain intensity [25]. However, whether it is experimental or clinical pain, the relationship between pain sensitivity and pain intensity is not straightforward [79]. For example, in the context of experimental pain, this relationship is highly variable depending on the pain modality, the examined body site, and the time of evaluation [87,178,179].

5.4.3. DMN CONNECTIVITY PROVIDES AN ADDITIONAL PREDICTIVE VALUE

Paper III revealed that pain-free DMN connectivity, specifically mPFC-lAG connectivity, at lower alpha oscillations, offered a significant predictive value to the prediction of peak pain intensity beyond the prediction of mood (negative affect and depression) and pain-related helplessness. This unique contribution indicates that individuals with high pain-free mPFC-lAG connectivity are more likely to report more intense pain, which suggests mPFC-lAG connectivity at alpha oscillations as an objective marker for identifying pain-related vulnerability. This result could be explained by the association between mPFC and lAG and self-related processing. For example, elevated mPFC activity is shown to signify increased focus on internal mentation involving self-referential thoughts and emotions [196]. Attributing emotions or actions to oneself rather than others is associated with increased activity in the lAG [54,72]. Based on these findings, the ability to monitor and recognize one's internal emotions, as reflected in strong connections between mPFC and lAG, could be a characteristic of individuals with greater pain intensity complaints. There is evidence linking individual differences in alpha activity to the variation in pain perception such as differences in peak alpha frequency [70,71,150,151]. The current results may provide further support for the role of alpha oscillations in pain perception.

CHAPTER 6. CONCLUSIONS AND IMPLICATIONS

This chapter restates the main objectives of the current PhD and provides a summary of the corresponding main findings **(Figure 6-1)**, as well as the conclusions drawn from these findings.

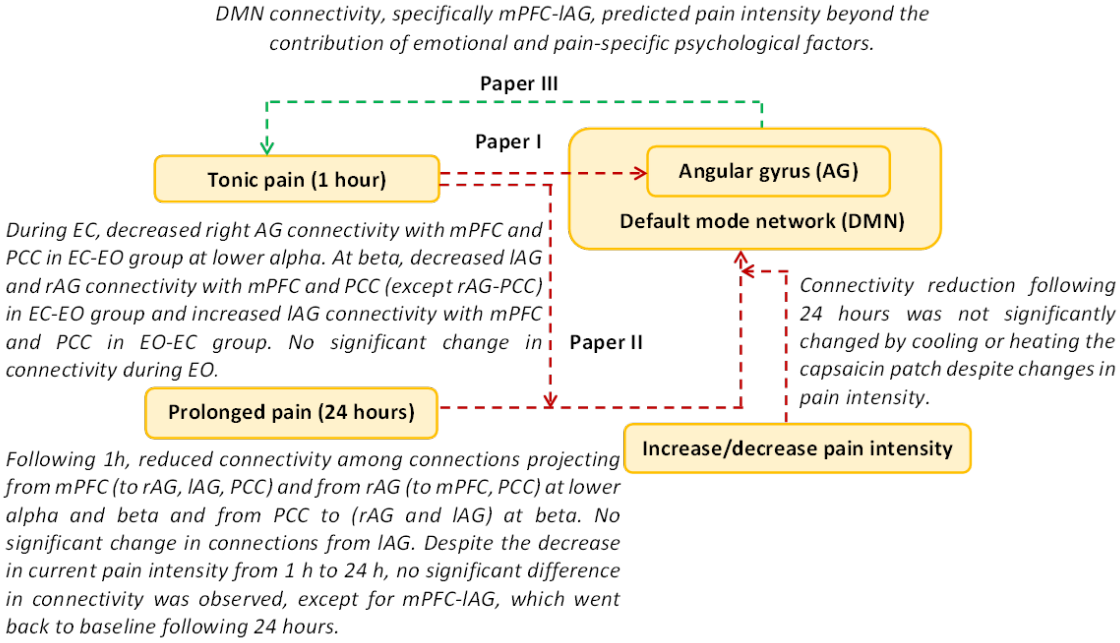

Figure 6-1. *Summary of Papers I-III results.*

With regards to the objectives stated in **Chapter 1**, *Paper I has investigated the effect of pain on AG connectivity within the DMN during EC and EO.* The results showed that at lower alpha, the rAG connectivity, was reduced, but exclusively during EC in EC-EO group. At beta, during EC, the results showed decreased lAG and rAG connectivity in EC-EO group and increased lAG connectivity in EO-EC group. Interestingly, no significant change in connectivity was observed during EO for both groups at both lower alpha and beta oscillations.

Reduced rAG connectivity may contribute to pain processing through regulating attention, which, during tonic pain, may function as a protective mechanism to avoid potential additional injury. Paper I highlights three methodological issues that may have an impact on the evaluation of EEG-based DMN connectivity during pain: (1) EC may be a more stable baseline, and (2) The eye order during EEG acquisition could influence connectivity when examining both eye-states, especially during EC, and (3) Minor sleep and mood disturbances could be serious confounders when assessing connectivity, especially during EO.

Paper II has examined changes in DMN connectivity between one hour (tonic) and 24 hours (prolonged) of capsaicin-induced pain. The findings showed that one hour of capsaicin-induced pain resulted in a connectivity reduction among connections from the mPFC and rAG at lower alpha oscillations and from mPFC, rAG, and PCC at beta oscillations, with no significant change in connectivity among connections projecting from the lAG. Despite reductions in current pain intensity, this connectivity reduction was not significantly different 24 hours later across all the aforementioned connections except mPFC-lAG. The connectivity reduction was bidirectional (i.e. occuring in loops) involving DMN regions whose activity is known to reflect attentional and emotional processes. Interestingly, this connectivity reduction was correlated positively with current pain intensity following one hour, but not following 24 hours. The persistent decrease in DMN connectivity following 24 hours, despite the reduction in current pain intensity, points towards a possible shift in pain processing to an attentionally/emotionally driven pain processing. This shift may be subject to the transition to more persistent pain states. This conclusion is further supported by the lack of correlation between current pain intensity and DMN connectivity following 24 hours. Finally, the absence of significant change in connections projecting from lAG in pain processing suggests a differential sensitivity within the DMN.

Paper II has also examined prolonged-pain-related changes in DMN connectivity in response to pain reduction or aggravation. The results showed that changes in DMN connectivity following 24 hours were not significantly altered despite perceived changes in pain intensity through cooling and heating the capsaicin patch. This persistence may provide further evidence of a possible emotional shift in pain processing following 24 hours.

Paper III investigated baseline pain-free DMN connectivity contribution to the variation in subsequent tonic pain intensity. The results showed that DMN

connectivity, specifically mPFC-lAG, explained individual differences in perceived peak pain intensity beyond the prediction of emotional and pain-specific psychological factors, suggesting that high mPFC-lAG connectivity may serve as a potential screening tool for identifying individuals with pain-related vulnerability. Those individuals may be more in touch with their emotions and thoughts and tend to involve in constant internal monitoring.

The generalizability of these findings is, however, limited by some factors including the small sample size and the lack of a salience control group. Nonetheless, this work has elucidated the role of the DMN in pain processing, highlighting possible emotional/attentional processes encoded in the DMN that may underlie the transition to more persistent pain states. Identifying these processes at the early stages of pain may help in designing therapeutic approaches that can address these processes before they contribute to pain persistence. This work has also offered pain-free DMN connectivity (at lower alpha) based on EEG measures as a potential screening tool for pain-related vulnerability, which could be easily utilized in clinical settings.

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