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Differences In Resting-State Functional Connectivity Of Chronic Migraine, With And Without Medication Overuse Headache, And The Effectiveness Of Sphenopalatine Ganglion Block As A Treatment For Repairing Dysfunctional Connectivity.

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by

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DEDICATION

I dedicate this thesis to my amazing partner in crime, Taylor Hanayik, and to the rest of my wonderfully crazy family. I would not have made it to this point without the continuous support from all of you! To my mother, Beth Krebs, for your teaching me to be kind and compassionate. To my father, Fred Krebs, for teaching me that there is nothing in this world that you can't figure out if you just google it enough. To my sisters, Jennica and Courtney, thank you for being born before me (because we all know the youngest is always the smartest), but also for providing me with great role models to look up to. To both my bother-in-laws, Michael and Joel, thank you for making family gatherings so much fun and for playing peace keepers between my sisters and I after a heated game of scrabble. To my nephew, Kellen, I know you are only 9 months old right now and can't read this, but if you ever pick this up when visiting your crazy aunt, know that you are loved so much by all of us, and always cherish your family because you have an excellent one.

And finally, to Taylor, you are the most incredible person I have ever met. I appreciate everything you do for me; for making me laugh when I get mad, for telling me "you're not dying" when I am being dramatic, for letting me have the last bit of cake, and for putting up with my crazy Krebs nature. Without you, I wouldn't be who I am, and I am so lucky to journey through life with you.

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ABSTRACT

Chronic Migraine (CM) is a debilitating neurological condition that occurs when the migraine frequency progresses to a chronic state of more than 15 headache days per month. The overuse of analgesic medication (MOH) is one of the most prominent risk factor of this chronification and little is known about why it is a cause. The repetitive inhibition of the Sphenopalatine Ganglion is one promising treatment that is used to treat chronic migraine. The purpose of this study is to determine if a specific pattern of disruption is present for chronic migraine, both with and without medication overuse headache, and if that disruption can be normalized after a series of Sphenopalatine Ganglion blocks. Resting state functional magnetic resonance imaging was used to analyze differences in intrinsic functional networks between CM patients with and without MOH, between each CM subgroup and age matched controls, and between a subset of CM patients before and after they received a series of SPG treatment. Three major intrinsic brain networks, including the Default Mode Network (DMN), Silence Network (SN) and Executive Control Network (ECN), were statistically less coherent with CM (both with MOH and without MOH) as compared to controls. There were also specific patterns of disruption to the intranetwork connectivity in each CM subgroup as compared to controls. After 6 weeks of treatment, overall improvements were seen in both the DMN and ECN. Our results suggest that there are underlying differences between CM with MOH and CM without MOH that may be caused by disruptions to smaller systems that exist within the SN and ECN. Additionally, in CM without MOH, a

disruption to the subcallosal area within the SN may be associated with the inability to inhibit the thalamus from sending pain signals to pain processing areas, causing chronic pain. This disruption was not seen in CM with MOH patients, suggesting that there is a different disruption present which accelerates the chronification process. After six weeks of SPG block treatment, overall improvements were seen in both the DMN and ECN, suggesting this treatment can help the normalization of these networks.

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CHAPTER 1:

INTRODUCTION

Chronic migraine (CM) is a debilitating neurological condition that affects approximately 140 million individuals in the global population and 8% of patients with migraine (Buse et al., 2012; May & Schulte, 2016). It is characterized by pain that is moderate to severe, pulsating/throbbing, and associated symptoms such as increased sensitivity to sensory stimuli and nausea/vomiting ("Headache Classification," 2013). Migraine can be classified as either episodic, with 0 to 14 headache days per month, or chronic, with ≥ 15 headache days and 8 migraine days per month ("Headache Classification," 2013). While the majority of the migraine population will stay in the classification of episodic migraines, approximately 2% to 3% of the patients will have their diagnosis transformed from episodic migraine to chronic migraine (May & Schulte, 2016; Manack, Buse, & Lipton, 2011). This transformation occurs when a patient's headache frequency increases to more than 15 days per month, and migraine frequency more than 8 days per month ("Headache Classification," 2013).

The mechanisms of migraine chronification are not completely understood, but several risk factors, such as heritability, genetics, stress, comorbid conditions, and environmental exposures, have been found (Bigal & Lipton, 2006; Lipton & Bigal, 2005).

One of the most prominent risk factors for migraine chronification is the overuse of medications such as triptans, opioids, and other over the counter (OTC) analgesics used for treating acute migraine attacks (May & Schulte, 2016; Katsarava et al., 2004; Paemeleire et al., 2008). This secondary chronic headache disorder, known as medication overuse headache (MOH), occurs when a patient, for more than 3 months, takes triptans, opioids, or a combination of medication for more than 10 days/month or simple analgesics for more than 15 days/month (Bigal & Lipton, 2006; Lipton & Bigal, 2005). However, it is important to note that the chronification of migraine can occur without any influence from medication overuse. Given that these different risk factors both lead to chronic migraine, it is not clear if there is a similarity in the neural mechanisms of these two disorders, however, with utilization of functional magnetic resonance imaging (fMRI), possible differences in functional connectivity of brain regions between the two groups can be investigated.

1.1 CHRONIC MIGRAINE AND RESTING STATE CONNECTIVITY:

Previous fMRI studies measuring blood oxygen level dependent (BOLD) signals have identified several task-independent networks of brain areas that are functionally linked during "intrinsic" brain activity (Fair et al., 2009). These networks are constructed by determining the functional correlations among different brain regions, either at rest or when evoked by a task (Fair et al., 2009). With the use of fMRI, certain clinical conditions are often being researched to determine if there are associated disruptions to these functional brain networks. The impact of migraine on functional brain connectivity is one such clinical condition now gaining popularity, as multiple studies have shown disrupted functional connectivity in individuals with migraines (Mathur et al., 2015;

Russo et al., 2012; Tessitore et al., 2013; Xue et al., 2012; Schwedt et al., 2013). Similarly, disrupted resting state connectivity has been reported in several different chronic pain conditions, including chronic back pain, neuropathic pain, and fibromyalgia (Baliki, Baria, & Apkarian, 2011; Baliki et al., 2012; Loggia et al., 2013; Tagliazucchi et al., 2010; Cauda et al., 2009; Cifre et al., 2012; Napadow et al., 2010). As migraine is largely accompanied by pain, variations in functional brain connectivity are thought to occur from the overwhelming need for the perception of pain (Xue et al., 2012). The perception of pain is a complex process that involves several brain regions, each individually contributing to a part of this perceptual process (Peyron, Laurent, & Garcia-Larrea, 2000).

Cognitive control is an important aspect of the perception of pain and has been the focus of many migraine research studies (Schwedt et al., 2013). Evidence suggest that persistent pain causes a reorganization of intrinsic brain networks, thus altering cognitive processing (Schwedt et al., 2013). One study showed that migraineurs had greater evoked pain related activity, compared to controls, in areas responsible with cognitive control over pain processing, such as the right dorsolateral prefrontal cortex, premotor cortex, and hippocampus (Schwedt et al., 2014a). Another study showed that when a painful stimuli is administered during a difficult task, chronic migraine patients, as compared to controls, had a widespread decrease in activation of task related brain areas that shared pain processing. This suggests that cognitive resources in migraineurs were diverted to "pain-reduction-related processes" (Mathur et al., 2015). Taken together, these findings imply that changes in functional cognitive brain activity is due to the interaction between overlapping pain networks and cognitive networks (Mathur et al., 2015).

For the purposes of this study, the default mode, task positive, salience, and executive control networks were chosen due to their implications of dysregulation in migraineurs (Russo et al., 2012; Tessitore et al., 2013; Xue et al., 2012; Schwedt et al., 2013).

1.2 DEFAULT MODE AND TASK POSITIVE NETWORK:

The default mode network (DMN), also referred to as the task-negative network, has been implicated in self-related cognition, with associated roles including autobiographical, self-monitoring, and social functions (Li, Mai, & Liu, 2014; Raichle et al., 2001). The DMN (Figure 1.1) includes the bilateral lateral parietal (LP), medial prefrontal cortex (mPFC), and posterior cingulate cortex (PCC)/Precuneus regions (Fox et al., 2005). The default mode network (DMN) is most notably associated with the task positive network (TPN) due to its strong anti-correlation relationship of spontaneous fluctuation in resting state signals over time (Fox et al., 2005; Biswal et al., 1995; Biswal et al., 2010; Greicius et al., 2003). This relationship is illustrated best during attention demanding cognitive tasks, which shows when the TPN is activated, the DMN will be deactivated. The TPN functions as a complement to active cognitive processes such as working memory, attention, and executive control (Hamilton et al., 2011). The TPN (Figure 1.2) includes bilateral precentral sulcus/frontal eye fields (FEF), bilateral intraparietal sulcus (IPS), and bilateral medial temporal (MT). Increased brain activity is typically observed within this network in response to focused attention and goal-oriented behavior (Fox et al., 2005). Both networks are reproducible within subjects and across subjects using resting state fMRI (Biswal et al., 1995; Biswal et al., 2010; Shehzad et al., 2009; Van Dijk & Alexander, 2014).

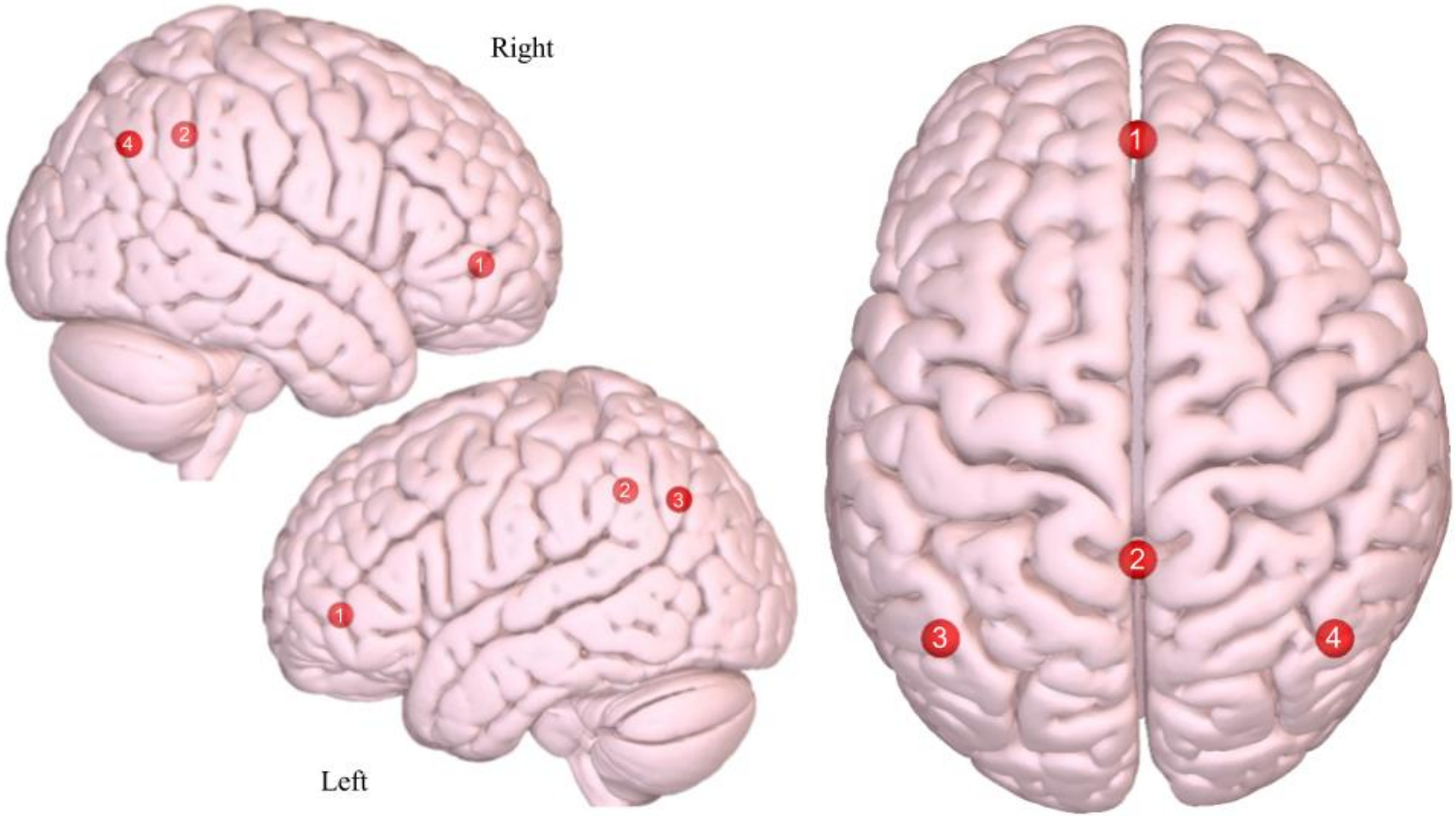


FIGURE 1.1: Axial and Sagittal view of the DMN. (1) Medial Prefrontal, (2) Precuneus/PCC, (3) Left Lateral Parietal, (4) Right Lateral Parietal. Images were made with "Surf Ice" (https://www.nitrc.org/projects/surfice/) using the exact MNI coordinate locations and sphere sizes (15mm).

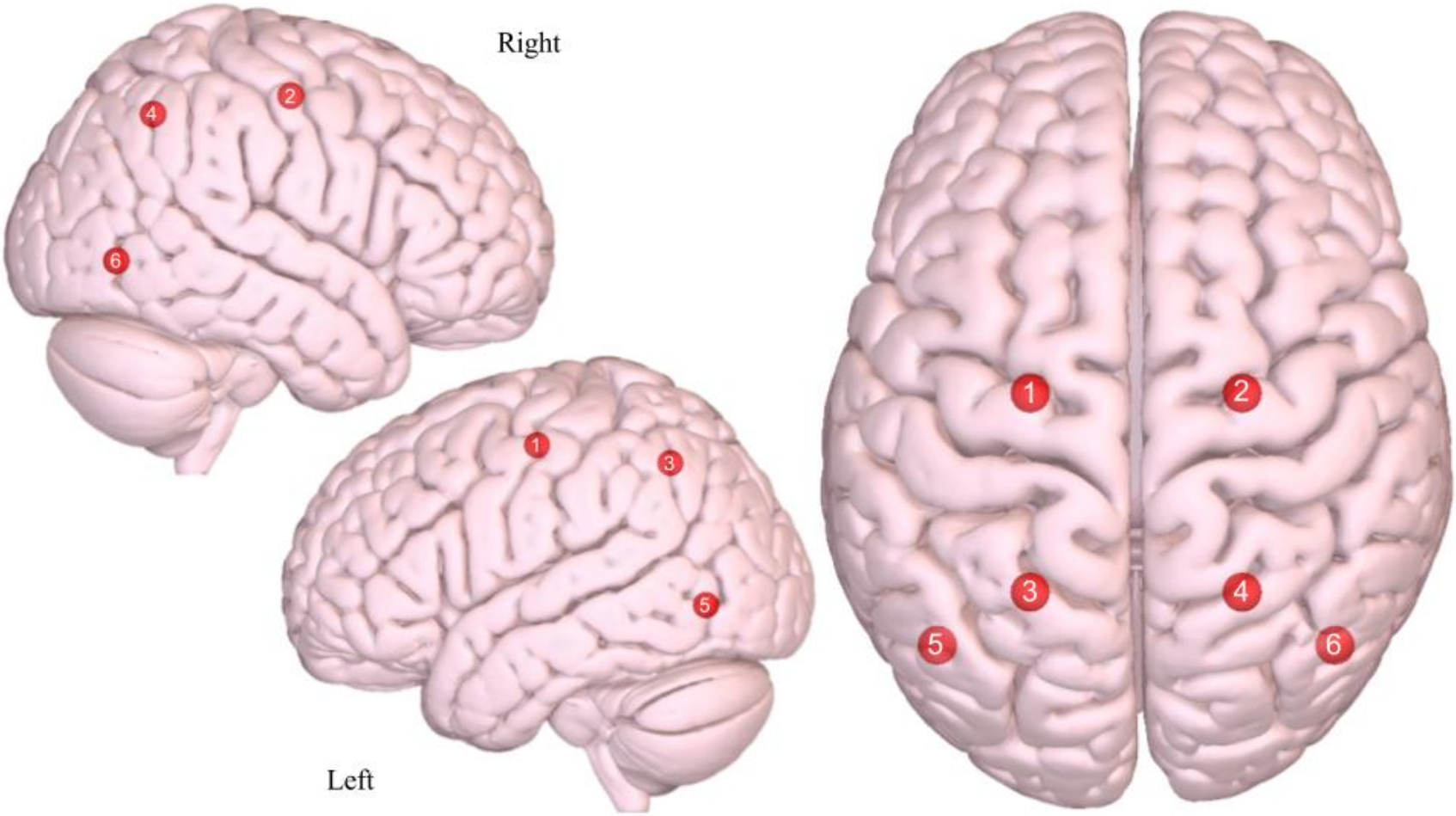


FIGURE 1.2: Axial and Sagittal view of the TPN. (1) Left Precentral Sulcus/FEF, (2) Right Precentral Sulcus/FEF, (3) Left Intraparietal Sulcus, (4) Right Intraparietal Sulcus, (5) Left Medial Temporal, (6) Right Medial Temporal. Images were made with "Surf Ice" (https://www.nitrc.org/projects/surfice/) using the exact MNI coordinate locations and sphere sizes (15mm).

It is suggested that this dichotomous relationship is reflective of competition between the processing of external and internal input, and proper communication between these two networks is postulated to be crucial for proper cognitive function (Fox et al., 2005; Wotruba et al., 2013). In the presence of pain, however, these two networks have shown to be affected. Specifically, with the presence of simultaneously experienced pain, the TPN is further enhanced, suggesting that pain acts as an additional cognitive load (Seminowicz & Davis, 2007; Mantini et al., 2009; Weissman-Fogel et al., 2011). The DMN, however, is deactivated when attending to painful stimuli (Mantini et al., 2009; Weissman-Fogel et al., 2011; Kong et al., 2010; Loggia et al., 2012).

One issue with the TPN is this network is very dependent on what task is being used, and can sometimes be co-activated with the DMN during autobiographical planning tasks (Spreng & Grandy, 2010). Additionally, the TPN has faced a lot of criticism, due to composition of two functionally and anatomically distinct networks that play different roles in cognition (Spreng, 2012). The frontoparietal control network is more recently being functionally coupled with the DMN due to its interactivity during internally directed cognition (Gao & Lin, 2012; Deshpande, Santhanam, & Hu, 2011; Seeley et al., 2007). There has been further dissociation of the frontoparietal network into two distinct "Salience" and "Executive Control" networks, which roles broadly are to identify salient information and how to act on that salient information (Seeley et al., 2007). For this reason, the addition of these established networks, such as the salience and executive control network, could provide a better understanding of this pain-cognition interaction.

1.3 SALIENCE NETWORK:

The salience network (SN) is an important network for preparing a person for action on objects or events that are significant at any given moment in time and plays a critical function in cognitive control due to its role as a mediator between internal and external action (Seeley et al., 2007). As such, abnormalities in this network could affect or disrupt other networks, such as the DMN, due to its involvement in cognitive control (Bonnelle et al., 2012). This network would most likely be active when a salient internal or external stimulus requires action, such as being aware of pain or focusing on what piece to move when playing chess (Seeley et al., 2007). The SN (Figure 1.3) includes the bilateral dorsal anterior cingulate cortex (dACC), bilateral dorsolateral prefrontal cortex (DLPFC), left frontal pole, bilateral hypothalamus, bilateral orbital frontal insula (Orb. FI), paracingulate cortex, bilateral subcallosal area, bilateral supramarginal gyrus (SMG), left periaqueductal gray (PAG), bilateral supplementary motor area (SMA)/pre SMA, bilateral substantia nigra/ventral tegmental area (SN/VTA), bilateral superior temporal, bilateral temporal pole, bilateral ventral striatum/pallidum (vSP), and right ventrolateral PFC (VLPFC). Network associated paralimbic structures, such as dACC and orbital frontal insula, have been found to be coactive in response to the emotion aspect of pain (Seeley et al., 2007). Interestingly, the insula and DLPFC (two regions found in the SN) have been postulated as "hubs" for dysregulation of intrinsic functional connectivity in chronic pain related disorders (Cifre et al., 2012; Čeko et al., 2015). It has been shown that reduced functional connectivity between SN and visual networks has been reported (interictally) in migraine with aura patients (Niddam et al., 2015). Unfortunately, the SN has not been adequately researched in the CM population (Schwedt et al., 2013)

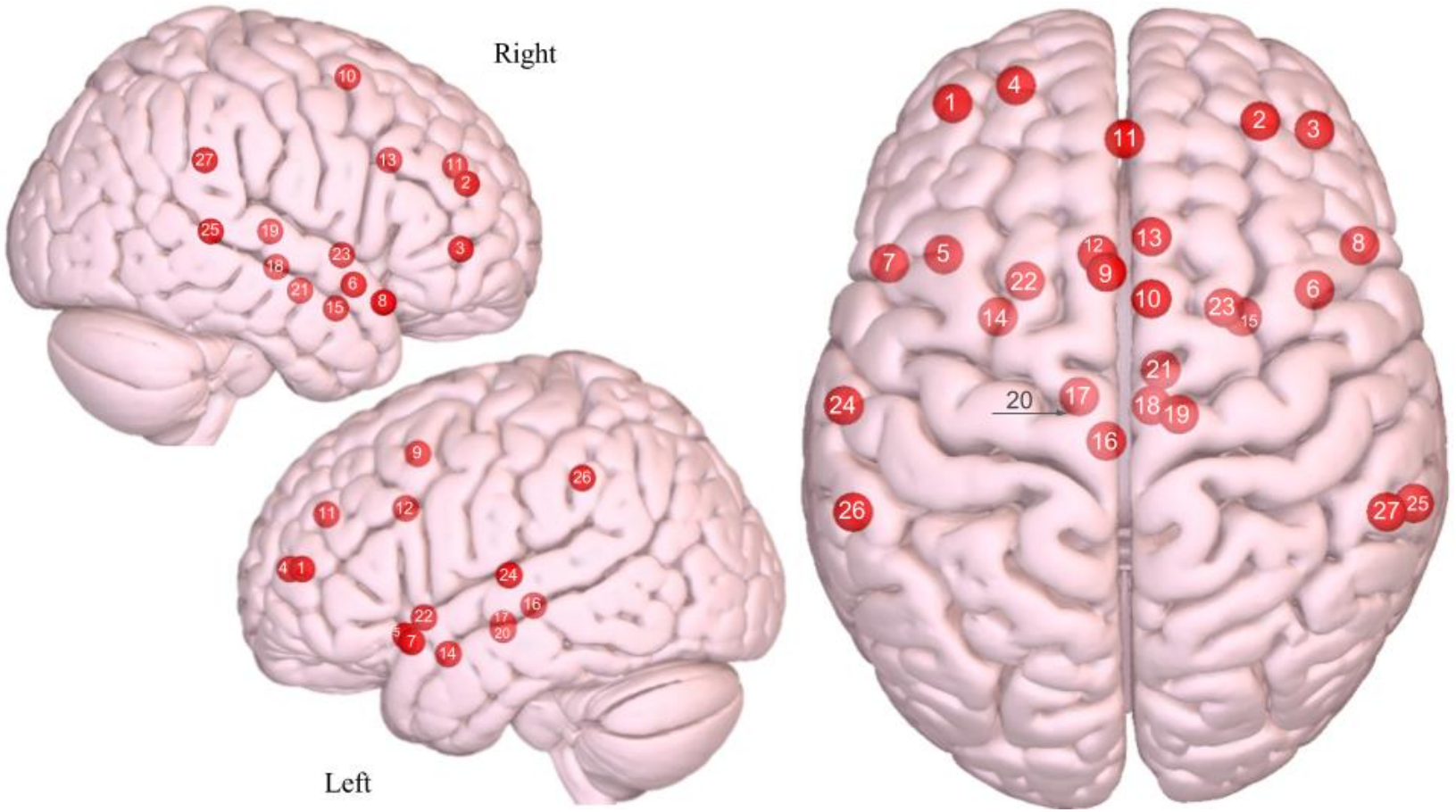


FIGURE 1.3: Axial and Sagittal view of the SN. (1) Left DLPFC, (2) Right DLPFC, (3) Right VLPFC, (4) Left frontal pole, (5) Left orbital frontal insula, (6) Right orbital frontal insula, (7) Left temporal pole, (8) Right temporal pole, (9) Left SMA/pre SMA, (10) Right SMA/pre SMA, (11) Paracingulate cortex,(12) Left dACC, (13) Right dACC, (14) Left subcallosal area,(15) Right subcallosal area, (16) Left periaqueductal gray (PAG), (17) Left hypothalamus, (18) Right hypothalamus, (19) Right dorsomedial thalamus, (20) Left SN/VTA, (21) Right SN/VTA, (22) Left ventral striatum/pallidum, (23) Right ventral striatum/ pallidum, (24) Left superior temporal, (25) Right superior temporal, (26) Left Supramarginal gyrus, (27) Right Supramarginal gyrus. Images were made with "Surf Ice" (https://www.nitrc.org/projects/surfice/) using the exact MNI coordinate locations and sphere sizes (15mm).

1.4 EXECUTIVE CONTROL NETWORK:

The executive control network (ECN) is associated with higher-order cognitive processes such as attention and working memory. Its primary function is to direct attention to salient input, maintaining relevant data in mind in order to select an action in response to fluctuating environmental self-regulating conditions. This network (Figure 1.4) consists of the bilateral anterior thalamus, bilateral dorsolateral PFC (DLPFC), bilateral dorsolateral PFC region of frontal eye fields (DLPFC/FEF), dorsal medial PFC (dmPFC), right inferior frontal gyrus (IFG)/frontal operculum, right inferior temporal, bilateral lateral parietal, left orbital frontal insula (OFI), bilateral ventrolateral PFC (VLPFC), bilateral dorsal caudate, and right ventromedial caudate (Seeley et al., 2007). A handful of studies have found that migraine with and without aura have reduced/disrupted ECN, however, virtually no studies have looked at the ECN in chronic migraine patients (Russo et al., 2012; Tessitore et al., 2013; Xue et al., 2012; Yu et al., 2012; Tessitore et al., 2015).

1.5 NEUROIMAGING STUDIES OF MOH:

Very few neuroimaging studies exist which evaluate MOH, with even fewer that compare CM w/ MOH to CM w/o MOH (Ferrero et al., 2012b, Zappaterra et al., 2011, Lai et al., 2016; Chen et al., 2016). Most studies that do exist merely examine pain perception in MOH patients, with most concluding that MOH patients exhibit a lower pain threshold, even more so than chronic migraineurs, due to central sensitization (Zappaterra et al., 2011; Munksgaard, Bendtsen, & Jensen, 2013; Perrotta et al., 2009; Perrotta et al., 2012; Zappaterra et al., 2011). This lower threshold in MOH patients is however reversible after detoxification (Munksgaard, Bendtsen, & Jensen, 2013).

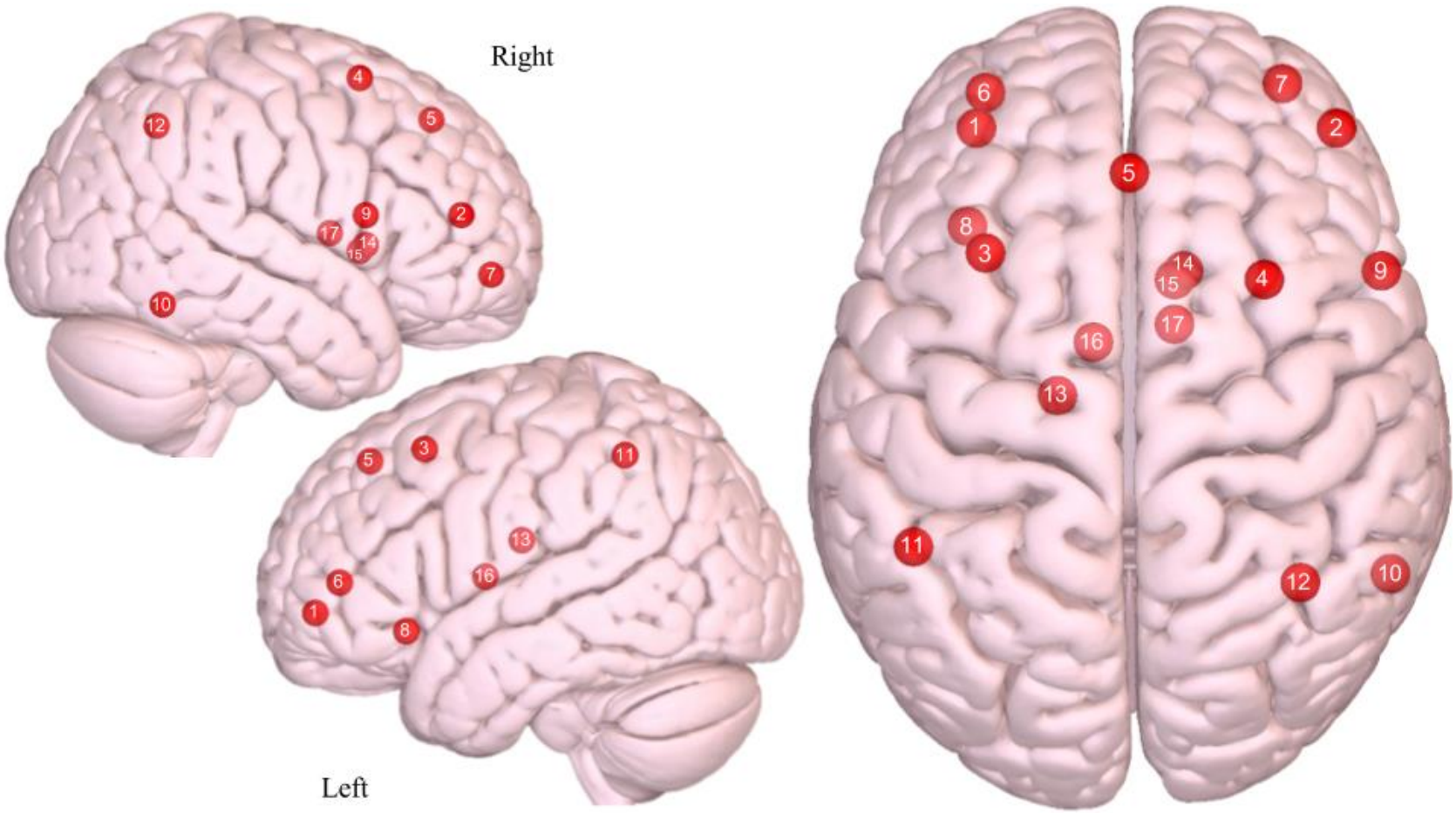


FIGURE 1.4: Axial and Sagittal view of the ECN. (1) Left DLPFC, (2) Right DLPFC, (3) Left DLPFC/FEF, (4) Right DLPFC/FEF, (5) DMPFC, (6) Left VLPFC, (7) Right VLPFC, (8) Left Orbital Frontal Insula, (9) Right Inferior Frontal Gyrus, (10) Right Inferior Temporal, (11) Left Lateral Parietal, (12) Right Lateral Parietal, (13) Left Dorsal Caudate, (14) Right Dorsal Caudate, (15) Right Ventromedial Caudate, (16) Left Anterior Thalamus, (17) Right Anterior Thalamus. Images were made with "Surf Ice" (https://www.nitrc.org/projects/surfice/) using the exact MNI coordinate locations and sphere sizes (15mm).

A similar reversible effect after detoxification is seen in a few functional fMRI/PET studies (Ferrero et al., 2012a; Ferrero et al., 2012b; Grazzi et al., 2010; Fumal et al., 2006). Areas of bilateral somatosensory cortex, bilateral inferior and superior parietal lobe, and right supramarginal gyrus were hypoactive during pain related activity, but was seen to reverse 6 months after detoxification (Ferrero et al., 2012a; Grazzi et al., 2010; Chiapparini et al., 2009). A similar PET study comparing MOH/detoxified MOH patients to healthy controls, revealed similar hypometabolic pain processing regions, such as bilateral thalamus, OFC, ACC, insula, ventral striatum, and right inferior parietal lobe, with all areas, except the OFC, recovering after detoxification (Fumal et al., 2006).

In a study which compared the task related activity of CM w/MOH and w/o MOH to healthy controls, hyperactivity is present for both patient groups in the bilateral VMPFC and PCC/Precuneus, however, hypoactivity in the SN/VTA was only seen in the MOH patients. This same study also compared detoxified MOH patients to controls, which revealed that the VMPFC and PCC/Precuneus hyperactivity had normalized, but the hypoactivity in the SN/VTA was still persistent (Ferrero et al., 2012b).

It is important to note evidence, using voxel-based morphometry (VBM), that MOH has a significant effect on gray matter volume (GMV) for the brain structures involved in the DMN, SN, and ECN. (Chanraud et al., 2014; Riederer et al., 2012; Lai et al., 2016). VBM studies report that MOH patients had a significant increase of GMV in thalamus and ventral striatum; and a significant decrease of GMV in bilateral ACC, OFC, insula, nucleus accumbens/rectal gyrus, inferior frontal gyrus, right DLPFC, left frontal pole, and precuneus (Riederer et al., 2012; Lai et al., 2016). Additionally, GMV has been negatively correlated with years with migraine in bilateral orbito-frontal, left superior

frontal gyrus (frontal pole), left precuneus, right caudate, and right hippocampus (Chanraud et al., 2014).

To our knowledge, there has only been one resting state functional connectivity study, in which MOH was compared to controls and episodic migraineurs (Chanraud et al., 2014). In this study, the precuneus was used as a seed region, therefore their results are only comparable within the DMN. Lower functional connectivity was seen in precuneus to right lateral parietal and right mPFC in the DMN (Chanraud et al., 2014).

1.6 TREATMENT OF CHRONIC MIGRAINE:

Currently, there are several different acute and preventative treatments available for chronic migraine patients. However, these treatments are generally regarded as being suboptimally effective, expensive, and likely to lead to multiple side effects (Magis, Jensen, & Schoenen, 2012). The Sphenopalatine ganglion (SPG) has been a popular clinical target for the treatment of headaches for nearly 100 years (Slunder, 1909).

The SPG is the largest extracranial, parasympathetic ganglion in the head, located on each side of the pterygopalatine fossa (Lang, 1995). Within the SPG, there are both parasympathetic and sympathetic fibers present, however, only the parasympathetic fibers synapse within the SPG. Additionally, the SPG has a sensory component due to the neural projections from the trigeminal nerve, which also passes through the SPG via the maxillary division. The parasympathetic fibers that project from the SPG are distributed to several glands, including the lacrimal, nasal, palatine, and pharyngeal gland, via the ophthalmic and maxillary divisions of the trigeminal nerve. There are several branches that project from the SPG towards the orbital cavity, which innervates the meningeal and

cerebral blood vessels (Larsson et al., 1976; Nozaki et al., 1993; Ruskell, 2004; Suzuki & Hardebo, 1992).

The SPG has often been thought to play a role in migraine pathogenesis through activation of the trigemino-autonomic reflex (Khan, Schoene, & Ashina, 2014; Robbins et al., 2015). A hypothesis called the "Unitary Hypothesis", proposed by Burstein and Jakubowski, suggests that the superior salivatory nucleus is the primary reactant for multiple migraine triggers. The superior salivatory nucleus is a preganglionic parasympathetic nucleus that receives inputs from multiple areas, such as hypothalamus, limbic and cortical systems. These cortical and limbic centers, when triggered by variations of stimuli ("migraine triggers"), would activate the superior salivatory nucleus, and in turn, activate the SPG (Burstein & Jakubowski, 2005). The SPG then triggers a vasodilation of the meningeal vessels, resulting in a release of inflammatory chemicals that initiate migraine pain (Moskowitz, 1990; Goadsby, Lipton, & Ferrari, 2002).

This hypothesis implies that the SPG plays a key role in the activation of migraine pain, thus creating a logical therapeutic target. The idea behind developing therapeutic approaches to "block" the sphenopalatine ganglion lends itself to the unitary hypothesis, in that inhibiting the parasympathetic outflow of the SPG will ultimately inhibit pain and the autonomic symptoms that accompany migraine attacks (Robbins et al., 2015). Another interesting theory behind SPG target therapy, is that by modulating the autonomic nerve, there is a "neurophysiological reboot" that occurs in the dysregulated central or trigeminal autonomic systems (Candido et al., 2013).

Since the discovery of the SPG, neuromodulation methods have included surgery, electrical stimulation, microvascular decompression, and radiofrequency ablation; all of

which are performed in a surgical setting. Unfortunately, these invasive methods were often accompanied by extensive adverse events (Windsor & Jahnke, 2004; Candido et al., 2013). With the increased interest in the SPG as a target for treatment, several new medical devices have become available (Robbins et al., 2015). One of these devices, the Tx360, was developed as a minimally invasive SPG modulation (Candido et al., 2013). The Tx360 device has a soft, flexible applicator that is designed to curve around the inferior turbinate in order to administer an anesthetic spray to the anterior, lateral, and superior area of the mucosa that covers the SPG (Candido et al., 2013). This device allows a more successful (and accurate) delivery of the sphenopalatine ganglion blocking agent in a noninvasive manner (Candido et al., 2013). In the clinical setting, the SPG blockade is used on chronic migraine patients, both with and without medication overuse headache, in a series of twelve treatments that are administered over a 6-week period.

Though most of this treatment has been used in the refractory cluster headache population, more clinical indications, such as chronic migraine, are being researched (Cady et al., 2015a; Cady et al., 2015b). Recently, a double blinded, placebo controlled, randomized clinical trial demonstrated the effectiveness of the FDA approved Tx360 on chronic migraine (Cady et al., 2015a; Cady et al., 2015b). In this study, and an additional follow up study by the same group, the Tx360 was shown to be a relatively inexpensive, minimally invasive, and well tolerated treatment for Chronic Migraine (Cady et al., 2015a; Cady et al., 2015b). This was seen by the significant improvement of migraine disability and clinical outcomes, such as Headache Impact Scale (HIT-6), sleep disturbance, and function at work, after 6 weeks of treatment.

For a portion of the current study, we will examine the four intrinsic brain networks listed earlier, both before and after a series of SPG blocks, to determine if there is any change in patterns of functional connectivity.

1.7 SIGNIFICANCE:

Though there is a plethora of research on the pathophysiology and treatment of migraine, little is known of the long term, lasting effects migraine has on brain structure and function. Measuring the perception of pain can be difficult as individuals may experience pain differently, therefore it is vital to determine another means of measuring the long term effects of migraine. Chronic pain, as opposed to acute pain, has been linked to impairments of interoceptive and cognitive control function due to the constant demand of cognitive resources (Apkarian et al., 2004; McCracken & Iverson, 2001; Eccleston & Crombez, 1999; Nes, Roach, & Segerstrom, 2009). As the DMN, SN, and ECN have previously been used to test these interoceptive and cognitive control functions, investigation into the specific effects that chronic migraine has on these networks may prove to be a useful tool in understanding the complexities of this disorder, and why the overuse of medication additionally contributes to chronification.

Using these same networks, additional information can be obtained by investigating how treatments, such as the SPG block, alleviate some of the clinical symptoms of chronic migraine. Furthermore, the conceptualization of using intrinsic brain networks to quantify restoration of functional connectivity to a normalized state could ultimately prove to be a useful tool for the testing and development of therapeutic treatments (Maleki & Gollub, 2016).

1.8 SPECIFIC AIMS:

The overall aim of this study is to investigate the impact of chronic migraine has on rs-functional connectivity, and if treatment, such as the repetitive inhibition of the SPG, can help to modulate the dysfunctional networks. Additionally, we aim to determine if there is a distinct pattern of altered functional connectivity associated with medication overuse headache.

Specific Aim 1: To assess differential patterns of network connectivity in specific intrinsic resting state networks between chronic migraine patients, both with medication overuse headache and without medication overuse headache, to healthy controls. This aim will be tested by examining the differences in the DMN, TPN, SN, and ECN when comparing CM patients to controls. *We hypothesize that the chronic migraine population, both with and without medication overuse headache, will have an overall decrease in their network connectivity, for all networks examined, when compared to controls.*

Specific Aim 2: To determine differences in predefined intrinsic functional networks in the chronic migraine population based on the presence or absence of medication overuse headache. To test this aim, we will directly compare the functional connectivity difference between CM with MOH and CM without MOH as measured using the intranetwork connections within the DMN, TPN, SN, and ECN. *We hypothesize that there will be differences in the intranetwork connections between CM with MOH and CM without MOH due to the nature of their disorder*.

Specific Aim 3: To evaluate the effect of Sphenopalatine ganglion blockade in chronic migraine patients by determining if this treatment can normalize patterns of resting state functional connectivity within the networks discussed above. This will be

accomplished by comparing pretreatment resting state data with 30-minute post treatment and 6-week post treatment resting state data, specifically in the DMN, TPN, SN, and ECN. Additionally, clinical and behavioral scores will also be compared pre and post treatment. *We hypothesize that after long-term, recurrent inhibition of the SPG in chronic migraine, there will be an increase in overall resting state brain connectivity compared to baseline.*

CHAPTER 2:

METHODS

2.1 INCLUSION/EXCLUSION CRITERIA:

All subjects enrolled were diagnosed with chronic migraine, either with or without medication overuse headache, using the ICHD-III beta criteria ("Headache Classification," 2013). Subjects were excluded if they had contraindication for MRI, neurological disorders other than migraine, history of hypertension, diabetes, or inability to follow study protocol while completing questionnaires and assessments. Anxiety and depression were not considered as exclusion criteria as these are common comorbid conditions with chronic migraine. All healthy control (HC) participants were screened for any previous history of chronic headache, migraine, any pain disorders, any prior history of chronic illness, family history of migraine, or use of OTC or prescription pain medication for more than 5 days per month.

The treatment group had the additional exclusion criteria of any previous SPG treatment, inability to complete the SPG treatment within 6 weeks, or inability to follow study protocol while completing questionnaires and assessments. Subjects were instructed to not change prophylactic medication or dosage during their treatment.

2.2 CLINICAL PARAMETERS:

Data collected from each participant prior to MRI included basic demographics and a detailed migraine history that included:(1) age of first migraine; (2) years with CM; (3) Family History of Migraine; (4) Current medication; (5) Body Mass Index (BMI);

(6) Headache Impact Test (HIT-6) (Shin et al., 2008); (7) Patient Health Questionnaire (PHQ-9) (Seo & Park, 2015); (8) Allodynia Symptom Checklist (ASC)(Lipton et al., 2008); (9) number of headache days in a month (moderate to severe); (10) Type and Frequency of headache abortive medication.

The Hit-6 scale is a six-question test developed by headache experts to measure the impact of a patient's headache on their ability to function at work, school, home or in social situations. Each question has the same set of responses each with a weighted value on a 5 point Likert scale, with a higher total score indicating a greater impact. The severity of impact can be determined by the score, which indicates little or no impact (≤49), some impact (50-55), substantial impact (56-59), or severe impact (≥60) (Shin et al., 2008; Seo & Park, 2015). This test has been found to be a reliable and valid tool for determining the impact of headaches for episodic and chronic migraine (Shin et al., 2008). The patient health questionnaire (PHQ-9) is a nine-question test to measure the severity of a patient's depression. A PHQ-9 score can indicate if depression is mild (5-9), moderate (10-14), moderate-severe (15-19) or severe (≥20). As anxiety and depression are common comorbidities of migraine, this tool is often used in conjunction with other headache questionnaires and has been proven to be a reliable screening tool in episodic and chronic migraine patients (Seo & Park, 2015). The Allodynia symptom checklist (ASC) is a series of questions which quantifies the presence of cutaneous allodynia, a pain that is provoked by stimulation of the skin which would not ordinarily produce pain (Lipton et al., 2008). The ASC measures overall allodynia and has been tested to be associated with cutaneous allodynia experienced in migraine population (Lipton et al., 2008).

2.3 MR IMAGING:

The first 10 participants (5 CM and 5 HC) were scanned using a 12-channel head coil on a Siemens Magnetom Trio 3T scanner and the remaining participants (28 CM and 16 HC) were scanned using a 20-channel head coil and the upgraded Siemens Prisma 3T scanner model (McCausland Center for Brain Imaging, Columbia, South Carolina). All participants were scanned in the same room with the same lighting. Participants were instructed to keep their eyes closed, stay awake, relax, and not focus on anything during the scans.

The Siemens Trio scans consisted of a 6-minute high-resolution T1 weighted magnetization-prepared rapid gradient echo (MP-RAGE) series (repetition time [TR] = 2250 ms, echo time [TE] =4.15 ms, 192 slices, 50% slice gap, flip angle = 9°, voxel size = 1.0 mm^3, 256 mm^2 Field of View [FOV], iPAT factor of 2, and using a sagittal, ascending, single shot acquisition). The 15-minute functional imaging scans used a T2* weighted BOLD contrast-sensitive sequence ([TR] = 1550 ms, [TE] = 34 ms, 42 slices, 20% slice gap, flip angle = 71°, voxel size = 2.5 mm^3, 215 mm^2 FOV, and using a transversal, descending, interleaved acquisition).

After the scanner upgrade, all remaining participants were scanned with a 6-minute high resolution T1 weighted magnetization-prepared rapid gradient echo (MP-RAGE) series ([TR] = 2250 ms, [TE] =4.11 ms, 192 slices, 50% slice gap, flip angle 9°, voxel size = 1.0 mm^3, 256 mm^2 FOV, iPAT factor of 2, and using a sagittal, ascending, single shot acquisition). The 15-minute functional imaging used a T2* weighted BOLD contrast-sensitive sequence ([TR] = 1100 ms, [TE] = 35ms, 56 slices, 20% slice gap, flip

angle = 72°, voxel size = 2.4 x. 2.4 x 2.0 mm^3, 216 mm^2 FOV, and using a transversal, ascending, interleaved acquisition).

2.4 MRI PREPROCESSING:

MRI preprocessing was a multistep process carried out using a resting state analysis pipeline script developed by Chris Rorden (https://github.com/neurolabusc/nii_preprocess). First, each participant's T1 weighted anatomical image was tissue segmented and normalized to MNI space using the Statistical Parametric Mapping 12 (SPM12) toolbox and the unified segmentation-normalization functions (Ashburner & Friston, 2005) with associated tissue probability maps for each tissue type (i.e. gray matter, white matter, CSF). Next, each rfMRI session for each participant was motion corrected to the mean rfMRI image using SPM's realignment functions. Then, the mean rfMRI from the motion correction stage was coregistered to the participant's T1 weighted image so that the normalization parameters computed from the T1 could then be applied to the rfMRI data. The application of the normalization parameters produced rfMRI datasets in standard MNI space. After normalization of resting state images, a brain mask was generated from the normalized, segmented T1 scan, and was used in the detrending stage to eliminate irrelevant voxels from analysis. The detrending stage of preprocessing consisted of removing linear, cubic, and quadratic signal noise in the rfMRI time series including the mean signal in white matter and CSF, and the six motion parameters calculated during the motion correction stage earlier (x, y, z, pitch, roll, and yaw). This noise information was removed from the rfMRI data for each session before temporal filtering (Hallquist, Hwang, & Luna, 2013). After detrending for noise, the functional images were smoothed using a 6mm FWHM

Gaussian kernel. Lastly, each rfMRI session was bandpass filtered with a low pass frequency threshold of 0.1Hz and a high pass frequency threshold of 0.01Hz (inspired by the REST toolkit; Song et al., 2011). These low frequencies have been shown to be related to spontaneous neural activity, and contain meaningful information related to a brain region's function (Logothetis et al., 2001; Lu et al., 2007).

Analyses of the resting state functional connectivity were completed using a region of interest (ROI) based approach with our four preselected networks. Connectivity atlases for each network were derived using spherical ROIs centered (15 mm diameter) on the peak Montreal Neurological Institute (MNI) coordinates reported by Fox et al (2005), for DMN, and Seeley et al (2007), for the ECN and SN. Exact MNI coordinates for all areas used in the networks are listed in "Appendix A: Supplemental Methods" (Table A.1).

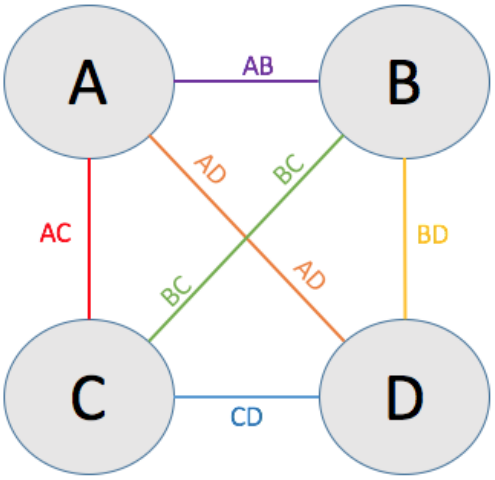
2.5 STATISTICAL ANALYSIS:

Using the generated ROIs, functional connectivity matrices were created by extracting the mean BOLD time course from each ROI in each network, and then Pearson r correlation coefficients were calculated between each ROI and all other ROIs in the same network. This method has been used in many functional connectivity studies (Baliki et al., 2012; Chen et al., 2016; Schwedt et al., 2013). In all networks, all Pearson correlation (r) coefficient values were Fischer's Z transformed (to convert to a normal distribution) to produce the "functional connectivity strengths" that are used in the analysis. Comparison groups were formed to investigate the relationship between the following groups: CM w/MOH vs HC, CM w/o MOH vs HC, and CM w/MOH vs CM w/o MOH.

Differences in functional connectivity strengths between all the comparison groups were investigated on three levels: Overall network connectivity strength, average nodal connectivity strength, and intranetwork connectivity strength. The intranetwork connectivity strengths is defined as the correlation coefficient (fisher Z transformed Pearson r value) generated for each pair of nodes within the network investigated. The average nodal connectivity strength is the average of all unique intranetwork connectivity strengths for one particular node. To obtain the overall network connectivity, we averaged the sum of each unique intranetwork connection within the network investigated. For an example of how each one of these functional connectivity strengths was obtained, please see figure 2.1.

When comparing a CM group (either with or without MOH) to their matched group of healthy controls (abbreviated as CM vs CON), we used an one tailed, two sampled t-test. When comparing between the CM groups (CM w/MOH vs CM w/o MOH), a two tailed, two sampled t-test was used. Corrected p values of < 0.05 were considered significant for overall network strength differences (CM vs CON), average nodal connectivity strength difference (CM vs CON), and intranetwork connection strength differences (CM w/MOH vs CM w/o MOH). Corrected p values of < 0.01 were considered significant for intranetwork connection strength differences (CM vs CON).

For the treatment group, the comparison groups used consisted of the time point comparison from baseline to 30-minutes post treatment and baseline to 6-weeks post treatment. The same statistical analysis method was utilized with the exception of the use of a paired t-test.



	A	B	C	D
A	AA	AB	AC	AD
B	AB	BB	BC	BD
C	AC	BC	CC	CD
D	AD	BD	CD	DD

The <u>intranetwork connectivity strengths:</u>
AB, AD, AC, BC, BD, CD
The <u>average ($\bar{x}$) nodal connectivity strength</u>:
Node A: $\bar{x}$ A = (AB+AC+AD)/3
Node B: $\bar{x}$ B = (AB+BC+BD)/3
Node C: $\bar{x}$ C = (AC+BC+CD)/3
Node D: $\bar{x}$ D = (AD+BD+CD)/3
The <u>overall network connective</u> strength:
Network ABCD = (AB + AD + AC + BC+ BD +CD)/6

FIGURE 2.1: Example network ABCD.

A one-tailed t-test was used for the overall network differences and difference in nodal connectivity strength, whereas, a two-tailed t-test was used for intranetwork connection strength differences. Corrected *p* values of < 0.05 were considered significant for all statistical tests in the treatment group.

All statistical tests were conducted using permutation thresholding (10,000 permutations) to control for multiple comparisons (Winkler et al., 2014). Scanner type was added as a nuisance variable to the GLM analyses, using the Freedman-Lane approach, to account for any variance caused by two different scanner types (Freedman & Lane, 1983).

2.6 CLINICAL CORRELATIONS:

To assess associations between functional connectivity strength (overall and intranetwork) and clinical parameters, Pearson correlations were conducted between the functional connection strengths and several clinical parameters including depression and anxiety scores (PHQ-9), headache severity (HIT-6), and Allodynia (ASC). Correlations between functional connection strength and clinical characteristics (i.e. years with migraine, years with CM, number of moderate to severe headache per month) were also calculated. Correlations with an uncorrected $p \leq 0.001$ were considered significant.

CHAPTER 3:

CHRONIC MIGRAINE VS CONTROLS - RESULTS

3.1 STUDY PARTICIPANTS:

A total of 33 subjects with Chronic Migraine were enrolled into the study. A total of 4 participants were excluded for the following reasons: motion artifact (n=1), incidental finding (n=2), and delayed reporting of comorbid pain condition (n=1). All Chronic Migraine participants were separated into two groups based on the presence of medication overuse headache (MOH) as defined by the ICHD 3. These two group were: Chronic Migraine with MOH (CM w/ MOH) and Chronic Migraine without MOH (CM w/o MOH). Amongst the healthy control (HC) subjects (n=21) average age was 37 ± 11 years and all 21 subjects were female. Of the control 2 subjects were excluded for the following reasons: motion artifact (n=1) and incidental findings (n=1). From the pool of 19 HC, a sample of 16 and 14 age and gender matched controls were selected for the CM w/ MOH and CM w/o MOH groups, respectively. Individual characteristics for each group are summarized in Table 3.1.

3.2 OVERALL NETWORK CONNECTIVITY:

Network strength averages for each chronic migraine group were compared to a subset of age and gender matched healthy controls to reveal if there is a statistically significant difference between each comparison group and their matched controls for the DMN, TPN, SN, and ECN. For all comparison groups, DMN, SN, and ECN averages were all significantly different from their matched control group (Table 3.2).

TABLE 3.1: Demographic and clinical features of subjects based on CM subgroup.

Demographics:	**CM w MOH**	**CM w/o MOH**	**HC**
n	16	13	19
Age	39 ± 14	39 ± 12	37 ± 11
BMI	26 ± 6	31 ± 4	26 ± 5
Race/Ethnicity	10 Caucasian 6 African American	10 Caucasian 3 African American	12 Caucasian 7 African American

Clinical Features:	**CM w MOH**	**CM w/o MOH**	***p*-value**
Mod/Severe HA days	21 ± 7	15 ± 5	0.005*
Cranial Autonomic Symptoms	n=8	n=2	n/a
Family History (1st degree)	n=13	n=7	n/a
History of Migraine (years)	21 ± 13	20 ± 13	0.371
History of CM (years)	2 ± 1	3 ± 3	0.135
Hit-6 Score	67 ± 3	64 ± 4	0.03*
PHQ-9 Score	10 ± 6	5 ± 3	0.006*
Allodynia (ASC) Score	6 ± 3	5 ± 6	0.22
*significant			

TABLE 3.2: Overall network connectivity strength and significance value for each comparison group.

Comparison Group (Avg± SD)	**DMN**	**TPN**	**SN**	**ECN**
CM with MOH	0.51 ± 0.16	0.19 ± 0.17	0.05 ± 0.13	0.03 ± 0.09
Matched Control	0.61 ± 0.15	0.28 ± 0.13	0.14 ± 0.10	0.13 ± 0.08
p-value	**0.029***	**0.089**	**0.023***	**0.003***
CM w/o MOH	0.50 ± 0.17	0.20 ± 0.16	0.07 ± 0.11	0.06 ± 0.07
Matched Control	0.64 ± 0.13	0.27 ± 0.14	0.15 ± 0.11	0.14 ± 0.08
p-value	**0.016***	**0.096**	**0.016***	**0.015***
CM w/MOH vs CM w/o MOH**	**0.756**	**0.568**	**0.812**	**0.835**
*significant; **two-tailed t-test				

3.3 AVERAGE NODAL CONNECTIVITY:

Comparison of the average nodal connectivity strengths between CM groups to age/gender matched controls revealed multiple significant individual node differences. Some of the nodes are similar between the two groups and some are unique to each group (Table 3.3). A list of all the significant average nodal strength, along with averages, standard deviations, and *p* values for each group, are listed in "Appendix B: Supplemental Results" (Table B.1).

The average nodal connectivity strength for left orbital frontal insula (SN: p=0.057), right superior temporal (SN: p=0.057), and right DLPFC (ECN: p=0.052) were borderline significant for the MOH vs control comparison, whereas, the left DLPFC (ECN: p=0.052) was borderline significant for the CM w/o MOH vs control comparison. For these four nodes, their counterparts in the opposite comparison group were significant, therefore, making assumptions about these four nodes as delineating differences between CM w/MOH and CM w/o MOH may not be appropriate. For the purposes of this study, these four nodes will not be considered different between CM w/MOH and CM w/o MOH groups.

3.4 INTRANETWORK CONNECTIVITY:

Comparison of the individual intranetwork connections for each comparison group revealed multiple significantly differed intranetwork node-to-node connections. All significant intranetwork connections were lower in CM patients when compared to controls. A detailed list of all the significant intranetwork connection, along with averages, standard deviations and *p* values for each group, are listed in "Appendix B: Supplemental Results" (Table B.2).

TABLE 3.3: Significant differences in average nodal connectivity strength for each comparison group.

DMN	TPN	SN	ECN
Both CM groups (with and without MOH) vs matched controls			
Left Lateral Parietal	Left FEF	Bilateral Ventral Striatum-Pallidum Bilateral SN/VTA Bilateral Hypothalamus Bilateral Orbital Frontal Insula* Right Superior Temporal*	Left Lateral Parietal Right Inferior Frontal Gyrus Bilateral VLPFC Right DLPFC/FEF Bilateral DLPFC* Left Anterior Thalamus*
CM w/MOH vs matched controls only			
Right Lateral Parietal Medial Prefrontal		Left Frontal Pole Bilateral DLPFC Right VLPFC Bilateral Supramarginal Gyrus Left SMA/preSMA	Dorsomedial PFC Left Orbital Frontal Insula Right Anterior Thalamus Right Dorsal Caudate Right Ventromedial Caudate
CM w/o MOH vs matched controls only			
Precuneus/PCC		Bilateral Subcallosal Area Bilateral ACC Left Temporal Pole	Left DLPFC/FEF
***** Borderline significant in other comparison group (see section 3.3) NOTE: Statistical differences determined using a one tailed t-test with a threshold of $p<0.05$			

The only significant intranetwork connection in the DMN (left lateral parietal to precuneus/PCC, p=0.003) and TPN (left FEF to right intraparietal sulcus, p=0.006) was lower in CM without MOH patients when compared to the matched controls. In the SN, three intranetwork connections (Right DLPFC to right supramarginal gyrus and right VLPFC; and right VLPFC to right SMA/preSMA) were significantly lower in both CM groups when compared to controls. In the ECN, two intranetwork connections (left DLPFC/FEF to DMPFC, and left anterior thalamus to right VLPFC) were significantly different in both CM groups when compared to controls. The remaining significant connections were unique to each comparison group (CM w/MOH vs controls, or CM w/o MOH vs controls). All significantly different intranetwork connections and average nodal strengths in the SN and ECN are displayed in Figure 3.1 and 3.2, respectively.

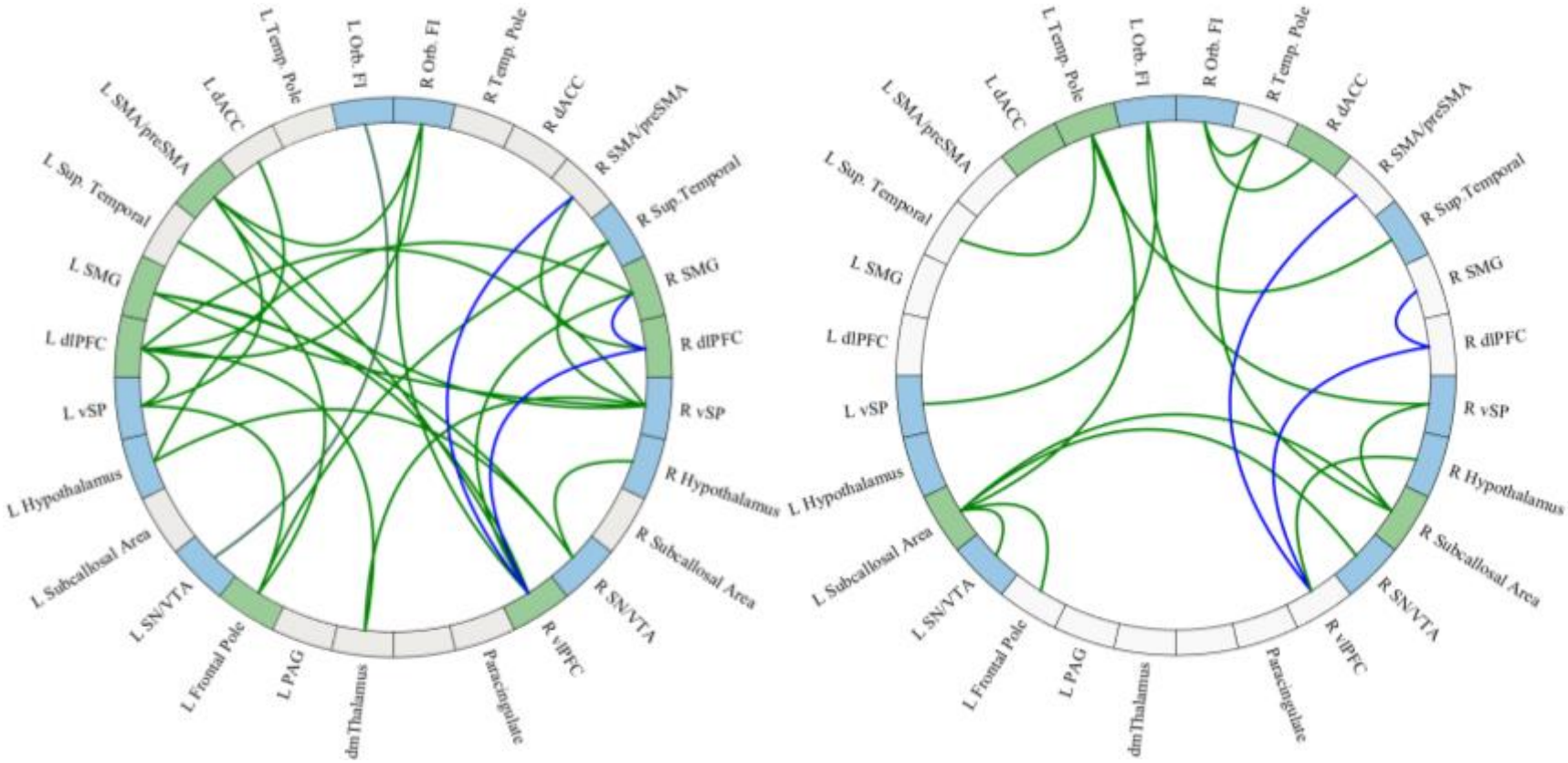


FIGURE 3.1: Significant intranetwork connectivity and average nodal difference in SN between CM w/MOH vs controls (left) and CM w/o MOH vs controls (right). Colored bar and line represents a significant nodal and intranetwork connectivity difference (respectively) between the CM groups vs their matched controls. Green represents a unique difference to that comparison group and blue represents a shared difference in both comparison groups. Images were generated using the Matlab application "Circro" (https://github.com/bonilhamusclab/circro).

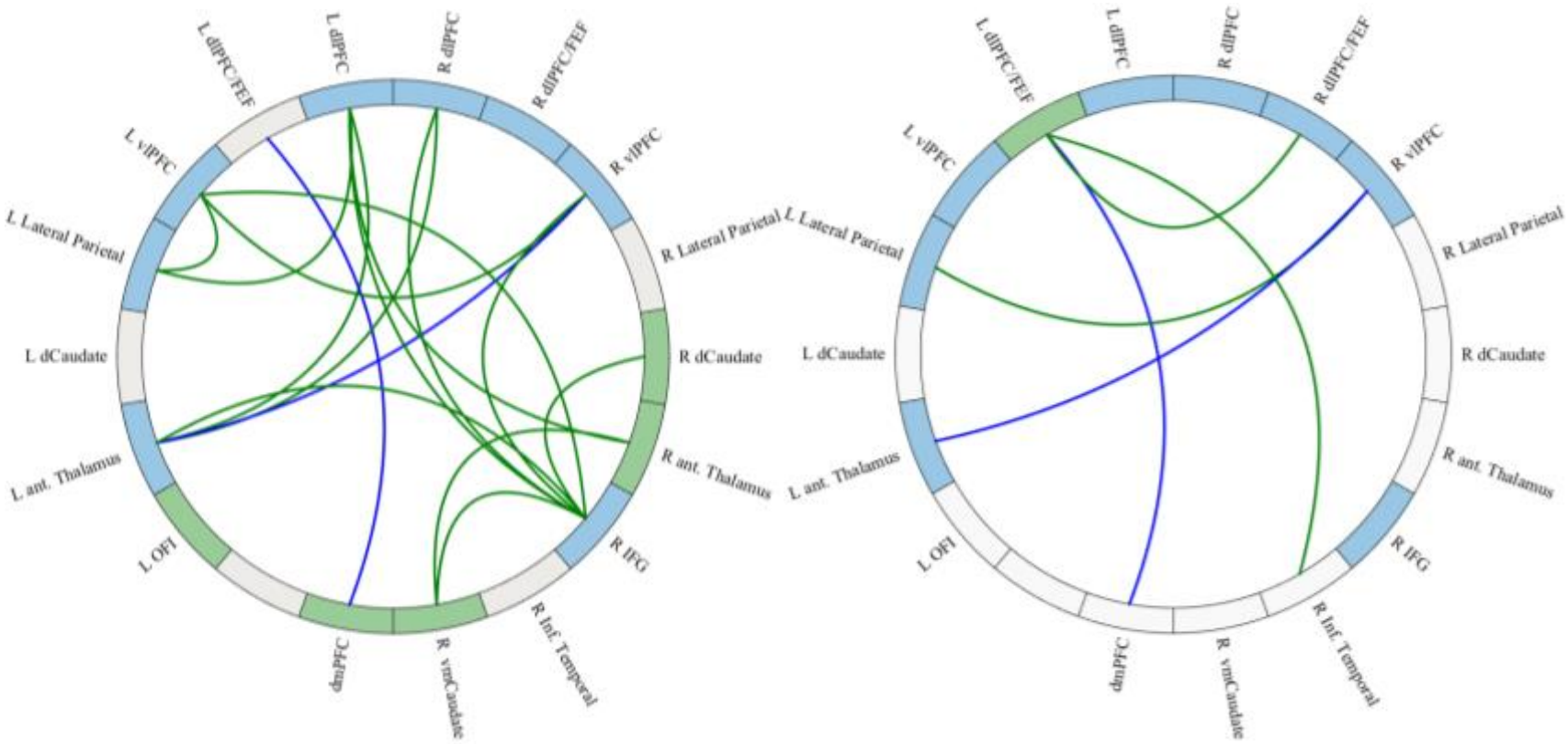


FIGURE 3.2: Significant intranetwork connectivity difference in ECN between CM w/MOH vs controls (left) and CM w/o MOH vs controls (right). Colored bar and line represents a significant nodal and intranetwork connectivity difference (respectively) between the CM groups vs their matched controls. Green represents a unique difference to that comparison group and blue represents a shared difference in both comparison groups. Images were generated using the Matlab application "Circro" (https://github.com/bonilhamusclab/circro).

3.5 COMPARISON BETWEEN CM GROUPS:

When comparing CM with MOH and CM w/o MOH, there was no statistically significant difference for overall network strength for DMN (p=0.76), TPN (p=0.57), SN (p=0.81), and ECN (p=0.84). Additionally, no average nodal strengths appeared to be significantly different between these two groups. When examining intranetwork connectivity differences, there were 8 intranetwork connections in the SN and 3 intranetwork connections in the ECN that were significantly different. These intranetwork differences are summarized in Table 3.4 and visualized in Figure 3.3.

3.6 CLINICAL CORRELATIONS:

Of the clinical features, only the number of moderate to severe headache days (Mod/Severe HA days), Hit-6 scores, and PHQ-9 scores was significantly different between the CM w/MOH group and CM w/o MOH group, and therefore the clinical features compared separately for each CM group. Years with migraine, years with chronic migraine, and allodynia (ASC score) were not statically different when comparing CM w/MOH vs CM w/o MOH, therefore all correlations involving these variables were conducted using the full CM population. The relationship between medication use and intranetwork connections were only evaluated in the CM w/MOH group, as there were only a few individuals in the CM w/o MOH who used any medication. There were no significant intranetwork connections in the DMN that correlated to any clinical parameter. These correlations are summarized in Table 3.5. Connections that are significantly different between two group are marked by an asterisk

TABLE 3.4: Significant differences of intranetwork connections when comparing CM w/MOH vs CM w/o MOH.

Salience Network	CM w/MOH (Avg ± SD)	CM w/o MOH (Avg ± SD)	*p*-value
CM w/MOH < CM w/o MOH			
Left Frontal Pole x Right Orbital Frontal insula	0.57 ± 0.26	0.81 ± 0.12	0.018
Left Ventral Striatum/Pallidum x Left SMA/preSMA*	0.26 ± 0.15	0.44 ± 0.19	0.026
Left DLPFC x Left Ventral Striatum/Pallidum*	0.16 ± 0.15	0.37 ± 0.16	0.009
Left DLPFC x Right Ventral Striatum/Pallidum*	0.12 ± 0.15	0.32 ± 0.16	0.010
Left DLPFC x Left Dorsal ACC*	0.14 ± 0.16	0.36 ± 0.21	0.015
Left DLPFC x Right Dorsal ACC	0.44 ± 0.27	0.64 ± 0.14	0.036
CM w/MOH > CM w/o MOH			
Right SN/VTA x Paracingulate	0.10 ± 0.15	0.04 ± 0.10	0.043
Right Subcallosal Area x Left Subcallosal Area**	0.82 ± 0.31	0.55 ± 0.24	0.044
Executive Control Network			
CM w/MOH < CM w/o MOH			
Right Inferior Frontal Gyrus x Left DLPFC*	0.08 ± 0.15	0.24 ± 0.22	0.040
CM w/MOH > CM w/o MOH			
Left DLPFC/FEF x Right VLPFC	0.41± 0.24	0.22 ± 0.27	0.007
Left DLPFC/FEF x Right DLPFC	0.21 ± 0.32	0.00 ± 0.29	0.043

*Intranetwork connection was found to be significant in MOH vs Control group
**Intranetwork connection was found to be significant in nonMOH vs Control group
NOTE: Statistical differences determined using a two-tailed t-test with a threshold of $p<0.05$

TABLE 3.5: Statically significant correlations between clinical features and intranetwork connectivity strength.

Correlated Clinical Measure	Network	CM Group	*r*-value	*p*-value
Years with CM				
Left Subcallosal Area x Left Frontal Pole*	SN	CM (all)	-0.60	0.001
Allodynia Score				
Right Hypothalamus x Left Dorsal ACC	SN	CM (all)	0.60	0.001
HIT-6 Score				
Right SMA/PreSMA x Left PAG	SN	CM w/MOH	0.82	<0.001
Number of Triptans/month (MOH group only)				
Right SN/VTA x Left Orbital Frontal Insula	SN	CM w/MOH	-0.82	<0.001
Right SN/VTA x Right Subcallosal Area	SN	CM w/MOH	0.86	<0.001
Left DLPFC/FEF x Right DLPFC	ECN	CM w/MOH	-0.77	0.001
Right Inferior Temporal x DMPFC	ECN	CM w/MOH	0.77	0.001

*significantly different in one of the comparison groups
Note: significance threshold was $p\leq0.001$

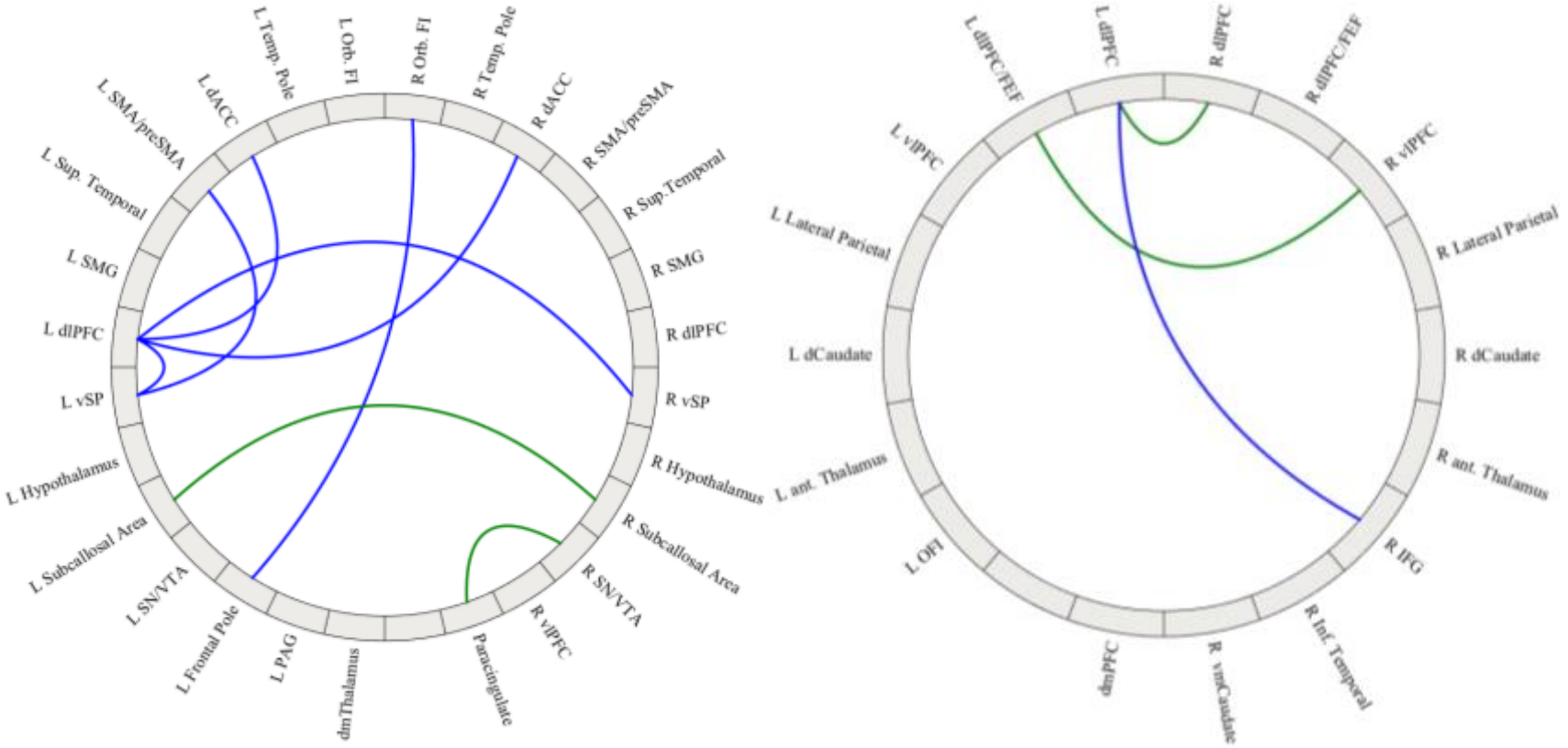


FIGURE 3.3: Significant intranetwork connectivity difference between CM w/MOH and CM w/o MOH in the SN (left) and ECN (right). Colored line represents a intranetwork connectivity difference between the CM w/MOH vs CM w/o MOH. Green represents a that the intranetwork connection was lower in CM w/o MOH patients (CM w/MOH > CM w/o MOH) and blue represents a that the intranetwork connection was lower in CM w/MOH patients (CM w/MOH < CM w/o MOH). Images were generated using the Matlab application “Circro” (https://github.com/bonilhamusclab/circro).

CHAPTER 4:

TREATMENT STUDY RESULTS

4.1 STUDY PARTICIPANTS:

An age and gender matched subset of 14 subject were recruited into the treatment group. Four subjects were excluded due to the following reasons: motion artifact (n=1), scanner error (n=2), and unreported comorbid pain condition (n=1). Each subject underwent a series of MRI scans at three time points: immediately before their first SPG treatment, 30 minutes after their first SPG treatment, and 30 minutes after their last SPG treatment (6-weeks post treatment). Two subjects were missing one of their three scans (one was missing 30-minute post treatment scan; another was missing 6-week scan) but they were still included in comparisons involving the scan sets that were completed. Individual characteristics for the treatment group are summarized in Table 4.1.

4.2 OVERALL NETWORK CONNECTIVITY CHANGES:

Each individual's before treatment network strength averages were compared to their network strength averages at two other two time points: 30-minutes and 6-week post treatment. Separate comparisons were made for the following networks: DMN, TPN, SN, and ECN. When comparing before treatment with 30-minutes post treatment, only the ECN showed a significant increase in overall network connectivity strength ($p = 0.004$). When comparing before treatment with 6-week post treatment, both the DMN and ECN showed a significant increase in overall network connectivity strength (DMN: $p = 0.046$; ECN: $p = 0.003$). Network strength averages and p values are summarized in Table 4.2.

TABLE 4.1: Demographic and clinical features of subject in treatment group.

Demographics:		**Clinical Features:**	
n	10	**Mod/Severe HA days**	21 ± 7
Age	43 ± 13	**History of CM (years)**	2 ± 1
BMI	28 ± 8	**Family History (1st degree)**	n=8 (1 uk)
Gender	10 females	**History of Migraine (years)**	26 ± 12
Race/Ethnicity	8 Caucasian 2 African American	**Cranial Autonomic Symptoms**	n=5

Quality of Life Scales:	**Before TX**	**After TX**	***p*-value**
Hit-6 Score	66 ± 3	60 ± 4	<0.01*
PHQ-9 Score	13 ± 6	6 ± 4	0.008*
Allodynia (ASC) Score	6 ± 3	5 ± 4	0.238
Number Mod/Severe HA Days	21 ± 7	11 ± 6	<0.01*
*significant			

TABLE 4.2: Overall network connectivity strengths and significance value when comparing Baseline to 30-minute and 6 weeks post first treatment.

Baseline vs 30-minutes (Avg ± SD)	**DMN**	**TPN**	**SN**	**ECN**
Before Treatment	0.56 ± 0.14	0.11 ± 0.11	0.01 ± 0.11	0.01 ± 0.08
30-min Post Treatment	0.62 ± 0.19	0.06 ± 0.10	0.00 ± 0.07	0.07 ± 0.05
p-value	**0.404**	**0.230**	**0.203**	**0.004***
Baseline vs 6 weeks (Avg ± SD)				
Before Treatment	0.55 ± 0.15	0.11 ± 0.11	-0.01 ± 0.10	0.00 ± 0.08
6-weeks Post Treatment	0.59 ± 0.14	0.14 ± 0.13	0.01 ± 0.12	0.03 ± 0.09
p-value	**0.046***	**0.087**	**0.205**	**0.003***
*significant				

4.3 AVERAGE NODAL CONNECTIVITY CHANGES:

When comparing baseline average nodal strength to 30-minute post treatment average nodal strength, 2 nodes in the SN and 8 nodes in the ECN are significantly increased. When comparing baseline average nodal strength to 6-week post treatment average nodal strength, 2 nodes in the DMN, 2 nodes in the Salience, and 4 nodes in the ECN were significantly increased. No changes were observed in the TPN in either time point comparison. Significant average nodal differences, when comparing baseline to 30 minute and 6 weeks post treatment, are listed in Table 4.3 and illustrated in Figure 4.1, 4.2, and 4.3. A detailed list of all the significant average nodal strength for each time point comparison is located in "Appendix B: Supplemental Results" (Table B.3).

4.4 INTRANETWORK CONNECTIVITY CHANGES:

Comparison of the individual intranetwork connections for each time point comparison revealed multiple significantly different intranetwork connectivity strengths (Table 4.3). No changes were observed in the TPN in either time point comparison and in the DMN when comparing baseline to 6 weeks post treatment. All significant intranetwork connections increased after treatment, except for one in the SN (Left Superior Temporal to Right Supramarginal Gyrus). This one intranetwork connection was non-significantly lower in Controls when comparing CM to controls, which may reflect a normalization after treatment. Significantly different intranetwork connections for DMN, SN and ECN are seen in Figure 4.1, 4.2, and 4.3, respectively. A detailed list of all the significant intranetwork connectivity differences each time point comparison is located in "Appendix B: Supplemental Results" (Table B.4).

TABLE 4.3: Significantly different nodal connectivity strengths in a network when comparing baseline to 30-minute and 6 weeks post first treatment.

Network	Baseline vs 30 minutes	Baseline vs 6 Weeks
DMN	None	Right Lateral Parietal Precuneus/PCC
SN	Left Frontal Pole Right SN/VTA	Left Frontal Pole Right SN/VTA
ECN	Bilateral VLPFC Bilateral DLPFC/FEF Bilateral DLPFC Left Anterior Thalamus Right Lateral Parietal	Left VLPFC Bilateral DLPFC/FEF Left DLPFC

NOTE: Statistical differences determined using a one-tailed t-test with a threshold of $p<0.05$

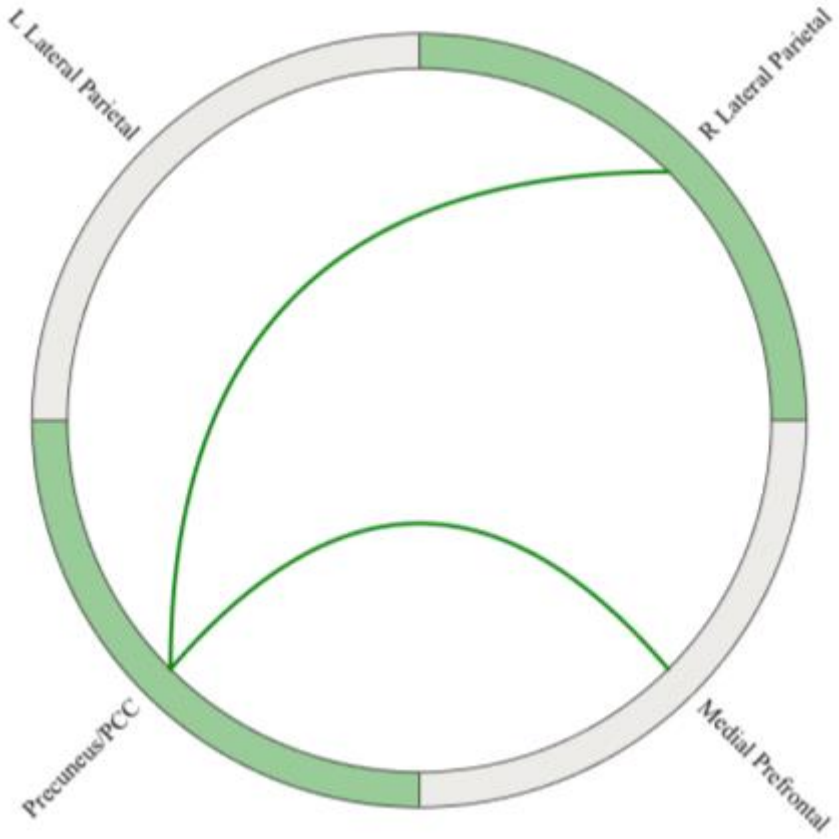


FIGURE 4.1: Significant differences in the DMN when comparing baseline to 6 weeks. Green lines and bars represent an improvement of intranetwork connectivity strength and average nodal strength after treatment.

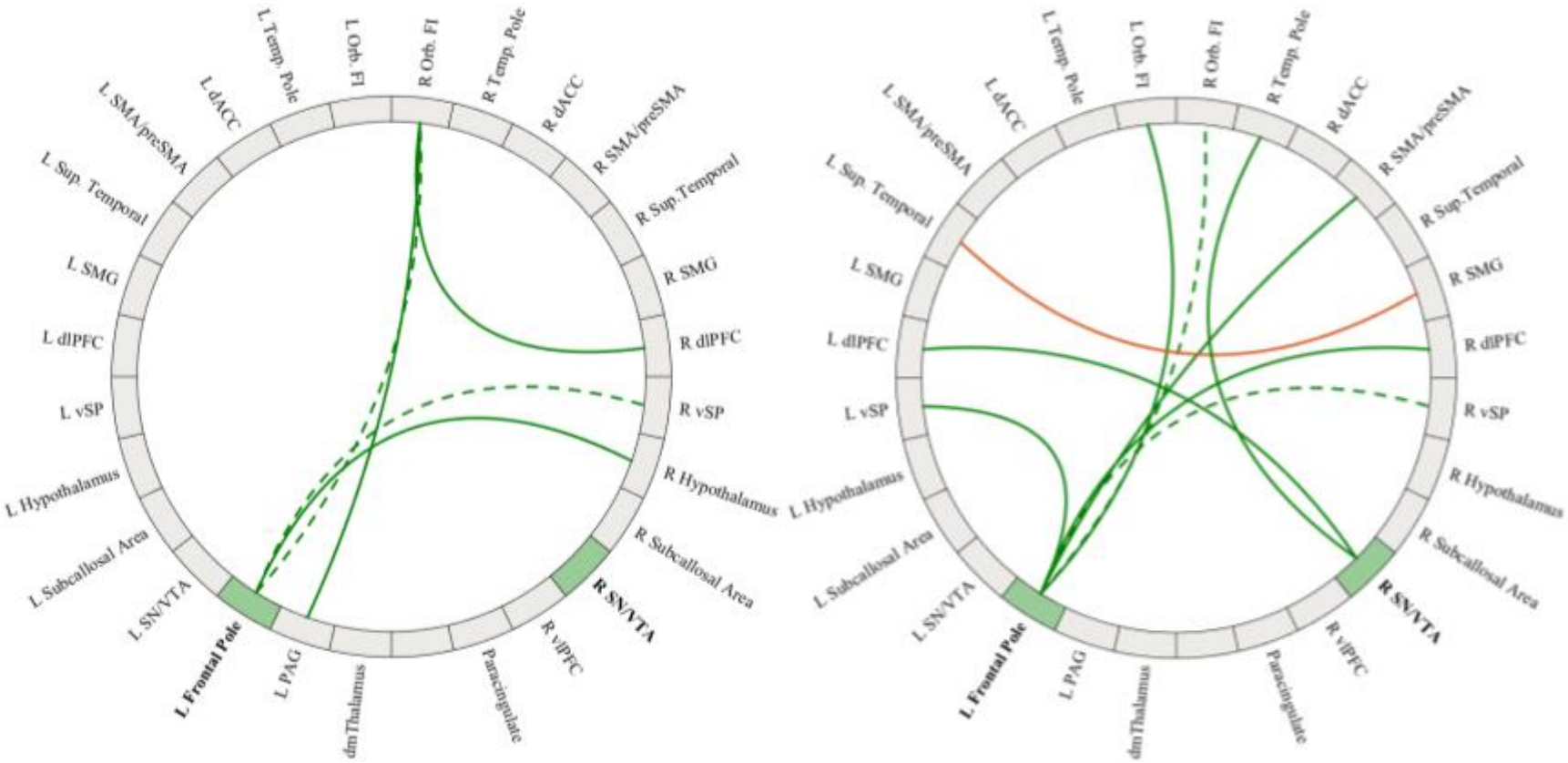


FIGURE 4.2: Significant intranetwork connectivity and average nodal difference in the SN when comparing baseline to 30-minute (left) and 6 weeks post first treatment (right). Green lines and bars represent an improvement of intranetwork connectivity strength and average nodal strength after treatment. The red line represents the one intranetwork connectivity strength that decreased after treatment (see section 4.4). Dashed line and bolded text represents similar improvements that are seen when comparing both time points. Images were generated using the Matlab application "Circro" (https://github.com/bonilhamusclab/circro).

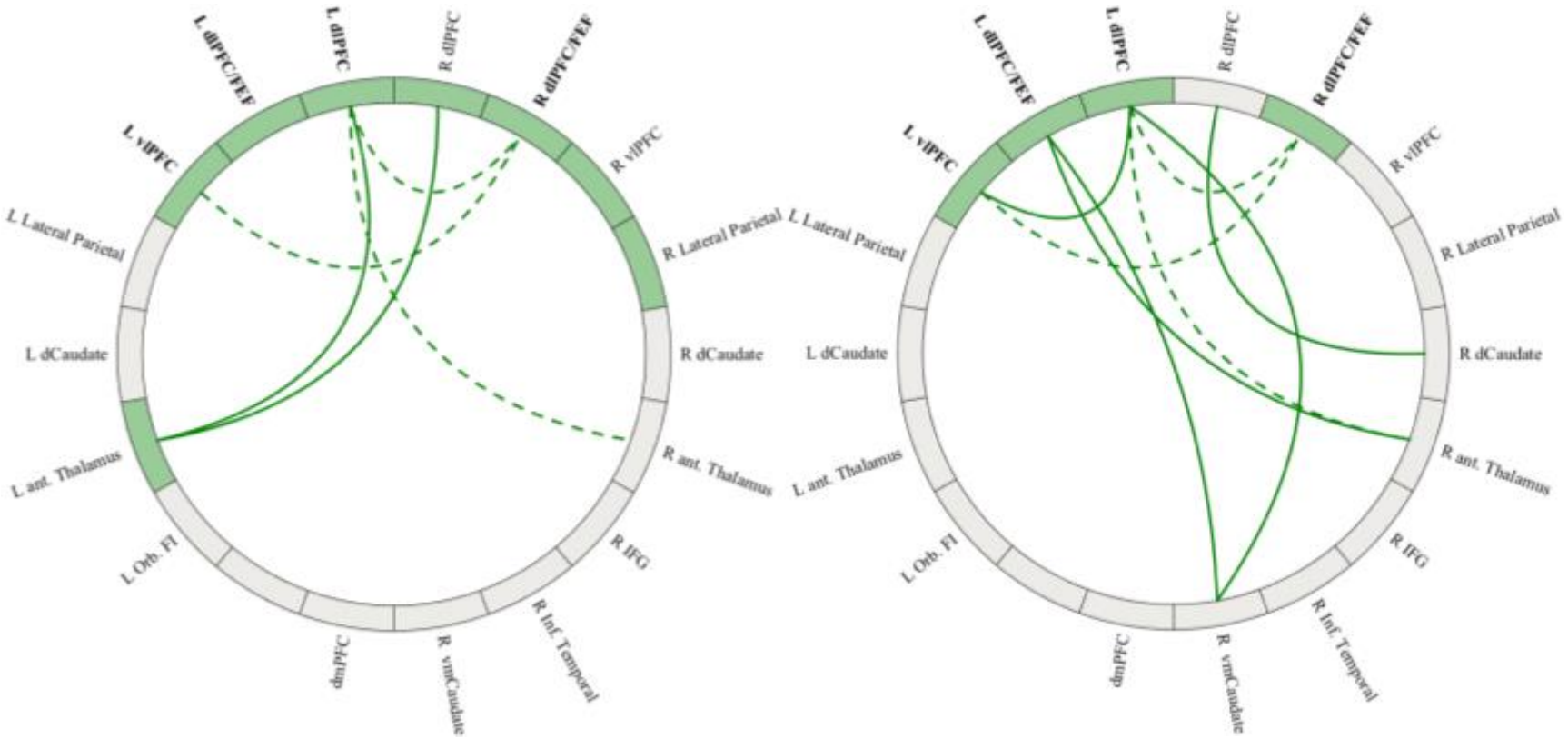


FIGURE 4.3: Significant intranetwork connectivity and average nodal difference in the ECN when comparing baseline to 30-minute (left) and 6 weeks post first treatment (right). Green lines and bars represent an improvement of intranetwork connectivity strength and average nodal strength after treatment. Dashed line and bolded text represents similar improvements that are seen when comparing both time points. Images were generated using the Matlab application "Circro" (https://github.com/bonilhamusclab/circro).

4.5 CLINICAL CORRELATIONS WITH NETWORK CHANGES:

When evaluating the relationship between improvements (delta) in clinical measures (i.e number of moderate to severe headache days/month, and quality of life scores) and changes in intranetwork functional connectivity, after 6 weeks of SPG treatment, there appears to be several relationships between improvements of these clinical measures and increased intranetwork functional connectivity (Table 4.4). A reduction of moderate to severe headache (HA) days and improved PHQ-9 scores were correlated with increased intranetwork functional connectivity in the SN. Improved HIT-6 scores were correlated to increased functional connectivity in the ECN. Only one intranetwork connection (left subcallosal area to left SMA/preSMA) had a negative correlation, indicating that a reduction to the number of moderate to severe headaches days after treatment is related to a weaker intranetwork functional connectivity between those regions in the SN.

TABLE 4.4: Statically significant correlations between changes in clinical measures (delta) and changes in intranetwork connectivity strength after 6 weeks of treatment.

Delta Number of Moderate to Severe HA Days	**Network**	***r*-value**	***p*-value**
Left Subcallosal Area x Left SMA/preSMA	SN	-0.86	0.001
Left Frontal Pole x Left Orbital Frontal Insula	SN	0.87	0.001
Left Ventral Striatum/Pallidum x Left DLPFC	SN	0.86	0.001
Right DLPFC x Right Dorsal ACC	SN	0.93	<0.001
Right SN/VTA Right DLPFC	SN	0.90	<0.001
Right SN/VTA x Right Hypothalamus	SN	0.87	0.001
Delta Hit-6 Score			
Right Lateral Parietal x Left VLPFC	ECN	0.87	0.001
Right DLPFC/FEF x Left VLPFC*	ECN	0.87	0.001
Delta PHQ-9			
Right Ventral Striatum/Pallidum x Right DLPFC	SN	0.87	0.001
*connection was significantly different at one of the time points Note: significance threshold was $p \leq 0.001$			

CHAPTER 5:

DISCUSSION

5.1 OVERALL CHANGES IN FUNCTIONAL NETWORKS:

For both CM with and without MOH, we report a significant decrease in overall network strength in the DMN, SN, and ECN when compared to healthy controls. This relative decrease in overall network strength can be interpreted as a dysregulation of one or more regions within each respective network. Dysfunctional intrinsic resting-state networks have previously been observed in chronic pain conditions. However, it is very difficult to determine if changes in these brain networks causal or consequential to having chronic pain (Baliki, Baria, & Apkarian, 2011; Baliki et al., 2014; Malinen et al., 2010; Napadow et al., 2010; Napadow et al., 2012).

It is important to point out that "dysfunction" in, or "disruption" of overall network/nodal strengths can occur due to either the strengthening or weakening of existing intranetwork functional connections. Both changes would result in the overall degradation of overall network coherence. Therefore, our methods do not allow us to interpret an increase or decrease of network activity, so for the purposes of this discussion we will use the term "increased" to refer to greater functional coherence in experimental as compared to control groups, and "decreased" to refer to lesser functional coherence in experimental as compared to control groups.

When comparing each CM group to a set of age matched controls, we observed similar patterns of impaired connectivity for both groups. Similarly, impaired regions ("nodes") of connectivity, within their respective networks, involve areas of the limbic/basal ganglia (hypothalamus, anterior thalamus, SN/VTA, ventral striatum/pallidum), frontal cortex (DLPFC, VLPFC, FEF, insula, inferior frontal gyrus) and pain processing/sensory areas (left lateral parietal and right superior temporal).

5.2 DYSFUNCTIONAL FC IN CM WITH AND WITHOUT MOH:

One of this study's aim was to investigate the similarities and differences between intrinsic brain networks in CM patients with MOH and without MOH. By examining our a priori networks of interest (DMN, TPN, SN, and ECN), we could determine specific patterns of neuromodulation associated with the pathophysiology of these two types of chronic migraine. To the best of our knowledge, no resting-state functional connectivity study has made direct comparisons between CM w/MOH and CM w/o MOH patients.

As both chronic migraine groups exhibited an overall dysfunction to these networks, as well as several similarly disrupted nodes within a network, it has proven difficult to determine the difference between these two groups based on just those results. However, by examining the intranetwork connectivity within a given network, we believe that possible underlying systems ("subnetworks") will help shed light on the differences between CM with and without MOH. Some of these subnetworks include fronto-striatal and cortical-thalamic systems, such as the mesocorticolimbic dopaminergic system and the cortico-basal ganglia-thalamic system. As these subnetworks play a role in the SN and ECN, it may be necessary to break apart these two networks to see if there are disruptions to these smaller, embedded systems, which

may ultimately cause widespread network dysfunctions. Due to the nature of this study, we cannot examine causality within these subnetworks. However, for the purposes of this discussion, we will use these subnetworks to hypothesize possible mechanisms that cause the chronification of migraine, and how medication overuse plays into those mechanisms.

The mesocorticolimbic dopaminergic pathway is a dopamine distribution system that plays important roles in reward, emotional salience, cognitive control, and motivation (Wise, 2009; Laviolette, Nadar, & van der Kooy, 2002). Starting in the VTA, this system branches off into two smaller ones based on where the VTA transmits dopamine to: the mesocortical system (SN/VTA, ACC, OFC, VMPFC, and DLPFC) and mesolimbic system (SN/VTA, ventral pallidum/nucleus accumbens) (Bowers, Chen, & Bonci, 2010; Wise, 2009; Everitt et al., 2007; Draganski et al., 2008). With the exception of VMPFC, all regions of the mesocorticolimbic dopamine pathways are present in the salience network and alterations to this pathway can possibly provide a tool for evaluating chronic migraine, both with and without MOH.

As the basal ganglion has been postulated to play an important role in chronic pain, other systems partially comprised of the basal ganglia may be important to investigate (Borsook et al., 2010; Wood et al., 2007). The cortico-basal ganglia-thalamic system (sometimes referred to as “striato-thalamo-orbitofrontal” and “fronto–striato–subthalamic–pallidal”) is another subnetwork based around the basal ganglion and its connection to cortical and thalamic regions (Jahanshahi et al., 2015). This pathway is also interconnected with DLPFC, insula, and ACC and includes glutamatergic (excitatory) innervations of the PFC to amygdala, nucleus accumbens and VTA

(Adinoff, 2004). It also includes innervations to the mesocortical dopaminergic systems (Jahanshahi et al., 2015; Gardner & Ashby, 2000).

This system is believed to have three distinct functions, each involving some of the intranetwork connection listed above. These three functions are motor (motor cortex-basal ganglia-thalamus), associative/cognitive (frontal lobe-caudate-thalamus), and emotion/limbic (ACC-basal ganglia-thalamus) (Jahanshahi et al., 2015). These functionally divided pathways can be seen in both the SN (emotional/limbic) and ECN (motor and associated/cognitive), each involved with different regions of the basal ganglia (ventral striatum and dorsal striatum/caudate, respectively) (Haber, 2003).

5.3 FC DYSFUNCTIONS IN CM WITH MOH PATIENTS:

The constant negative reinforcement of taking analgesic medication may contribute to a development of addictive/compulsive traits. This reinforcement has led previous researchers to hypothesize that addiction may play an important role in MOH pathophysiology (Lundqvist et al., 2010; Sances et al., 2010; Di Lorenzo et al., 2007; Di Lorenzo et al., 2009; Navratilova et al., 2012). Evidence of addiction related neuromodulation is observed in our MOH subgroup, with the unique patterns of dysfunctions seen in the SN's mesocortical dopaminergic system and the ECN's cortico-basal ganglia- thalamic systems. Metabolic changes to both of these subnetworks are believed to contribute to addiction and compulsive drug seeking behavior (Luscher & Malenka, 2011; Asensio et al., 2010; Paulus et al., 2002; Goldstein et al., 2007; Bolla et al., 2003; Ersche & Sahakian, 2007; de Greck et al.,2009; Wrase et al.,2007; Zhang et al., 2009; London et al., 2000; Volkow & Fowler, 2000; Volkow, Fowler, & Wang GJ, 2004; Verdejo-García et al., 2006).

Specifically, within the SN, dysfunctional connectivity was observed between regions of the mesocortical dopaminergic system (DLPFC, OFC, ACC) and in between frontal lobe regions and other limbic structures. Within the ECN, unique patterns of dysfunctions were seen in regions involved with the "associative/cognitive" function of the cortico-basal ganglia-thalamic network, such as the orbital frontal insula, dorsomedial PFC, anterior thalamus, right dorsal and ventromedial caudate. Most notably, disruptions between the DLPFC and bilateral anterior thalamus were unique to CM with MOH patients. Dysfunction to these regions coincides with altered GM volume reported in previous VBM studies on MOH patients (Chanraud et al., 2014; Riederer et al., 2012; Lai et al., 2016).

As compared to the CM without MOH cohort, MOH patients had more widespread disruptions in frontal lobe connectivity to other regions the SN (frontal pole, DLPFC, VLPFC, and SMA/preSMA) and ECN (inferior frontal gyrus, DLPFC, and VLPFC). This finding may also be explained by previous addiction studies, as impairments in regions of the frontal cortex are believed to result in increased craving and inhibition of cognitive control in drug abusers (Goldstein & Volkow, 2002; Goldstein et al., 2004; Goldstein et al., 2007; Yang et al., 2009).

5.4 FC DYSFUNCTIONS IN CM WITHOUT MOH PATIENTS:

CM has been hypothesized to be caused by central sensitization, which is a non-associative learned response after repeated administration of a noxious stimulation, resulting in the amplification of the response (Woolf, 2011; Filatova, Latysheva & Kurenkov, 2008; Bendtsen, 2000; Ashina et al., 2006; Zaman et al., 2015). The increased connectivity of the basal ganglia to regions involved in integrative pain

processing (such as the insula, OFC, ACC, PCC, and temporal pole) in migraine may have contributed to a learned sensitization (Yuan et al., 2013; Malaki et al., 2011). It is not clear which neural mechanism may be the cause of this hypersensitivity to pain, however, some research has suggested that chronic pain is a result of dysfunctional endogenous inhibition of pain (Lewis et al., 2012; Granovsky & Yarnitsky, 2013; Granovsky, 2013; Ablin & Buskila, 2013; Bouwense et al., 2013; Williams et al., 2013). The disinhibition of pain may manifest in the SN in the form of impaired habituation mechanisms, and in the ECN, in the lack of cognitive modulation of pain.

Two studies in episodic migraine do suggest that habituation, or lack thereof, may be a factor in migraine (Coppola et al., 2013; Stankewitz, Schulz, & May, 2013). In fact, there are many chronic pain studies that suggest that lack of habituation of continuous painful stimuli could play a role in the chronification of pain, however, it is not clear if this is a cause or effect of chronic pain (Bingel et al., 2007; Mirci & Savas 2002; Flor, Diers, & Birbaumer, 2004; Peters, Schmidt, & Van den Hout, 1989; Cecchini et al., 2003; Valerian et al., 2003).

In our study, one of the most intriguing findings is the prominent dysfunction of the SN's bilateral subcallosal area in CM without MOH. This dysfunction is not found in the CM with MOH subgroup, which upon review of the raw data, shows that the MOH group's network strengths involving the subcallosal area is comparable to that of controls. The subcallosal area, also known in literature as the parolfactory or sublenticular extended amygdala, is a region of the frontal lobe that is connected to areas in the vlPFC, OFC, and ACC areas (Mark et al., 1994). The posterior region of the subcallosal area also overlaps with the anterior nucleus accumbens (NAc), part of the

ventral striatum (Blood & Zatorre, 2001; Gruber, Hussain, & O'Donnell, 2009). Within the salience network, the subcallosal area has been functionally linked to areas, such as the ventral striatum/nucleus accumbens, dorsomedial thalamus, hypothalamus, and periaqueductal gray area. (JohansenBerg et al., 2008; Ongur and Price, 2000; Ongur, Ferry, & Price, 2003; Drevets, Ongur, & Price, 1998)

The subcallosal area has been reported in chronic tinnitus models as a "hub" that links the limbic-affective systems with thalamo-cortical perceptual systems. In these models, the subcallosal area, with the help of the interconnected areas of vmPFC and NAc, acts as an inhibitory gating mechanism (a "switch"), which, when "turned on", will signal to the brain stem/thalamus to habituate the auditory signal. However, when this area fails to habituate the signal, the auditory signal is relayed from the thalamus to the sensory areas resulting in chronic tinnitus (Rauschecker, Leaver, & Muhlau, 2010). The author of this study hypothesized that the cause of this dysfunction in the subcallosal area was due to the constant hyperactivity of the nucleus accumbens, which induced excitotoxicity in this region (Rauschecker, Leaver, & Muhlau, 2010). This hypothesis may be plausible, however, there is not enough research on this topic to determine it this explanation could extend to migraine.

The author of this chronic tinnitus model also suggest that this same model could be translated to chronic pain (Rauschecker, Leaver, & Muhlau, 2010). Even though the subcallosal area was not directly mentioned, previous chronic pain studies have already suggested that modulation between the NAc and mPFC is a possible cause of pain chronification (Bingel & Tracey, 2008; Becerra et al., 2001; Kuchinad et al., 2007; Schweinhardt et al., 2009; Baliki et al., 2006; Baliki et al., 2010; Baliki et al., 2012;

Hashmi et al., 2013). In chronic migraine, the dysfunction of the subcallosal areas could contribute to central sensitization; that is, hyperalgesia is a result of the dysfunction in this region's ability to inhibit the thalamus from relaying pain to sensory regions. Chronic migraine could very well be a result of disinhibition of the thalamus due to the dysfunctional gating mechanisms at the subcallosal area.

Our findings also indicated a possible role of the SN's subcallosal areas in the habituation of pain. To our knowledge, this is the first study to report a dysfunction of the subcallosal area in chronic migraine. It is possible that this region only appears to be dysfunctional within the confines of the SN, therefore it has not been observed in other fMRI studies on CM.

5.5 CM WITH MOH VS CM WITHOUT MOH:

For both MOH and non MOH patients, the overall network strength of the DMN appears to be lower than healthy controls. When you examine the individual nodes, both groups appear to have a common decrease in connectivity between the left lateral parietal area and other nodes within the DMN network. However, differences between the two groups (when compared to controls) manifest as dysfunctionality of the right lateral parietal and medial PFC, in the MOH patients, and precuneus/PCC, in the nonMOH patients. Previous reports of decreased connectivity between left lateral parietal and precuneus regions in chronic pain patients, is consistent with our findings for the non MOH group, but not the MOH group (Glass et al., 2011). As there were no significant differences between MOH and nonMOH patients when compared to each other, it is hard to speculate if these differences in the DMN were caused by chronic pain, the overuse of medication, or a combination of both.

A more logical explanation to the observed impairment of the DMN is that its relationship with the SN and ECN is consequentially causing a disruption to the DMN. As the DMN is functionally coupled with the SN and ECN, it is possible that disruptions to the DMN are a consequence of impaired SN and ECN (Gao & Lin, 2012; Deshpande, Santhanam, & Hu, 2011; Seeley et al., 2007). Unfortunately, our methods did not directly measure the relationship between DMN and the SN/ECN, therefor this is merely speculative.

Within the SN, both CM groups presented with disruptions to the mesolimbic dopaminergic pathways. In particular, similar disruptions were seen in connections involving the basal ganglia. This is not surprising as the basal ganglia has a central role in the mesolimbic system, and its functions include reinforcement learning, motivation, and reward (Schultz, 1997; Houk & Adams, 1995; Graybiel, 1998). However, due to the associations of chronic pain and addiction to alternate mesocorticolimbic dopamine pathways, it cannot be assumed that similar disruption to these areas are cause by the same pathophysiology (Luscher & Malenka, 2011; Asensio et al., 2010; Paulus et al., 2002; Goldstein et al., 2007; Bolla et al., 2003; Ersche & Sahakian, 2007; de Greck et al.,2009; Wrase et al.,2007; Zhang et al., 2009; Borsook et al., 2010; Wood et al., 2007).

Differences in the SN between the MOH and nonMOH groups are most apparently in that widespread disruption of connections involving prefrontal regions and the subcallosal area, respectively. When comparing MOH to nonMOH patients, the intranetwork connections within the SN that were significantly lower in MOH patients all included connections to the frontal lobe. As disruptions are present in non-MOH patients in prefrontal regions of the ECN, but not the SN, it can be deduced that the

addiction aspect of MOH may be causing additional dysfunctions of the mesocortical system within the SN.

Additionally, when directly comparing the two groups, the intranetwork connections between bilateral regions of the subcallosal area was more disrupted in nonMOH patients. This was also observed when comparing the CM to controls, as nonMOH patients mainly showed disrupted connectivity between the subcallosal area and other regions of the SN, where MOH patients did not. It is curious that the subcallosal area did not appear to be affected within the SN of the MOH group. Assuming that MOH patients also develop chronic migraine as a result of dysfunctional thalamic inhibition systems, proposed in the previous section, the impairment may be located in a downstream location of the thalamic inhibition system. In other words, as the subcallosal area is indirectly connected to the thalamus, it is possible that impairments to this thalamic inhibition system may have occurred in one of the pathways indirectly connecting the subcallosal area to the thalamus, such as the globus pallidum or thalamic reticular nucleus (O'Donnell et al., 1997; Guillery & Sherman, 2002).

Another possible explanation for the preservation of this area comes from the result of a recent study by Chen et al. (2016) comparing CM with MOH vs CM without MO. In this study, the marginal division of the neostriatum, located on the caudal border of the striatum and rostral edge of globus pallidus, was found to be affected in CM without MOH, but not CM with MOH. The author of that study suspected that the use of medication inhibited the modulatory function of the marginal division of the neostriatum, which therefore protected that area and its connectivity (Chen et al., 2016).

Perhaps a similar mechanism is responsible for somewhat "sparing" the subcallosal area in MOH patients. However, in order to test this hypothesis, additional research on these relay areas would be needed.

In regards to the ECN, the similar disruption of the frontal cortex may be a result of an impaired downstream modulation of pain. The prefrontal cortex has long been thought to play a key role in the cognitive modulation of pain, specifically with the ability to initiate the downstream modulation of pain (Bingel & Tracey, 2008). Increased activation of the frontal pole and VLPFC is related to an analgesic effect of pain, due to the inhibition of functional connectivity between the thalamus and midbrain regions (Lorenz, Minoshima, & Casey, 2003; Salomons et al., 2007; Wiech et al., 2006). The DLPFC is often upregulated in chronic pain patients due to the increased use in the descending modulation of pain. **(**Wager et al., 2004; Lorenz, Minoshima, & Casey, 2003; Seminowicz et al., 2013) This constant activation of the DLPFC in chronic pain may cause functional and anatomical neuromodulation evident by the decreased cortical thickness observed in chronic pain conditions (Apkarian et al., 2004; Seminowicz et al., 2011). Consequently, this neurodegeneration could have a negative impact on descending pain modulation, thus contributing to a chronic pain state (Tracey & Mantyh, 2007). In contrast to the SN, which may use frontal regions to determine the salience of the pain, we posit that within the executive network, frontal regions of the brain are disrupted in both CM groups is due to the consistent upregulation of the descending pain modulation

Taken together, we speculate that chronic migraine is the result of dysfunctional inhibition mechanisms responsible for inhibiting the thalamus from relaying to pain processing areas of the brain. This would possibly explain the neural mechanism behind

the central sensitization hypothesis, in which the brain can no longer habituate to innocuous stimuli resulting in frequent headaches/ migraine. We propose that there is a similar mechanism at play in MOH patients, however, due to the overuse of medication, this impairment may have manifested in a downstream location of the thalamic inhibition system. Additionally, we postulate that the overuse of medication accelerates the transformation of episodic migraine to chronic migraine due to the additional role of negative reinforcement in pain relief (reward incentive). Compared to non MOH patients, this increased salience of reward is apparent in the dysregulation of the prefrontal regions/mesocorticolimbic system within the SN.

5.6 EFFECTS OF SPG TREATMENT ON FC:

After receiving 6 weeks of SPG block treatment, an overall improvement is seen in both the ECN and the DMN. Though the ECN is also significantly improved 30 minutes after the first treatment, the additional restoration of the DMN at the 6 week post first treatment shows promise that repetitive inhibition of the SPG helps normalize functional connectivity. This is supported by evidence that the DMN and ECN are functionally coupled with each other (Gao & Lin, 2012; Deshpande, Santhanam, & Hu, 2011; Seeley et al., 2007).

One of the most promising results is the 6-week post treatment connectivity improvement of the precuneus/PCC region of the DMN. Specifically, its intranetwork connectivity increased to right lateral parietal and medial PFC, relative to baseline connectivity measures. Our baseline data mirror a previous resting-state functional connectivity study in MOH patients which found lower functional connectivity between precuneus to right lateral parietal and right mPFC in the DMN (Chanraud et al., 2014).

Here, we show that these functional connections are not permanently disordered, rather, they begin to normalize after six weeks of treatment. Additionally, in another MOH study, hyperactivity in the precuneus/PCC region appeared to normalize after they detoxified (Fumal et al., 2006). Unfortunately, it is unknown if the improvement from the precuneus to mPFC is due to the improvement in depression scores, as this connection has previously been reported as a "mediator" between pain severity and depression scores (Schweinhardt et al., 2006).

At both timepoints the left frontal pole and right substantia nigra/VTA are significantly improved, compared to baseline measurements, within the salience network as. The left frontal pole has been thought to be involved in analgesic effects of pain modulation and regulation of emotional influence on other pain processing (Kalisch et al., 2005; Salomons et al., 2007; Wiech et al., 2006). As compared to changes seen at 30 minutes, 6-weeks post treatment reflected an increased connectivity of left frontal pole with ipsilateral mesocortical regions (orbitofrontal insular and ventral striatum/pallidum) as well as contralateral frontal regions (DLPFC and SMA/preSMA). Similarly, the mesocortical region of right SN/VTA showed increased connectivity to contralateral DLPFC 6 weeks post treatment. As most of the treatment patients had medication overuse prior to the treatment, improvements in regions associated with the mesocortical dopamine pathway this may be evidence of normalization of impairments caused by medication overuse (discussed in "mesocorticolimbic pathway" section).

Changes in the ECN at 30-minutes post treatment displayed more improved connections on a nodal level, than changes at 6-weeks. When comparing changes at 30-minutes post treatment, bilateral VLPFC, bilateral DLPFC, bilateral DLPFC/FEF, left

anterior thalamus, and right lateral parietal significantly improved within the network. However, when comparing baseline to 6 weeks post treatment, only bilateral DLPFC, left VLPFC, and left DLPFC improved. The overwhelming involvement of the PFC regions within the ECN in both 30 minute and 6 weeks would suggest that the regions of the PFC that improved were not due to long term improvements but rather due to the cognitive component of pain modulation.

Intranetwork connectivity changes at 30 minutes (for ECN) appear to improve between regions of the PFC, and between the anterior thalamus and PFC. While these results are similar to changes at 6 weeks, there are more improvements between regions of the DLPFC and both dorsal and ventromedial caudate. This increase in functional connectivity between DLPFC regions with caudate seems to be a more prominent long term benefit of the SPG treatment. This may imply that medication overuse induced impairments to regions associated with the cortico-basal ganglia-thalamic pathway discussed earlier may be normalizing.

In order to assess the relationship of improvements of number of headache days and QOL measures (PHQ-9, HIT-6), a correlation analysis was conducted on the changes in network strength (see results section for more details). These correlations indicate a positive relationship between intranetwork functional connectivity strength and improved clinical measures. Specifically, less moderate to severe HA days/month and improved PHQ-9 scores were related to increased fc in the SN, and improved HIT-6 scores were related to increased fc in the ECN. Interestingly, there was one intranetwork connection in the SN, however, that had a negative relationship with reduced HA days/month after treatment. Though this intranetwork connection was not significantly different when

comparing baseline to 6 week functional connectivity, this negative relationship indicates that a reduction to the number of moderate to severe headaches days/month after treatment is related to a weaker intranetwork functional connectivity between the left subcallosal areas and left SMA/preSMA.

Unfortunately, as the SN and ECN changes mostly reflect PFC and basal ganglia regions, it is hard to determine if these improvements are related to pain modulation or a placebo response (Kong et al., 2007; Scott et al., 2008).

5.7 STUDY LIMITATIONS:

As with most scientific studies, the methods of this study are not free from possible confounds. One possible confound is the variability in analgesic drug use, which may have had an impact on resting state connectivity. Another potential confound is that several psychiatric comorbidities of migraine (i.e. anxiety, depression) are associated with several areas in all the networks examined. However, it is unclear if these comorbidities are a consequence of modulated brain networks or if they contribute to the dysfunction. Even though both groups (MOH and nonMOH) had varying degrees of anxiety/depression (measured with PHQ-9), the MOH group did have a significantly higher score. However, the average scores for both groups were classified as mild (nonMOH) and moderate (MOH).

Similarly, allodynia seems to play a large role in connectivity, and both these groups had varying degrees of allodynia. In a study by Schwedt et al (2014), the presence of allodynia was indicative of stronger functional connectivity between PAG and other regions in that are in both our SN and ECN (Schwedt et al., 2014b). This may have contributed to why we did not observe any functional connectivity differences for

the PAG, as reported by other migraine studies (Mainero, Boshyan, & Hadjikhani, 2011; Schwedt et al., 2013; Schwedt et al., 2014b). Additionally, disease duration has also been shown to have an impact on resting state networks (Chanraud et al., 2014). However, only one intranetwork connection (left subcallosal area to frontal pole) was negatively correlated with years with chronic migraine in the nonMOH vs control group.

Lastly, literature on functional connectivity differences in migraine populations is heavily influenced by episodic migraine and migraine with/without aura. Very few studies have been completed regarding chronic migraine. Therefore, generalizations between chronic migraine and other migraine populations is difficult. Additionally, as we do not have a cohort group of episodic migraineurs, we cannot make assumptions for that group.

As for the treatment portion of this study, there are a few limitations. One is that since the treatment was given right before both the "30-minute post treatment scan" and before the "6 weeks post treatment scan", it is hard to determine if there is a placebo response. Another limitation to this study is the small sample size. A larger cohort would possibly allow more subtle changes to be discovered. Additionally, any neural plasticity that may have occurred due to the SPG treatment may be too small to detect only after 6 weeks of treatment. A study with a longer follow up period might help improve this detection.

5.8 FUTURE DIRECTIONS:

Based on the results of this study, further investigation into the mechanisms of thalamic inhibition systems would help provide a better understanding of its role in the chronification of pain. For CM without MOH, the impairment seen in the subcallosal

area will require additional investigation into how this region works with areas outside the SN. For CM with MOH, a more detailed investigation into the mesocorticolimbic dopamine and cortico-basal ganglia-thalamic systems may help shed light on a similar dysfunction to thalamic inhibition systems. Due to the method of this study, there are many limited factors that cannot determine directionality and relationship between networks. Future studies would benefit by utilizing granger causality to predict directionality (Bressler & Menon, 2010).

Investigation into these smaller systems may also help with understanding how SPG blockade works. With regards to the treatment study, a more comprehensive study with more patients and additional post treatment scans is warranted. For both parts of this study, we did collect DTI data, however we lacked resources to analyze this methodology. Investigation into white matter modulations would also add to this limited knowledge of the topic we are investigating.

5.9 CONCLUSIONS:

Based on the results of our study, we propose that chronic migraine is a result of modulated functional brain networks induced by repetitive migraine attacks. By examining the intranetwork connections, we discovered that disruptions to these networks could be a consequence of the dysfunction of several smaller systems that make up the SN and ECN. Both CM groups show similarly disrupted regions of limbic (SN) and frontal cortex (ECN), however, the two groups present with different intranetwork connectivity disruptions. Specifically, nonMOH patients appear to have a widespread disruption between regions of the subcallosal area and other regions of the SN. Furthermore, in MOH patients we observed additional disruptions to mesocortical

dopamine (SN) and cortico-basal ganglia-thalamic systems (ECN), which may be a result of abuse of pain medication. These finding suggest that there is a different pattern of connectivity impairment unique to each CM group investigated.

In conclusion, we believe that the SN of chronic migraine patients is less coordinated due to the overwhelmingly increased salience of pain. Additionally, we propose that the frontal cortex dysfunction of the ECN is a result of conflict of overlapping resources involved in the cognitive modulation of pain. The DMN, which is functionally coupled with both the SN and ECN, is consequently manifesting incoherence. However, this dysfunction may not be permanent, as there is evidence of ECN and DMN normalization in CM patients after the treatment of repetitive inhibition of the SPG.

REFERENCES

Ablin, J. N., & Buskila, D. (2013). Fibromyalgia syndrome–Novel therapeutic targets. *Maturitas*, *75*(4), 335-340.

Adinoff, B. (2004). Neurobiologic processes in drug reward and addiction. *Harvard review of psychiatry*, *12*(6), 305-320.

Apkarian, A. V., Sosa, Y., Krauss, B. R., Thomas, P. S., Fredrickson, B. E., Levy, R. E., ... & Chialvo, D. R. (2004). Chronic pain patients are impaired on an emotional decision-making task. *Pain*, *108*(1), 129-136.

Asensio, S., Romero, M. J., Romero, F. J., Wong, C., Alia-Klein, N., Tomasi, D., ... & Goldstein, R. Z. (2010). Striatal dopamine D2 receptor availability predicts the thalamic and medial prefrontal responses to reward in cocaine abusers three years later. *Synapse*, *64*(5), 397-402.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage*, *26*(3), 839-851.

Ashina, S., Bendtsen, L., Ashina, M., Magerl, W., & Jensen, R. (2006). Generalized hyperalgesia in patients with chronic tension-type headache. *Cephalalgia*, *26*(8), 940-948

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., & Apkarian, A. V. (2006). Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience*, *26*(47), 12165-12173.

Baliki, M. N., Geha, P. Y., Fields, H. L., & Apkarian, A. V. (2010). Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron*, *66*(1), 149-160.

Baliki, M. N., Baria, A. T., & Apkarian, A. V. (2011). The cortical rhythms of chronic back pain. *The Journal of Neuroscience*, *31*(39), 13981-13990.

Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., ... & Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature neuroscience*, *15*(8), 1117-1119.

Baliki, M. N., Mansour, A. R., Baria, A. T., & Apkarian, A. V. (2014). Functional reorganization of the default mode network across chronic pain conditions. *PloS one*, *9*(9), e106133.

Becerra, L., Breiter, H. C., Wise, R., Gonzalez, R. G., & Borsook, D. (2001). Reward circuitry activation by noxious thermal stimuli. *Neuron*, *32*(5), 927-946.

Bendtsen, L. (2000). Central sensitization in tension-type headache—possible pathophysiological mechanisms. *Cephalalgia*, *20*(5), 486-508.

Bigal, M. E., & Lipton, R. B. (2006). Modifiable risk factors for migraine progression. *Headache: The Journal of Head and Face Pain*, *46*(9), 1334-1343.

Bingel, U., Schoell, E., Herken, W., Büchel, C., & May, A. (2007). Habituation to painful stimulation involves the antinociceptive system. *Pain*, *131*(1), 21-30.

Bingel, U., & Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology*, *23*(6), 371-380.

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic resonance in medicine*, *34*(4), 537-541.

Biswal, B. B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. M., ... & Dogonowski, A. M. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences*, *107*(10), 4734-4739.

Blood, A. J., & Zatorre, R. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences*, *98*(20), 11818-11823.

Bolla, K. I., Eldreth, D. A., London, E. D., Kiehl, K. A., Mouratidis, M., Contoreggi, C. E. E. A., ... & Funderburk, F. R. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage*, *19*(3), 1085-1094.

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., & Sharp, D. J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences*, *109*(12), 4690-4695.

Borsook, D., Upadhyay, J., Chudler, E. H., & Becerra, L. (2010). A key role of the basal ganglia in pain and analgesia-insights gained through human functional imaging. *Molecular pain*, *6*(1), 1.

Bouwense, S. A., Olesen, S. S., Drewes, A. M., Frøkjær, J. B., van Goor, H., & Wilder-Smith, O. H. (2013). Is altered central pain processing related to disease stage in

chronic pancreatitis patients with pain? An exploratory study. *PloS one*, *8*(2), e55460.

Bowers, M. S., Chen, B. T., & Bonci, A. (2010). AMPA receptor synaptic plasticity induced by psychostimulants: the past, present, and therapeutic future. *Neuron*, *67*(1), 11-24.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in cognitive sciences*, *14*(6), 277-290.

Burstein, R., & Jakubowski, M. (2005). Unitary hypothesis for multiple triggers of the pain and strain of migraine. *Journal of Comparative Neurology*, *493*(1), 9-14.

Buse, D. C., Manack, A. N., Fanning, K. M., Serrano, D., Reed, M. L., Turkel, C. C., & Lipton, R. B. (2012). Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache: The Journal of Head and Face Pain*, *52*(10), 1456-1470.

Cady, R., Saper, J., Dexter, K., & Manley, H. R. (2015a). A Double-Blind, Placebo-Controlled Study of Repetitive Transnasal Sphenopalatine Ganglion Blockade With Tx360® as Acute Treatment for Chronic Migraine. *Headache: The Journal of Head and Face Pain*, *55*(1), 101-116.

Cady, R. K., Saper, J., Dexter, K., Cady, R. J., & Manley, H. R. (2015b). Long-Term Efficacy of a Double-Blind, Placebo-Controlled, Randomized Study for Repetitive Sphenopalatine Blockade With Bupivacaine vs Saline With the Tx360® Device for Treatment of Chronic Migraine. *Headache: The Journal of Head and Face Pain*, *55*(4), 529-542.

Candido, K. D., Massey, S. T., Sauer, R., Darabad, R. R., & Knezevic, N. N. (2013). A novel revision to the classical transnasal topical sphenopalatine ganglion block for the treatment of headache and facial pain. *Pain physician*, *16*(6), E769.

Cauda, F., Sacco, K., Duca, S., Cocito, D., D'Agata, F., Geminiani, G. C., & Canavero, S. (2009). Altered resting state in diabetic neuropathic pain. *PloS one*, *4*(2), e4542.

Cecchini, A. P., Sandrini, G., Fokin, I. V., Moglia, A., & Nappi, G. (2003). Trigeminofacial reflexes in primary headaches. *Cephalalgia*, *23*(s1), 33-41.

Čeko, M., Shir, Y., Ouellet, J. A., Ware, M. A., Stone, L. S., & Seminowicz, D. A. (2015). Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. *Human brain mapping*, *36*(6), 2075-2092.

Chanraud, S., Di Scala, G., Dilharreguy, B., Schoenen, J., Allard, M., & Radat, F. (2014). Brain functional connectivity and morphology changes in medication-overuse headache: Clue for dependence-related processes?. *Cephalalgia*, *34*(8), 605-615.

Chen, Z., Chen, X., Liu, M., Liu, S., Shu, S., Ma, L., & Yu, S. (2016). Altered functional connectivity of the marginal division in migraine: a resting-state fMRI study. *The Journal of Headache and Pain*, 17(1), 89.

Chiapparini, L., Grazzi, L., Ferraro, S., Mandelli, M. L., Usai, S., Andrasik, F., ... & Bussone, G. (2009). Functional-MRI evaluation of pain processing in chronic migraine with medication overuse. *Neurological sciences*, *30*(1), 71-74.

Cifre, I., Sitges, C., Fraiman, D., Muñoz, M. Á., Balenzuela, P., González-Roldán, A., ... & Montoya, P. (2012). Disrupted functional connectivity of the pain network in fibromyalgia. *Psychosomatic medicine*, *74*(1), 55-62.

Coppola, G., Di Lorenzo, C., Schoenen, J., & Pierelli, F. (2013). Habituation and sensitization in primary headaches. *The journal of headache and pain*, *14*(1), 1.

De Greck, M., Supady, A., Thiemann, R., Tempelmann, C., Bogerts, B., Forschner, L., ... & Northoff, G. (2009). Decreased neural activity in reward circuitry during personal reference in abstinent alcoholics—A fMRI study. *Human brain mapping*, *30*(5), 1691-1704.

Deshpande, G., Santhanam, P., & Hu, X. (2011). Instantaneous and causal connectivity in resting state brain networks derived from functional MRI data. *Neuroimage*, *54*(2), 1043-1052.

Di Lorenzo, C., Sances, G., Di Lorenzo, G., Rengo, C., Ghiotto, N., Guaschino, E., ... & Siracusano, A. (2007). The wolframin His611Arg polymorphism influences medication overuse headache. *Neuroscience letters*, *424*(3), 179-184.

Di Lorenzo, C., Di Lorenzo, G., Sances, G., Ghiotto, N., Guaschino, E., Grieco, G. S., ... & Pierelli, F. (2009). Drug consumption in medication overuse headache is influenced by brain-derived neurotrophic factor Val66Met polymorphism. *The journal of headache and pain*, *10*(5), 349-355.

Draganski, B., Kherif, F., Klöppel, S., Cook, P. A., Alexander, D. C., Parker, G. J., ... & Frackowiak, R. S. (2008). Evidence for segregated and integrative connectivity patterns in the human basal ganglia. *The Journal of Neuroscience*, *28*(28), 7143-7152.

Drevets, W. C., Öngür, D., & Price, J. L. (1998). Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Molecular psychiatry*, *3*(3).

Eccleston, C., & Crombez, G. (1999). Pain demands attention: A cognitive–affective model of the interruptive function of pain. *Psychological bulletin*, *125*(3), 356.

Ersche, K. D., & Sahakian, B. J. (2007). The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychology review*, *17*(3), 317-336.

Everitt, B. J., Hutcheson, D. M., Ersche, K. D., Pelloux, Y., Dalley, J. W., & Robbins, T. W. (2007). The orbital prefrontal cortex and drug addiction in laboratory animals and humans. *Annals of the New York Academy of Sciences*, *1121*(1), 576-597.

Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U., Church, J. A., Miezin, F. M., ... & Petersen, S. E. (2009). Functional brain networks develop from a "local to distributed" organization. *PLoS Computional Biology*, *5*(5).

Ferraro, S., Grazzi, L., Mandelli, M. L., Aquino, D., Di Fiore, D., Usai, S., ... & Chiapparini, L. (2012a). Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. *Pain medicine*, *13*(2), 255-262.

Ferraro, S., Grazzi, L., Muffatti, R., Nava, S., Ghielmetti, F., Bertolino, N., ... & Epifani, F. (2012b). In Medication-Overuse Headache, fMRI Shows Long-Lasting Dysfunction in Midbrain Areas. *Headache: The Journal of Head and Face Pain*, *52*(10), 1520-1534.

Filatova, E., Latysheva, N., & Kurenkov, A. (2008). Evidence of persistent central sensitization in chronic headaches: a multi-method study. *The Journal of Headache and Pain*, *9*(5), 295-300.

Flor, H., Diers, M., & Birbaumer, N. (2004). Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. *Neuroscience letters*, *361*(1), 147-150.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673-9678.

Freedman, D., & Lane, D. (1983). A nonstochastic interpretation of reported significance levels. *Journal of Business & Economic Statistics*, *1*(4), 292-298.

Fumal, A., Laureys, S., Di Clemente, L., Boly, M., Bohotin, V., Vandenheede, M., ... & Schoenen, J. (2006). Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain*, *129*(2), 543-550.

Gao, W., & Lin, W. (2012). Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Human brain mapping*, *33*(1), 192-202.

Gardner, E. L., & Ashby, C. R. (2000). Heterogeneity of the mesotelencephalic dopamine fibers: physiology and pharmacology. *Neuroscience & Biobehavioral Reviews*, *24*(1), 115-118.

Glass, J. M., Williams, D. A., Fernandez-Sanchez, M. L., Kairys, A., Barjola, P., Heitzeg, M. M., ... & Schmidt-Wilcke, T. (2011). Executive function in chronic pain patients and healthy controls: different cortical activation during response inhibition in fibromyalgia. *The Journal of Pain*, *12*(12), 1219-1229.

Goadsby, P. J., Lipton, R. B., & Ferrari, M. D. (2002). Migraine—current understanding and treatment. *New England Journal of Medicine*, *346*(4), 257-270.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*. *159*(10), 1642-1652.

Goldstein, R. Z., Leskovjan, A. C., Hoff, A. L., Hitzemann, R., Bashan, F., Khalsa, S. S., ... & Volkow, N. D. (2004). Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia*, *42*(11), 1447-1458.

Goldstein, R. Z., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L. A., Maloney, T., ... & Samaras, D. (2007). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction?. *American Journal of Psychiatry*, *164*(1), 43-51.

Granovsky, Y., & Yarnitsky, D. (2013). Personalized pain medicine: the clinical value of psychophysical assessment of pain modulation profile. *Rambam Maimonides Medical Journal*, *4*(4).

Granovsky, Y. (2013). Conditioned pain modulation: a predictor for development and treatment of neuropathic pain. *Current pain and headache reports*, *17*(9), 1-7.

Graybiel, A. M. (1998). The basal ganglia and chunking of action repertoires. *Neurobiology of learning and memory*, *70*(1), 119-136.

Grazzi, L., Chiapparini, L., Ferraro, S., Usai, S., Andrasik, F., Mandelli, M. L., ... & Bussone, G. (2010). Chronic migraine with medication overuse pre–post withdrawal of symptomatic medication: clinical results and fMRI correlations. *Headache: The Journal of Head and Face Pain*, *50*(6), 998-1004.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253-258.

Gruber, A. J., Hussain, R. J., & O'Donnell, P. (2009). The nucleus accumbens: a switchboard for goal-directed behaviors. *PloS one*, *4*(4).

Guillery, R. W., & Sherman, S. M. (2002). Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron*, *33*(2), 163-175.

Haber, S. N. (2003). The primate basal ganglia: parallel and integrative networks. *Journal of chemical neuroanatomy*, *26*(4), 317-330.

Hallquist, M. N., Hwang, K., & Luna, B. (2013). The nuisance of nuisance regression: spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. *Neuroimage*, *82*, 208-225.

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biological psychiatry*, *70*(4), 327-333.

Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., ... & Apkarian, A. V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*, *136*(9), 2751-2768.

Headache Classification Committee of the International Headache Society (IHS. (2013). The international classification of headache disorders, (beta version). *Cephalalgia*, *33*(9), 629-808.

Houk, J. C., & Adams, J. L. (1995). A Model of How the Basal Ganglia Generate and Use Neural Signals That Predict Reinforcement. *Models of information processing in the basal ganglia*, 249.

Jahanshahi, M., Obeso, I., Rothwell, J. C., & Obeso, J. A. (2015). A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. *Nature Reviews Neuroscience*, *16*(12), 719.

Johansen-Berg, H., Gutman, D. A., Behrens, T. E. J., Matthews, P. M., Rushworth, M. F. S., Katz, E., ... & Mayberg, H. S. (2008). Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cerebral cortex*, *18*(6), 1374-1383.

Kalisch, R., Wiech, K., Critchley, H. D., Seymour, B., O'Doherty, J. P., Oakley, D. A., ... & Dolan, R. J. (2005). Anxiety reduction through detachment: subjective, physiological, and neural effects. *Journal of cognitive neuroscience*, *17*(6), 874-883.

Katsarava, Z., Schneeweiss, S., Kurth, T., Kroener, U., Fritsche, G., Eikermann, A., ... & Limmroth, V. (2004). Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology*, *62*(5), 788-790.

Khan, S., Schoenen, J., & Ashina, M. (2014). Sphenopalatine ganglion neuromodulation in migraine: What is the rationale?. *Cephalalgia*, *34*(5), 382-391.

Kong, J., Kaptchuk, T. J., Polich, G., Kirsch, I., & Gollub, R. L. (2007). Placebo analgesia: findings from brain imaging studies and emerging hypotheses. *Reviews in the Neurosciences*, *18*(3-4), 173-190.

Kong, J., Loggia, M. L., Zyloney, C., Tu, P., LaViolette, P., & Gollub, R. L. (2010). Exploring the brain in pain: activations, deactivations and their relation. *Pain*, *148*(2), 257-267.

Kuchinad, A., Schweinhardt, P., Seminowicz, D. A., Wood, P. B., Chizh, B. A., & Bushnell, M. C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain?. *The Journal of neuroscience*, *27*(15), 4004-4007.

Lai, T. H., Chou, K. H., Fuh, J. L., Lee, P. L., Kung, Y. C., Lin, C. P., & Wang, S. J. (2016). Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia*.

Lang, J. (1995). *Clinical anatomy of the masticatory apparatus parapharyngeal spaces*. Thieme.

Larsson, L. I., Edvinsson, L., Fahrenkrug, J., Håkanson, R., & Owman, C. (1976). Immunohistochemical localization of a vasodilatory polypeptide (VIP) in cerebrovascular nerves. *Brain research*, *113*(2), 400-404.

Laviolette, S. R., Nader, K., & van der Kooy, D. (2002). Motivational state determines the functional role of the mesolimbic dopamine system in the mediation of opiate reward processes. *Behavioural brain research*, *129*(1), 17-29.

Lewis, G. N., Luke, H., Rice, D. A., Rome, K., & McNair, P. J. (2012). Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*, *17*(2), 98-102.

Li, W., Mai, X., & Liu, C. (2014). The default mode network and social understanding of others: what do brain connectivity studies tell us. *Frontiers in human neuroscience*, *8*, 74.

Lipton, R. B., & Bigal, M. E. (2005). Migraine: epidemiology, impact, and risk factors for progression. *Headache: The Journal of Head and Face Pain*, *45*(s1), S3-S13.

Lipton, R. B., Bigal, M. E., Ashina, S., Burstein, R., Silberstein, S., Reed, M. L., ... & Stewart, W. F. (2008). Cutaneous allodynia in the migraine population. *Annals of neurology*, *63*(2), 148-158.

Loggia, M. L., Edwards, R. R., Kim, J., Vangel, M. G., Wasan, A. D., Gollub, R. L., ... & Napadow, V. (2012). Disentangling linear and nonlinear brain responses to evoked deep tissue pain. *PAIN*, *153*(10), 2140-2151.

Loggia, M. L., Kim, J., Gollub, R. L., Vangel, M. G., Kirsch, I., Kong, J., ... & Napadow, V. (2013). Default mode network connectivity encodes clinical pain: an arterial spin labeling study. *PAIN*, *154*(1), 24-33.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150-157.

London, E. D., Ernst, M., Grant, S., Bonson, K., & Weinstein, A. (2000). Orbitofrontal cortex and human drug abuse: functional imaging. *Cerebral cortex*, *10*(3), 334-342.

Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain*, *126*(5), 1079-1091.

Lu, H., Zuo, Y., Gu, H., Waltz, J. A., Zhan, W., Scholl, C. A., ... & Stein, E. A. (2007). Synchronized delta oscillations correlate with the resting-state functional MRI signal. *Proceedings of the National Academy of Sciences*, *104*(46), 18265-18269.

Lundqvist, C., Aaseth, K., Grande, R. B., Benth, J. Š., & Russell, M. B. (2010). The severity of dependence score correlates with medication overuse in persons with secondary chronic headaches. The Akershus study of chronic headache. *PAIN®*, *148*(3), 487-491.

Lüscher, C., & Malenka, R. C. (2011). Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron*, *69*(4), 650-663.

Magis, D., Jensen, R., & Schoenen, J. (2012). Neurostimulation therapies for primary headache disorders: present and future. *Current opinion in neurology*, *25*(3), 269-276.

Mainero, C., Boshyan, J., & Hadjikhani, N. (2011). Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Annals of neurology*, *70*(5), 838-845.

Maleki, N., Becerra, L., Nutile, L., Pendse, G., Brawn, J., Bigal, M., ... & Borsook, D. (2011). Migraine attacks the basal ganglia. *Molecular pain*, *7*(1), 1.

Maleki, N., & Gollub, R. L. (2016). What Have We Learned From Brain Functional Connectivity Studies in Migraine Headache?. *Headache: The Journal of Head and Face Pain*.

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M., Ramkumar, P., Forss, N., ... & Hari, R. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proceedings of the National Academy of Sciences*, *107*(14), 6493-6497.

Manack, A. N., Buse, D. C., & Lipton, R. B. (2011). Chronic migraine: epidemiology and disease burden. *Current pain and headache reports*, *15*(1), 70-78.

Mantini, D., Caulo, M., Ferretti, A., Romani, G. L., & Tartaro, A. (2009). Noxious Somatosensory Stimulation Affects the Default Mode of Brain Function: Evidence from Functional MR Imaging 1. *Radiology*, *253*(3), 797-804.

Mark, L. P., Daniels, D. L., Naidich, T. P., Hendrix, L. E., & Maas, E. (1994). Anatomic moment. The septal area. *American journal of neuroradiology*, *15*(2), 273-276.

Mathur, V. A., Khan, S. A., Keaser, M. L., Hubbard, C. S., Goyal, M., & Seminowicz, D. A. (2015). Altered cognition-related brain activity and interactions with acute pain in migraine. *NeuroImage: Clinical*, *7*, 347-358.

May, A., & Schulte, L. H. (2016). Chronic migraine: risk factors, mechanisms and treatment. *Nature Reviews Neurology*, *12*(8), 455-464.

McCracken, L. M., & Iverson, G. L. (2001). Predicting complaints of impaired cognitive functioning in patients with chronic pain. *Journal of pain and symptom management*, *21*(5), 392-396.

Mirci, S., & Savas, S. (2002). The auditory event related potentials in episodic and chronic pain sufferers. *European Journal of Pain*, *6*(3), 239-244.

Moskowitz, M. A. (1990). Basic mechanisms in vascular headache. *Neurologic clinics*, *8*(4), 801-815.

Munksgaard, S. B., Bendtsen, L., & Jensen, R. H. (2013). Modulation of central sensitisation by detoxification in MOH: Results of a 12-month detoxification study. *Cephalalgia*, *33*(7), 444.

Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis & Rheumatism*, *62*(8), 2545-2555.

Napadow, V., Kim, J., Clauw, D. J., & Harris, R. E. (2012). Brief report: decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. *Arthritis & Rheumatism*, *64*(7), 2398-2403.

Navratilova, E., Xie, J. Y., Okun, A., Qu, C., Eyde, N., Ci, S., ... & Porreca, F. (2012). Pain relief produces negative reinforcement through activation of mesolimbic reward–valuation circuitry. *Proceedings of the National Academy of Sciences*, *109*(50), 20709-20713.

Nes, L. S., Roach, A. R., & Segerstrom, S. C. (2009). Executive functions, self-regulation, and chronic pain: a review. *Annals of Behavioral Medicine*, *37*(2), 173-183.

Niddam, D. M., Lai, K. L., Fuh, J. L., Chuang, C. Y. N., Chen, W. T., & Wang, S. J. (2015). Reduced functional connectivity between salience and visual networks in migraine with aura. *Cephalalgia*, *36*(10), 53.

Nozaki, K., Moskowitz, M. A., Maynard, K. I., Koketsu, N., Dawson, T. M., Bredt, D. S., & Snyder, S. H. (1993). Possible origins and distribution of immunoreactive nitric oxide synthase-containing nerve fibers in cerebral arteries. *Journal of Cerebral Blood Flow & Metabolism*, *13*(1), 70-79.

O'Donnell, P., Lavín, A., Enquist, L. W., Grace, A. A., & Card, J. P. (1997). Interconnected parallel circuits between rat nucleus accumbens and thalamus revealed by retrograde transynaptic transport of pseudorabies virus. *The journal of neuroscience*, *17*(6), 2143-2167.

Öngür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral cortex*, *10*(3), 206-219.

Öngür, D., Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology*, *460*(3), 425-449.

Paemeleire, K., Bahra, A., Evers, S., Matharu, M. S., & Goadsby, P. J. (2006). Medication-overuse headache in patients with cluster headache. *Neurology*, *67*(1), 109-113.

Paulus, M. P., Hozack, N. E., Zauscher, B. E., Frank, L., Brown, G. G., Braff, D. L., & Schuckit, M. A. (2002). Behavioral and Functional Neuroimaging Evidence for Prefrontal Dysfunction in Methamphetamine-Dependent Subjects. *Neuropsychopharmacology*, *1*(26), 53-63.

Perrotta, A., Serrao, M., Sandrini, G., Burstein, R., Sances, G., Rossi, P., ... & Nappi, G. (2009). Sensitisation of spinal cord pain processing in medication overuse headache involves supraspinal pain control. *Cephalalgia*.

Perrotta, A., Arce-Leal, N., Tassorelli, C., Gasperi, V., Sances, G., Blandini, F., ... & Maccarrone, M. (2012). Acute Reduction of Anandamide-Hydrolase (FAAH) Activity is Coupled With a Reduction of Nociceptive Pathways Facilitation in

Medication-Overuse Headache Subjects After Withdrawal Treatment. *Headache: The Journal of Head and Face Pain*, *52*(9), 1350-1361.

Peters, M. L., Schmidt, A. J., & Van den Hout, M. A. (1989). Chronic low back pain and the reaction to repeated acute pain stimulation. *Pain*, *39*(1), 69-76.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiologie Clinique/Clinical Neurophysiology*, *30*(5), 263-288.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676-682.

Rauschecker, J. P., Leaver, A. M., & Mühlau, M. (2010). Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron*, *66*(6), 819-826.

Riederer, F., Marti, M., Luechinger, R., Lanzenberger, R., von Meyenburg, J., Gantenbein, A. R., ... & Sándor, P. S. (2012). Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety. *The World Journal of Biological Psychiatry*, *13*(7), 517-525.

Robbins, M. S., Robertson, C. E., Kaplan, E., Ailani, J., Charleston, L., Kuruvilla, D., ... & Vidwan, J. (2015). The sphenopalatine ganglion: Anatomy, pathophysiology, and therapeutic targeting in headache. *Headache: The Journal of Head and Face Pain*. *56*(2), 240-258.

Ruskell, G. L. (2004). Orbital passage of pterygopalatine ganglion efferents to paranasal sinuses and nasal mucosa in man. *Cells Tissues Organs*, *175*(4), 223-228.

Russo, A., Tessitore, A., Giordano, A., Corbo, D., Marcuccio, L., De Stefano, M., ... & Tedeschi, G. (2012). Executive resting-state network connectivity in migraine without aura. *Cephalalgia*, *32*(14), 1041-1048.

Salomons, T. V., Johnstone, T., Backonja, M. M., Shackman, A. J., & Davidson, R. J. (2007). Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex. *Journal of cognitive neuroscience*, *19*(6), 993-1003.

Sances, G., Galli, F., Anastasi, S., Ghiotto, N., De Giorgio, G., Guidetti, V., ... & Nappi, G. (2010). Medication-Overuse Headache and Personality: A Controlled Study by Means of the MMPI-2. *Headache: The Journal of Head and Face Pain*, *50*(2), 198-209.

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Current opinion in neurobiology*, *7*(2), 191-197.

Schwedt, T. J., Schlaggar, B. L., Mar, S., Nolan, T., Coalson, R. S., Nardos, B., ... & Larson-Prior, L. J. (2013). Atypical Resting-State Functional Connectivity of Affective Pain Regions in Chronic Migraine. *Headache: The Journal of Head and Face Pain*, *53*(5), 737-751.

Schwedt, T. J., Chong, C. D., Chiang, C. C., Baxter, L., Schlaggar, B. L., & Dodick, D. W. (2014a). Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. *Cephalalgia*, *34*(12), 947-958

Schwedt, T. J., Larson-Prior, L., Coalson, R. S., Nolan, T., Mar, S., Ances, B. M., ... & Schlaggar, B. L. (2014b). Allodynia and descending pain modulation in migraine: a resting state functional connectivity analysis. *Pain medicine*, *15*(1), 154-165.

Schweinhardt, P., Glynn, C., Brooks, J., McQuay, H., Jack, T., Chessell, I., ... & Tracey, I. (2006). An fMRI study of cerebral processing of brush-evoked allodynia in neuropathic pain patients. *Neuroimage*, *32*(1), 256-265.

Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H., & Bushnell, M. C. (2009). The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. *The Journal of neuroscience*, *29*(15), 4882-4887.

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of general psychiatry*, *65*(2), 220-231.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience*, *27*(9), 2349-2356.

Seminowicz, D. A., & Davis, K. D. (2007). Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. *Journal of neurophysiology*, *97*(5), 3651-3659.

Seminowicz, D. A., Wideman, T. H., Naso, L., Hatami-Khoroushahi, Z., Fallatah, S., Ware, M. A., ... & Stone, L. S. (2011). Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *The Journal of neuroscience*, *31*(20), 7540-7550.

Seminowicz, D. A., Shpaner, M., Keaser, M. L., Krauthamer, G. M., Mantegna, J., Dumas, J. A., ... & Naylor, M. R. (2013). Cognitive-behavioral therapy increases

prefrontal cortex gray matter in patients with chronic pain. *The Journal of Pain*, *14*(12), 1573-1584.

Seo, J. G., & Park, S. P. (2015). Validation of the Patient Health Questionnaire-9 (PHQ-9) and PHQ-2 in patients with migraine. *The journal of headache and pain*, *16*(1), 1.

Shehzad, Z., Kelly, A. C., Reiss, P. T., Gee, D. G., Gotimer, K., Uddin, L. Q., ... & Petkova, E. (2009). The resting brain: unconstrained yet reliable. *Cerebral cortex*, *19*(10), 2209-2229.

Shin, H. E., Park, J. W., Kim, Y. I., & Lee, K. S. (2008). Headache Impact Test-6 (HIT-6) scores for migraine patients: their relation to disability as measured from a headache diary. *Journal of Clinical Neurology*, *4*(4), 158-163.

Sluder, G. (1909). *The anatomical and clinical relations of the sphenopalatine (Meckel's) ganglion to the nose and its accessory sinuses*. AR Elliott Publishing Company.

Song, X. W., Dong, Z. Y., Long, X. Y., Li, S. F., Zuo, X. N., Zhu, C. Z., ... & Zang, Y. F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PloS one*, *6*(9), e25031.

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of cognitive neuroscience*, *22*(6), 1112-1123.

Spreng, R. N. (2012). The fallacy of a "task-negative" network. *Frontiers in psychology*, *3*, 145.

Stankewitz, A., Schulz, E., & May, A. (2013). Neuronal correlates of impaired habituation in response to repeated trigemino-nociceptive but not to olfactory input in migraineurs: an fMRI study. *Cephalalgia*, *33*(4), 256-265.

Suzuki, N., & Hardebo, J. E. (1992). The cerebrovascular parasympathetic innervation. *Cerebrovascular and brain metabolism reviews*, *5*(1), 33-46.

Tagliazucchi, E., Balenzuela, P., Fraiman, D., & Chialvo, D. R. (2010). Brain resting state is disrupted in chronic back pain patients. *Neuroscience letters*, *485*(1), 26-31.

Tessitore, A., Russo, A., Giordano, A., Conte, F., Corbo, D., De Stefano, M., ... & Tedeschi, G. (2013). Disrupted default mode network connectivity in migraine without aura. *The journal of headache and pain*, *14*(1), 1.

Tessitore, A., Russo, A., Conte, F., Giordano, A., De Stefano, M., Lavorgna, L., ... & Tedeschi, G. (2015). Abnormal Connectivity Within Executive Resting-State Network in Migraine With Aura. *Headache: The Journal of Head and Face Pain*, *55*(6), 794-805.

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, *55*(3), 377-391.

Valeriani, M., De Tommaso, M., Restuccia, D., Le Pera, D., Guido, M., Iannetti, G. D., ... & Tonali, P. (2003). Reduced habituation to experimental pain in migraine patients: a CO 2 laser evoked potential study. *Pain*, *105*(1), 57-64.

Van Dijk, K. R., & Drzezga, A. (2014). The Default Network of the Brain. In *PET and SPECT in Neurology* (pp. 169-181). Springer Berlin Heidelberg.

Verdejo-García, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society*, *12*(03), 405-415.

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral cortex*, *10*(3), 318-325.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology*, *47*, 3-13.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., ... & Cohen, J. D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science*, *303*(5661), 1162-1167.

Weissman-Fogel, I., Moayedi, M., Tenenbaum, H. C., Goldberg, M. B., Freeman, B. V., & Davis, K. D. (2011). Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. *PAIN*®, *152*(2), 384-396.

Wiech, K., Kalisch, R., Weiskopf, N., Pleger, B., Stephan, K. E., & Dolan, R. J. (2006). Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *The Journal of neuroscience*, *26*(44), 11501-11509.

Williams, A. E., Heitkemper, M., Self, M. M., Czyzewski, D. I., & Shulman, R. J. (2013). Endogenous inhibition of somatic pain is impaired in girls with irritable bowel syndrome compared with healthy girls. *The Journal of Pain*, *14*(9), 921-930.

Windsor, R. E., & Jahnke, S. (2004). Sphenopalatine ganglion blockade: a review and proposed modification of the transnasal technique. *Pain Physician*, *7*(2), 283-286.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage*, *92*, 381-397.

Wise, R. A. (2009). Roles for nigrostriatal—not just mesocorticolimbic—dopamine in reward and addiction. *Trends in neurosciences*, *32*(10), 517-524.

Wood, P. B., Schweinhardt, P., Jaeger, E., Dagher, A., Hakyemez, H., Rabiner, E. A., ... & Chizh, B. A. (2007). Fibromyalgia patients show an abnormal dopamine response to pain. *European Journal of Neuroscience*, *25*(12), 3576-3582.

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, *152*(3), S2-S15.

Wotruba, D., Michels, L., Buechler, R., Metzler, S., Theodoridou, A., Gerstenberg, M., ... & Heekeren, K. (2013). Aberrant coupling within and across the default mode, task-positive, and salience network in subjects at risk for psychosis. *Schizophrenia bulletin*, sbt161.

Wrase, J., Schlagenhauf, F., Kienast, T., Wüstenberg, T., Bermpohl, F., Kahnt, T., ... & Heinz, A. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage*, *35*(2), 787-794.

Xue, T., Yuan, K., Zhao, L., Yu, D., Zhao, L., Dong, T., ... & Tian, J. (2012). Intrinsic brain network abnormalities in migraines without aura revealed in resting-state fMRI. *PloS one*, *7*(12), e52927.

Yang, Z., Xie, J., Shao, Y. C., Xie, C. M., Fu, L. P., Li, D. J., ... & Li, S. J. (2009). Dynamic neural responses to cue-reactivity paradigms in heroin-dependent users: An fMRI study. *Human brain mapping*, *30*(3), 766-775.

Yu, D., Yuan, K., Zhao, L., Zhao, L., Dong, M., Liu, P., ... & Deneen, K. M. (2012). Regional homogeneity abnormalities in patients with interictal migraine without aura: a resting-state study. *NMR in biomedicine*, *25*(5), 806-812.

Yuan, K., Zhao, L., Cheng, P., Yu, D., Zhao, L., Dong, T., ... & Liang, F. (2013). Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. *The Journal of Pain*, *14*(8), 836-844.

Zaman, J., Vlaeyen, J. W., Van Oudenhove, L., Wiech, K., & Van Diest, I. (2015). Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain. *Neuroscience & Biobehavioral Reviews*, *51*, 118-125.

Zappaterra, M., Guerzoni, S., Cainazzo, M. M., Ferrari, A., & Pini, L. A. (2011). Basal cutaneous pain threshold in headache patients. *The journal of headache and pain*, *12*(3), 303-310.

Zheng, Y., Watakabe, A., Takada, M., Kakita, A., Namba, H., Takahashi, H., ... & Nawa, H. (2009). Expression of ErbB4 in substantia nigra dopamine neurons of monkeys and humans. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(4), 701-706.

APPENDIX A: SUPPLEMENTAL METHODS

TABLE A.1: MNI coordinates for each network

DMN	L/R	X	Y	Z	TPN	L/R	X	Y	Z
Lateral Parietal	Left	-45	-67	37	Frontal Eye Fields	Left	-24	-13	52
	Right	45	-67	37		Right	24	-13	52
Medial Prefrontal		0	47	-2	Medial Temporal	Left	-45	-70	-2
						Right	45	-70	-2
Precuneus/PCC		0	-49	40	Intraparietal Sulcus	Left	-24	-58	46
						Right	24	-58	46
SN	**L/R**	**X**	**Y**		**ECN**	**L/R**	**X**	**Y**	
DLPFC	Left	-38	52	10	DLPFC	Left	-34	46	6
	Right	30	48	22		Right	46	46	14
VLPFC					VLPFC	Left	-32	54	-4
	Right	42	46	0		Right	34	56	-6
Frontal Pole	Left	-24	56	10	Dorsal Medial PFC		0	36	46
Orbital Frontal Insula	Left	-40	18	-12	Orbital Frontal insula	Left	-36	24	-10
	Right	42	10	-12					
Subcallosal Area/SLEA (Parolfactory)	Left	-28	4	-18	DLPFC/FEF	Left	-32	18	50
	Right	26	4	-20		Right	30	12	60
Supramarginal Gyrus (Parietal Operculum)	Left	-60	-40	40	Inferior Frontal Gyrus (Frontal Operculum)	Right	56	14	14
	Right	58	-40	30					
Temporal Pole	Left	-52	16	-14	Inferior Temporal	Right	58	-54	-16
	Right	52	20	-18					
Superior Temporal	Left	-62	-16	8	Lateral Parietal	Left	-48	-48	48
	Right	64	-38	6		Right	38	-56	44
SMA/preSMA	Left	-4	14	48	Anterior Thalamus	Left	-8	-2	8
	Right	6	8	58		Right	10	2	8
Dorsal ACC	Left	-6	18	30	Dorsal Caudate	Left	-16	-14	20
	Right	6	22	30		Right	12	14	4
Paracingulate		0	44	28	Ventromedial Caudate	Right	10	12	2
Periaqueductal gray	Left	-4	-24	-2					
Substantia Nigra	Left	-10	-14	-10					
	Right	8	-8	-14					
Ventral Striatum Pallidum	Left	-22	12	-6					
	Right	22	6	-2					
Hypothalamus	Left	-10	-14	-8					
	Right	6	-16	-6					
Dorsomedial Thalamus	Right	12	-18	6					

APPENDIX B: SUPPLEMENTAL RESULTS

TABLE B.1: Significant differences in average nodal connectivity strength for each CM group compared to their matched controls.

	CM Group vs Matched Controls	CM Group (Avg ± SD)	Matched Controls (Avg ± SD)	*p*-value
DMN				
Both CM Groups vs Controls				
Left Lateral Parietal	CM w/MOH	0.56 ± 0.21	0.67 ± 0.12	0.025
	CM w/o MOH	0.49 ± 0.23	0.70 ± 0.10	0.002*
CM w/MOH vs Controls only				
Medial Prefrontal	CM w/MOH	0.39 ± 0.16	0.51 ± 0.17	0.028
Right Lateral Parietal	CM w/MOH	0.54 ± 0.17	0.65 ± 0.20	0.046
CM w/o MOH vs Controls only				
Precuneus/PCC	CM w/o MOH	0.53 ± 0.19	0.67 ± 0.12	0.018
TPN				
Both CM Groups vs Controls				
Left Frontal Eye Fields	CM w/MOH	0.11 ± 0.16	0.25 ± 0.11	0.005*
	CM w/o MOH	0.11 ± 0.17	0.24 ± 0.12	0.010*
SN				
Both CM Groups vs Controls				
Left Ventral Striatum-Pallidum	CM w/MOH	0.05 ± 0.17	0.19 ± 0.11	0.011
	CM w/o MOH	0.1 ± 0.1	0.19 ± 0.11	0.010
Right Ventral Striatum-Pallidum	CM w/MOH	0.02 ± 0.16	0.17 ± 0.11	0.005*
	CM w/o MOH	0.06 ± 0.11	0.16 ± 0.12	0.006*
Left SN/VTA	CM w/MOH	-0.01 ± 0.13	0.11 ± 0.1	0.007*
	CM w/o MOH	0.01 ± 0.12	0.12 ± 0.1	0.003*
Right SN/VTA	CM w/MOH	-0.16 ± 0.14	-0.06 ± 0.13	0.033
	CM w/o MOH	-0.19 ± 0.13	-0.06 ± 0.13	0.008*
Left Hypothalamus	CM w/MOH	0.1 ± 0.15	0.2 ± 0.12	0.047
	CM w/o MOH	0.12 ± 0.14	0.22 ± 0.12	0.012
Right Hypothalamus	CM w/MOH	0.08 ± 0.16	0.17 ± 0.1	0.048
	CM w/o MOH	0.11 ± 0.12	0.19 ± 0.09	0.005*
Right Orbital Frontal insula	CM w/MOH	0.14 ± 0.17	0.29 ± 0.12	0.008*
	CM w/o MOH	0.18 ± 0.17	0.29 ± 0.13	0.020

	CM Group vs Matched Controls	CM Group (Avg ± SD)	Matched Controls (Avg ± SD)	*p*-value
SN				
CM w/MOH vs Controls only				
Left Frontal Pole	CM w/MOH	-0.12 ± 0.14	0 ± 0.17	0.035
Right Supramarginal Gyrus	CM w/MOH	-0.01 ± 0.14	0.12 ± 0.11	0.009*
Left Supramarginal Gyrus	CM w/MOH	0.07 ± 0.12	0.15 ± 0.11	0.048
Left DLPFC	CM w/MOH	0 ± 0.16	0.12 ± 0.12	0.020
Right DLPFC	CM w/MOH	-0.06 ± 0.14	0.06 ± 0.17	0.033
Right VLPFC	CM w/MOH	-0.04 ± 0.16	0.11 ± 0.13	0.006*
Left SMA/preSMA	CM w/MOH	0.09 ± 0.15	0.2 ± 0.1	0.018
CM w/o MOH vs Controls only				
Left Subcallosal Area	CM w/o MOH	-0.04 ± 0.21	0.1 ± 0.17	0.026
Right Subcallosal Area	CM w/o MOH	0.06 ± 0.22	0.2 ± 0.15	0.015
Left Dorsal ACC	CM w/o MOH	0.19 ± 0.09	0.25 ± 0.13	0.030
Right Dorsal ACC	CM w/o MOH	0.19 ± 0.09	0.26 ± 0.12	0.013
Left Orbital Frontal insula**	CM w/o MOH	0.2 ± 0.15	0.27 ± 0.13	0.035
Right Superior Temporal**	CM w/o MOH	0.02 ± 0.2	0.12 ± 0.17	0.034
Left Temporal Pole	CM w/o MOH	0.06 ± 0.14	0.16 ± 0.17	0.041
ECN				
Both CM Groups vs Controls				
Left Lateral Parietal	CM w/MOH	0.11 ± 0.08	0.22 ± 0.08	<0.001*
	CM w/o MOH	0.12 ± 0.1	0.23 ± 0.08	0.003*
Right Inferior Frontal Gyrus	CM w/MOH	-0.05 ± 0.15	0.11 ± 0.11	<0.001*
	CM w/o MOH	0.01 ± 0.16	0.11 ± 0.12	0.030
Right VLPFC	CM w/MOH	0.09 ± 0.1	0.19 ± 0.08	0.001*
	CM w/o MOH	0.08 ± 0.1	0.2 ± 0.08	0.002*
Left VLPFC	CM w/MOH	0.08 ± 0.12	0.2 ± 0.08	0.001*
	CM w/o MOH	0.11 ± 0.11	0.2 ± 0.08	0.014
Right DLPFC/FEF	CM w/MOH	0.07 ± 0.13	0.17 ± 0.12	0.032
	CM w/o MOH	0.01 ± 0.15	0.14 ± 0.11	0.022
CM w/MOH vs Controls only				
Left DLPFC**	CM w/MOH	0.03 ± 0.12	0.17 ± 0.09	0.001*
Dorsal Medial PFC	CM w/MOH	0.12 ± 0.17	0.23 ± 0.11	0.032
Left Orbital Frontal insula	CM w/MOH	-0.01 ± 0.12	0.09 ± 0.12	0.017
Left Anterior Thalamus**	CM w/MOH	0.06 ± 0.11	0.17 ± 0.12	0.007*
Right Anterior Thalamus	CM w/MOH	0.09 ± 0.11	0.17 ± 0.12	0.045
Right Dorsal Caudate	CM w/MOH	-0.02 ± 0.15	0.07 ± 0.12	0.044
Right Ventromedial Caudate	CM w/MOH	0.01 ± 0.13	0.09 ± 0.1	0.031

	CM Group vs Matched Controls	CM Group (Avg ± SD)	Matched Controls (Avg ± SD)	*p*-value
CM w/o MOH vs Controls only				
Left DLPFC/FEF	CM w/o MOH	0.11 ± 0.09	0.18 ± 0.09	0.008*
Right DLPFC**	CM w/o MOH	0.07 ± 0.09	0.15 ± 0.11	0.029

*$p<0.01$
**borderline significant in the other CM comparison group (see Chapter 3.3)
NOTE: Statistical differences determined using a one-tailed t-test with a threshold of $p<0.05$

TABLE B.2: Significant differences of intranetwork connections for each CM group vs their set of age matched controls.

Intranetwork connection	CM Group vs Controls	CM Group (Avg ± SD)	Controls (Avg ± SD)	*p*-value
DMN				
CM w/o MOH vs Controls only				
Left Lateral Parietal x Precuneus/PCC	CM w/o MOH	0.49 ± 0.30	0.75 ± 0.18	0.003
TPN				
CM w/o MOH vs Controls only				
Left FEF x Right Intraparietal Sulcus	CM w/o MOH	0.17 ± 0.21	0.35 ± 0.14	0.006
SN				
Both CM Groups vs Controls				
Right DLPFC x Right Supramarginal Gyrus	CM w/MOH	0.29 ± 0.20	0.47 ± 0.15	0.003
	CM w/o MOH	0.22 ± 0.20	0.47 ± 0.16	0.001
Right DLPFC x Right VLPFC	CM w/MOH	0.48 ± 0.23	0.73 ± 0.19	0.003
	CM w/o MOH	0.47 ± 0.15	0.71 ± 0.20	0.001
Right VLPFC x Right SMA/preSMA	CM w/MOH	0.28 ± 0.20	0.46 ± 0.15	0.006
	CM w/o MOH	0.29 ± 0.18	0.46 ± 0.16	0.002
CM w/MOH vs Controls only				
Left Frontal Pole x Left Superior Temporal*	CM w/MOH	0.0 ± 0.17	0.20 ± 0.22	0.007
Left Frontal Pole x Right Superior Temporal	CM w/MOH	-0.01 ± 0.18	0.18 ± 0.19	0.007
Left Frontal Pole x Left Ventral Striatum/Pallidum*	CM w/MOH	0.06 ± 0.18	0.23 ± 0.16	0.008
Left SMA/preSMA x Right Orbital Frontal insula	CM w/MOH	0.47 ± 0.24	0.67 ± 0.14	0.008
Left SMA/preSMA x Right Ventral Striatum/Pallidum	CM w/MOH	0.23 ± 0.18	0.41 ± 0.17	0.007
Left SMA/preSMA x Left Ventral Striatum/Pallidum	CM w/MOH	0.26 ± 0.15	0.45 ± 0.17	0.002
Left SMA/preSMA x Right VLPFC	CM w/MOH	0.14 ± 0.21	0.39 ± 0.22	0.004

Intranetwork connection	CM Group vs Controls	CM Group (Avg ± SD)	Controls (Avg ± SD)	*p*-value
Right DLPFC x Right SMA/preSMA	CM w/MOH	0.29 ± 0.17	0.48 ± 0.19	0.006
Left DLPFC x Left Ventral Striatum/Pallidum	CM w/MOH	0.16 ± 0.15	0.34 ± 0.15	0.002
Left DLPFC x Right Ventral Striatum/Pallidum	CM w/MOH	0.12 ± 0.15	0.33 ± 0.16	<0.001
Left DLPFC x Right Orbital Frontal insula*	CM w/MOH	0.20 ± 0.19	0.39 ± 0.21	0.008
Left DLPFC x Dorsomedial Thalamus	CM w/MOH	0.14 ± 0.19	0.30 ± 0.13	0.008
Left DLPFC x Left Dorsal ACC	CM w/MOH	0.57 ± 0.26	0.79 ± 0.14	0.004
Right VLPFC x Right Orbital Frontal insula	CM w/MOH	0.21 ± 0.17	0.42 ± 0.23	0.007
Right VLPFC x Left Supramarginal Gyrus	CM w/MOH	0.30 ± 0.26	0.58 ± 0.29	0.006
Right VLPFC x Right Supramarginal Gyrus	CM w/MOH	0.33 ± 0.21	0.62 ± 0.19	<0.001
Left Supramarginal Gyrus x Right Ventral Striatum/Pallidum	CM w/MOH	0.17 ± 0.15	0.30 ± 0.13	0.009
Right Supramarginal Gyrus x Left Hypothalamus	CM w/MOH	0.21 ± 0.14	0.33 ± 0.09	0.004
Right Ventral Striatum/Pallidum x Dorsomedial Thalamus	CM w/MOH	0.24 ± 0.18	0.41 ± 0.18	0.009
Right Ventral Striatum/Pallidum x Right Sup Temporal	CM w/MOH	0.06 ± 0.19	0.26 ± 0.19	0.005
Left SN/VTA x Left Orbital Frontal insula	CM w/MOH	0.18 ± 0.19	0.36 ± 0.16	0.006
Right SN/VTA x Left Hypothalamus	CM w/MOH	0.11 ± 0.21	0.35 ± 0.22	0.003
Right SN/VTA x Right Hypothalamus	CM w/MOH	0.07 ± 0.23	0.32 ± 0.21	0.003
Right SN/VTA x Left Supramarginal Gyrus	CM w/MOH	-0.01 ± 0.14	0.15 ± 0.15	0.002
CM w/o MOH vs Controls only				
Left Subcallosal Area x Left Frontal Pole*	CM w/o MOH	-0.03 ± 0.17	0.15 ± 0.15	0.003
Left Subcallosal Area x Left Temporal Pole	CM w/o MOH	0.26 ± 0.21	0.45 ± 0.20	0.003
Left Subcallosal Area x Left SN/VTA	CM w/o MOH	0.17 ± 0.17	0.39 ± 0.21	0.006
Left Subcallosal Area x Right SN/VTA	CM w/o MOH	0.10 ± 0.21	0.36 ± 0.15	<0.001
Left Subcallosal Area x Right Subcallosal Area	CM w/o MOH	0.55 ± 0.24	0.80 ± 0.23	0.007
Right Subcallosal Area x Right Temporal Pole	CM w/o MOH	0.29 ± 0.24	0.48 ± 0.23	0.009
Right Subcallosal Area x Right Ventral Striatum/Pallidum	CM w/o MOH	0.41 ± 0.18	0.57 ± 0.14	0.009
Left Superior Temporal x Left Temporal Pole	CM w/o MOH	0.48 ± 0.26	0.71 ± 0.22	0.0099
Right Superior Temporal x Left Temporal Pole	CM w/o MOH	0.39 ± 0.29	0.57 ± 0.27	0.009
Right Orbital Frontal insula x Right Temporal Pole	CM w/o MOH	0.64 ± 0.24	0.89 ± 0.25	0.002

Intranetwork connection	CM Group vs Controls	CM Group (Avg ± SD)	Controls (Avg ± SD)	*p*-value
Left Orbital Frontal insula x Left Ventral Striatum/Pallidum	CM w/o MOH	0.37 ± 0.13	0.51 ± 0.13	0.005
Left Orbital Frontal insula x Right Ventral Striatum/Pallidum	CM w/o MOH	0.33 ± 0.12	0.46 ± 0.12	0.005
Right VLPFC x Right Hypothalamus	CM w/o MOH	0.20 ± 0.15	0.30 ± 0.13	0.007
Right Dorsal ACC x Right Orbital Frontal insula	CM w/o MOH	0.51 ± 0.17	0.67 ± 0.21	0.002
ECN				
Both CM Groups vs Controls				
Left DLPFC/FEF x Dorsal Medial PFC	CM w/MOH	0.53 ± 0.31	0.79 ± 0.19	0.006
	CM w/o MOH	0.56 ± 0.23	0.82 ± 0.19	<0.001
Left Anterior Thalamus x Right VLPFC	CM w/MOH	0.13 ± 0.14	0.25 ± 0.14	0.008
	CM w/o MOH	0.10 ± 0.12	0.25 ± 0.14	0.008
CM w/MOH vs Controls only				
Left Anterior Thalamus x Right DLPFC	CM w/MOH	0.07 ± 0.17	0.29 ± 0.16	<0.001
Left Anterior Thalamus x Left DLPFC	CM w/MOH	0.16 ± 0.13	0.32 ± 0.14	0.001
Right Anterior Thalamus x Left DLPFC	CM w/MOH	0.14 ± 0.12	0.27 ± 0.16	0.007
Right Inferior Frontal Gyrus x Left Anterior Thalamus	CM w/MOH	0.11 ± 0.21	0.38 ± 0.22	0.002
Right Inferior Frontal Gyrus x Right Anterior Thalamus	CM w/MOH	0.16 ± 0.23	0.38 ± 0.21	0.005
Right Inferior Frontal Gyrus x Left DLPFC	CM w/MOH	0.08 ± 0.15	0.37 ± 0.19	<0.001
Right Inferior Frontal Gyrus x Right DLPFC	CM w/MOH	0.39 ± 0.24	0.64 ± 0.16	<0.001
Right Inferior Frontal Gyrus x Left VLPFC	CM w/MOH	0.05 ± 0.19	0.24 ± 0.17	0.005
Right Inferior Frontal Gyrus x Right VLPFC	CM w/MOH	0.16 ± 0.18	0.30 ± 0.14	0.003
Right Inferior Frontal Gyrus x Right Ventromedial Caudate	CM w/MOH	0.03 ± 0.23	0.24 ± 0.10	0.001
Right Inferior Frontal Gyrus x Right Dorsal Caudate	CM w/MOH	0.04 ± 0.20	0.21 ± 0.17	0.006
Left VLPFC x Right VLPFC	CM w/MOH	0.57 ± 0.28	0.83 ± 0.23	0.005
Left Lateral Parietal x Left DLPFC	CM w/MOH	0.34 ± 0.24	0.61 ± 0.28	0.004
Left Lateral Parietal x Left VLPFC	CM w/MOH	0.45 ± 0.25	0.71 ± 0.25	0.007
CM w/o MOH vs Controls only				
Left Lateral Parietal x Right VLPFC	CM w/o MOH	0.35 ± 0.19	0.57 ± 0.22	0.002
Left DLPFC/FEF x Right Inferior Temporal	CM w/o MOH	0.19 ± 0.11	0.30 ± 0.10	0.004
Left DLPFC/FEF x Right DLPFC/FEF	CM w/o MOH	0.22 ± 0.17	0.43 ± 0.24	0.0095

*connection is correlated with a clinical feature (Hit-6, triptan use, PHQ-9, years with CM)
NOTE: Statistical differences determined using a one-tailed t-test with a threshold of p<0.01

TABLE B.3: Significantly different nodal connectivity strengths in a network when comparing baseline to 30-minute and 6 weeks post first treatment.

Baseline vs 30 minutes				
Network	**Node**	**Baseline (Avg ± SD)**	**30min (Avg ± SD)**	***p*-value**
SN	Left Frontal Pole	-0.15 ± 0.11	-0.12 ± 0.09	0.009
	Right SN/VTA	-0.16 ± 0.11	-0.12 ± 0.08	0.009
ECN	Left VLPFC	0.06 ± 0.13	0.11 ± 0.07	0.005
	Right VLPFC	0.07 ± 0.09	0.11 ± 0.04	0.048
	Left DLPFC/FEF	-0.02 ± 0.11	0.04 ± 0.09	0.041
	Right DLPFC/FEF	0.06 ± 0.07	0.13 ± 0.07	0.013
	Left DLPFC	0.02 ± 0.13	0.08 ± 0.11	0.0096
	Right DLPFC	0.04 ± 0.13	0.09 ± 0.11	0.026
	Left Anterior Thalamus	0.02 ± 0.10	0.13 ± 0.06	0.022
	Right Lateral Parietal	0.04 ± 0.07	0.10 ± 0.10	0.049
Baseline vs 6 Weeks				
Network	**Node**	**Baseline (Avg ± SD)**	**6 weeks (Avg ± SD)**	***p*-value**
DMN	Right Lateral Parietal	0.60 ± 0.17	0.64 ± 0.16	0.019
	Precuneus/PCC	0.60 ± 0.20	0.65 ± 0.18	0.036
SN	Left Frontal Pole	-0.16 ± 0.11	-0.09 ± 0.15	0.027
	Right SN/VTA	-0.18 ± 0.11	-0.16 ± 0.10	0.034
ECN	Left VLPFC	0.05 ± 0.13	0.12 ± 0.13	0.004
	Left DLPFC	0.00 ± 0.12	0.08 ± 0.13	0.004
	Left DLPFC/FEF	-0.02 ± 0.11	0.04 ± 0.10	0.009
	Right DLPFC/FEF	0.04 ± 0.07	0.08 ± 0.10	0.004

NOTE: Statistical differences determined using a one-tailed t-test with a threshold of $p<0.05$

TABLE B.4: Significantly different intranetwork connections strengths when comparing baseline to 30-minute and 6-weeks post treatment.

Baseline vs 30 minutes **SN**	**Before TX** **(Avg ± SD)**	**After TX** **(Avg ± SD)**	***p*-value**
Left Frontal Pole x Right Hypothalamus	0.07 ± 0.15	0.14 ± 0.12	0.046
Left Frontal Pole x Right Ventral Striatum Pallidum	0.04 ± 0.17	0.1 ± 0.12	0.041
Left Frontal Pole x Right Orbital Frontal insula	0.16 ± 0.18	0.23 ± 0.08	0.019
Right DLPFC x Right Orbital Frontal insula	0.21 ± 0.19	0.3 ± 0.13	0.009
Left PAG x Right Orbital Frontal insula	0.33 ± 0.2	0.36 ± 0.16	0.019
ECN			
Left DLPFC x Right DLPFC/FEF	0.21 ± 0.22	0.33 ± 0.25	0.019
Left DLPFC x Right Anterior Thalamus	0.16 ± 0.12	0.24 ± 0.08	0.021
Left DLPFC x Left Anterior Thalamus	0.17 ± 0.12	0.3 ± 0.1	0.010
Right DLPFC x Left Anterior Thalamus	0.07 ± 0.19	0.15 ± 0.09	0.028
Right DLPFC/FEF x Left VLPFC	0.25 ± 0.15	0.34 ± 0.12	0.010
Baseline vs 6 Weeks **DMN**	**Before TX** **(Avg ± SD)**	**After TX** **(Avg ± SD)**	***p*-value**
Precuneus/PCC x Right Lateral Parietal	0.72 ± 0.32	0.79 ± 0.29	0.005
Precuneus/PCC x Medial PFC	0.47 ± 0.19	0.55 ± 0.20	0.024
SN			
Left Frontal Pole x Left Orbital Frontal insula	0.03 ± 0.18	0.11 ± 0.21	0.046
Left Frontal Pole x Right Orbital Frontal insula	0.15 ± 0.18	0.26 ± 0.28	0.012
Left Frontal Pole x Left Ventral Striatum Pallidum	0.02 ± 0.19	0.14 ± 0.19	0.022
Left Frontal Pole x Right Ventral Striatum Pallidum	0.05 ± 0.17	0.22 ± 0.19	0.021
Left Frontal Pole x Right SMA/preSMA	0.25 ± 0.25	0.32 ± 0.3	0.038
Left Frontal Pole x Right DLPFC	0.43 ± 0.15	0.62 ± 0.2	0.032
Right SN/VTA x Left DLPFC	-0.1 ± 0.12	0.03 ± 0.17	0.040
Right SN/VTA x Right Temporal Pole	0.00 ± 0.23	0.08 ± 0.2	0.020
Left Superior Temporal x Right Supramarginal Gyrus**	0.19 ± 0.33	0.13 ± 0.25	0.030
ECN			
Left DLPFC x Left VLPFC	0.6 ± 0.14	0.61 ± 0.23	0.019
Left DLPFC x Right Anterior Thalamus	0.17 ± 0.11	0.27 ± 0.16	0.027
Left DLPFC x Right Ventromedial Caudate	0.15 ± 0.12	0.2 ± 0.17	0.049
Left DLPFC x Right DLPFC/FEF	0.2 ± 0.21	0.34 ± 0.23	0.021
Right DLPFC/FEF x Left VLPFC	0.24 ± 0.15	0.29 ± 0.18	0.043
Right DLPFC/FEF x Right Dorsal Caudate	0.01 ± 0.14	0.12 ± 0.18	0.028
Left DLPFC/FEF x Right Ventromedial Caudate	0 ± 0.14	0.04 ± 0.14	0.011
Left DLPFC/FEF x Right Anterior Thalamus	0.03 ± 0.17	0.18 ± 0.17	0.028

**Controls were non-significantly lower on average when comparing CM to controls
NOTE: Statistical differences determined using a two-tailed t-test with a threshold of $p<0.05$