DEFAULT MODE NETWORK FUNCTIONAL CONNECTIVITY AND ITS RELATIONSHIP WITH PAIN PROCESSING NETWORKS VIA LIDOCAINE

By

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To my amazing family for their endless support and encouragement
Les quiero y adoro como la vaca quiere al toro

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CCN	Cognitive Control Network
DMN	Default Mode Network
FNC	Functional Network Connectivity
IBS	Irritable Bowel Syndrome
NH	Natural History
RL	Rectal Lidocaine
SMN	Sensorimotor Network

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The default mode network (DMN), a group of brain regions implicated in passive thought processes, has been proposed as a potentially informative neural marker to aid in novel treatment development. However, the effect of current analgesics on DMN functional connectivity and its temporal relationship (i.e. functional network connectivity, FNC) with pain-related networks has not been explored, and therefore such research is important to inform whether this network is in fact sensitive to analgesic effects. We examined whether DMN connectivity and FNC with pain-related networks changed under lidocaine in irritable bowel syndrome (IBS) patients. Eleven females with IBS underwent a rectal balloon distension paradigm during fMRI in two conditions (i.e., natural history and lidocaine). Results showed increased DMN connectivity with pain-related regions during natural history and increased within-network connectivity of DMN structures under lidocaine. Further, there was a significantly greater lag time between two networks involved in cognitive and affective processes of pain, comparing lidocaine to natural history. These findings suggest that 1) DMN plasticity is sensitive to analgesic effects and 2) reduced pain ratings via analgesia reflect less DMN functional

connectivity with pain-related regions. Findings show potential implications of this network as an approach for understanding clinical pain management techniques.

CHAPTER 1
INTRODUCTION

Chronic pain is a major public health concern in the US, affecting approximately 100 million adults and costing about $635 billion per year in productivity loss and healthcare expenses.[24] To better understand mechanisms underlying the sensory, affective, and cognitive processes involved in chronic pain, research has increasingly focused on neuroimaging paradigms exploring functional connections between brain regions. Alterations in functional brain connectivity have been found across a variety of chronic pain populations.[9, 39, 41] Although early fMRI studies of chronic pain focused on co-activated brain regions during specific tasks, such as the processing of experimental pain, recent studies have examined how activity among task-negative neural networks influences the experience of chronic and experimental pain. One such network, the default mode network (DMN), has been hypothesized to potentially help highlight the complexities of pain mechanisms.[12] Recent reviews have also proposed the DMN as a potential marker of treatment effects for chronic pain, with implications for analgesic development.[2, 36, 49] However, there is little research on how current analgesics affect neural activity in the DMN or its temporal relationship (i.e. functional network connectivity, FNC) with pain-related neural networks.

The Default Mode Network (DMN)

The DMN is a set of cortical regions that have greater coherence of neural activity when an individual is not actively engaged in a goal-directed task.[21] The function of the DMN has been described as underlying processes in which an individual is awake and alert, but not actively engaged in a task that necessitates attention. Such processes include self-referential mental activity[23] and mind-wandering[8]. Further,

because patients under anesthesia show DMN activity, it has been proposed to be a network that is representative of baseline brain activity.[14] In healthy participants, common regions of the DMN include the posterior cingulate cortex (PCC), the ventral anterior cingulate cortex, and the medial prefrontal cortex (mPFC). Across a variety of clinical populations, however, studies have demonstrated altered functional connectivity of the DMN, suggesting that idiosyncratic patterns of the DMN might provide information about neural mechanisms underlying pathology and treatment effects.[2, 20]

DMN Functional Connectivity in Chronic Pain Patients

Research has shown that chronic pain is associated with abnormal connectivity patterns among DMN regions. Tagliazucchi and colleagues[44] found increased connectivity of DMN structures (orbitofrontal gyrus, right and left angular gyri) with the insular cortex in chronic back pain patients, suggestive of an interaction between persistent pain and emotional processes during rest. Increased DMN functional connectivity with pain- and emotion-related brain regions have also been reported in fibromyalgia and irritable bowel syndrome patients (IBS).[36, 45]

Conversely, another study showed that chronic back pain patients had decreased functional connectivity of the DMN during deactivation in an attention task, suggestive of persistent neuroplastic changes in basal brain activity caused by chronic pain.[1] Cauda and colleagues[7] also found decreased DMN functional connectivity in patients with diabetic neuropathy compared to controls. None of these studies, however, have reported the temporal relationship (i.e. FNC) between the DMN and pain-related networks, which might provide some insight about the aberrant DMN connectivity shown in chronic pain patients.

Temporal Relationships between the DMN and Pain-Related Networks

There has been one study that reported on the FNC between the DMN and pain-related neural networks. Otti and colleagues[37] showed that patients with somatoform pain disorder had two distinct pain-related networks [cingular-insular (affective reactions, CIN) and sensorimotor networks (sensory-discriminative processing, SMN)] and two subsystems of the DMN [anterior DMN (self-referential processing and cognitive control of emotions, aDMN) and posterior DMN (memory, pDMN)]. While the overall FNC pattern of these networks was not significantly different between the somatoform pain disorder and control groups, the authors suggested that their results might have been affected by the use of psychotropic medications in the patients with somatoform pain disorder because medication has been shown to alter DMN connectivity in clinical populations.

The Effects of Treatment on DMN Connectivity

Although there is little known about the effects of analgesics on DMN functional connectivity in chronic pain patients, studies across a variety of clinical populations have shown modulation of DMN connectivity as a result of medication. Patients with schizophrenia showed increases in DMN connectivity with the ventromedial prefrontal cortex while taking olanzapine, suggestive of restoration to the brain's temporal characteristics.[40] Additionally, patients with ADHD showed improved suppression of the DMN during an attention task under psychostimulants.[38] In patients with Alzhiemer's disease, increased DMN connectivity with the precuneus under memantine treatment has been shown, providing additional evidence for neuroplasticity among DMN brain regions following treatment.[29]

Few studies have reported treatment effects on abnormal DMN activity resulting from chronic pain. Therefore, the present study examined the effects of a peripheral analgesic, intrarectal lidocaine, has on DMN coherence in patients with IBS. Additionally, we examined the temporal relationship between the DMN and pain-related networks to determine whether the administration of lidocaine altered the FNC between these networks. Based on studies that reported the restorative effects of medication on the DMN in other clinical populations, we hypothesized that: 1) following the administration of a peripheral analgesic, the coherence of DMN activity would be more consistent with that typically seen in healthy controls; 2), we also hypothesized that the within-subject design of this protocol for clinically relevant pain would allow us to identify significant changes in FNC between baseline (i.e., natural history) and analgesic conditions, because lidocaine was expected to decrease visceral pain and subsequently alter the FNC between the DMN and neural networks associated with pain.

CHAPTER 2
METHODS

The present study is a secondary data analysis from a study investigating the effects of rectal lidocaine on pain in patients with irritable bowel syndrome (IBS). Although the original study was a double blind clinical trial involving three sessions of fMRI data collection (i.e., baseline, placebo, rectal lidocaine), only two of these conditions were included in the present analyses. The current study uses a within-subjects design to examine task-negative related functional brain connectivity during two conditions in which participants with IBS were exposed to a clinically relevant pain protocol (i.e., rectal distention). The first is a baseline, or natural history condition (NH), during which the rectal balloon was coated with a saline gel prior to insertion. In the second, rectal lidocaine (RL) condition, the rectal balloon was coated with lidocaine gel prior to insertion to produce peripherally induced analgesia. This study was approved by the University of Florida and Gainesville Veterans Administration Institutional Review Boards and performed at the University of Florida McKnight Brain Institute in Gainesville, FL. Prior to enrollment, all participants completed an informed consent form stating that they would receive either an active analgesic (i.e. lidocaine) or a placebo agent during the treatment sessions.

Participants

MRI data from 11 female patients with Irritable Bowel Syndrome (IBS) were used in this study (mean age = 31.26 years, SD = 7.55 years). Ethnically, eight participants were Caucasian, two were African American, and one was Hispanic. Inclusion criteria for the study was: 1) persistent spontaneous pain for at least six months, 2) a diagnosis of IBS based on ROME II criteria with the exclusion of organic disease,[27] 3) no history of

medical or psychological comorbidities other than those closely related to IBS, and 4) the discontinued use of pain medications, serotonin uptake inhibitors, serotonin antagonists or tricyclic antidepressants at the time of the study. All patients were required to fast 12 hours before each MRI session and self-administered one Fleets® enema (CB Fleet Co., Inc., Lynchberg, VA) at least two hours prior to the session, which was confirmed by the gastroenterologist who administered study materials.

Experimental Materials

To induce visceral pain, we used a clinically relevant rectal balloon distention paradigm.[46] A visceral stimulator (Metronics, Minn., MN) delivered distensions to the rectal balloon at a rapid rate (870mL/min) and constant pressure plateau between 10 and 55mmHg. Pressure, volume, and compliance measures were simultaneously monitored and recorded.[32, 35, 50] The balloon was a 500ml polyethylene bag secured on a rectal catheter (Zinetics Medical, Inc., Salt Lake City, UT) using unwaxed dental floss and parafilm (American National Can, Greenwich, CT) to ensure a tight seal. For both conditions, the balloon was lubricated (Surgilube, E fougera and CO, Melville, NY 11747) and placed into the rectum by a gastroenterologist. The balloon was inserted 4cm from the anal sphincter to stimulate approximately 4cm of the rectum during the inflation period. The gastroenterologist who performed study procedures was the physician with whom the majority of the patients normally consulted in the clinic. In contrast to the NH condition, which used a lubricating saline gel, during the RL condition, 300mg of lidocaine gel (Astra USA, Inc., Westborough, MA) was applied to the entire area of the rectum that would be distended.

Experimental Procedures

During each testing session, patients were greeted in the waiting room at the Gastroenterology Clinic, escorted to an examination room, and introduced to study procedures. Then, each patient's response to visceral stimuli was tested using different amounts of balloon distension pressure applied in ascending order (i.e., 10, 20, 30, 40, and 50mmHg). Patients rated their pain after each stimulus using a pain rating scale of 0 to 100, where 0 represented "no pain" and 100 represented "the most intense pain imaginable."[47] Once a pain rating of 40 or above was reached, the corresponding pressure was recorded for use during the fMRI scans. All patients were hyperalgesic (i.e., none were excluded).

Patients completed three MRI sessions with no more than one week between each session. The first session for all patients was the NH condition, during which they were informed that treatment would not be used. In the subsequent two sessions, the RL condition was counterbalanced with a placebo condition, wherein either lidocaine gel or saline gel was administered on a double blind basis. Prior to the start of scanning, patients were informed that they would receive either lidocaine or saline gel. The patients were not given any auditory or visual clues that they were to receive a stimulus. To maintain consistency in pain sensitivity across sessions, patients were only scanned on days when their spontaneous, ongoing abdominal pain ratings were at least 30.

Data Acquisition and Image Pre-Processing

All structural and functional MRI data were collected using a research-dedicated head scanner with a standard 8-channel RF head-coil (Siemens Allegra, 3.0T). Each MRI session included collection of a high-resolution 3D structural image, followed by 7 functional MRI (fMRI) scans. The high-resolution 3D anatomical images were acquired

using a T1-weighted MP-RAGE protocol with the following parameters: 128 1mm axial slices; repetition time (TR) = 2000ms, echo time (TE) = 4.13ms, flip angle (FA) = 8°, matrix = 256 x 256mm, field of view (FOV) = 24cm). Functional images were acquired from a T2-gradient echo planar imaging (EPI) sequence using 33 contiguous axial slices of the whole brain parallel to the anterior commissure–posterior commissure (AC–PC) plane. Additional parameters included: TR/TE = 2000ms/30ms, FA = 90°, FOV = 240 x 240mm, matrix = 64 x 64; 3.75mm^3 isotropic voxels with 0.4mm slice gap. The stimulus onset of all fMRI scans was TR time-locked to the onset of scan acquisition. Each scan lasted for 44s, during which the first 24s were a rest period followed by 20s of visceral pain caused by rectal distension. Immediately after each fMRI scan, patients provided ratings of pain and unpleasantness using a verbal rating (Figure 2-1).

To reduce saturation effects from an inhomogeneous B_0 field, the first two volumes of each functional run were discarded at the scanner and two additional volumes were discarded during preprocessing. Image preprocessing was carried out using AFNI (http://afni.nimh.nih.gov/afni/) and consisted of temporal concatenation of the fMRI scans for each subject, 3D motion correction (motion censor limit = 0.3mm per TR), spatial smoothing (FWHM = 4mm), slice scan time correction, and spatial normalization to a standardized MNI template.

To examine the possibility that movement artifacts might have on subsequent analyses, we examined the movement parameters and found that average displacement was less than the 2mm voxel dimension (NH = 1.615mm, RL = 1.675mm). Analysis of condition-related effects did not reveal any significant differences (NH =

0.124, RL = 0.129; $p > .05$) in movement, suggesting that observed condition-level differences in activation were not due to systematic differences in head movement.

Independent Component Analysis

The initial network analysis for this study was done with the Group ICA of fMRI Toolbox (GIFT v1.3b; http://icatb.sourceforge.net/) for Matlab v7. ICA is a data-driven statistical analysis technique that yields independent components (ICs), which isolate sources of variance within the data. Each IC represents a group of brain regions with synchronized activity over a unique temporal pattern (i.e., time course) and can be conceptualized as a neural network.[5] The GIFT procedure occurred in three stages, and involved 1a) reduction of data dimensionality and 1b) estimation of the optimal number of components using the MDL algorithm (22 were estimated), 2) estimation of group signal sources and reduction of mutual information among those sources, and 3) back reconstruction of group-level ICs to single-subject level.

Condition-Level Analyses

Following the ICA analysis, each participant's ICs, from both conditions were correlated with the DMN template provided by the GIFT toolbox to identify the IC that best represented the DMN. Once the IC representing the DMN in each condition was identified, we used NeuroElf (http://neuroelf.net/) to conduct a paired samples t-test to identify significant spatial differences in the ICs representing the DMN in each condition (i.e., NH and RL). Differences in spatial patterns of the DMN comparing the conditions were considered significant at $p \leq 0.01$ (corrected for family-wise error) with a minimum cluster size of 30 contiguous voxels.

Functional Network Connectivity

Although each IC represents a group of brain regions that follows a specific temporal pattern over the course of the fMRI scan (i.e., time course), correlations can exist among the time courses of different ICs. In addition to producing a spatial map of each IC, GIFT outputs each IC's time course. This output shows a waveform, which represents fluctuations in the IC's activity over time, and correlations among the ICs' time courses are calculated based on the pattern of each IC's waveform. Moreover, temporal lags can be calculated to show whether there is a significant relationship between the onsets of the ICs' waveforms.[25] These temporal relationships can be assessed with the Functional Network Connectivity Toolbox (FNC; http://mialab.mrn.org/software /#fnc), an extension of GIFT.

For this study, we identified three distinct ICs related to processes in the experience of pain (i.e., sensation, affect, cognition) in addition to the DMN. These pain-related ICs were selected based on their inclusion of brain regions typically associated with each respective pain process. Using the FNC toolbox, we examined: 1) correlations between the ICs' time courses and 2) the amount of delay between time courses (i.e., lag values) in each condition. As Jafri and colleagues[25] described, we used a band-pass Butterworth filter between 0.03Hz and 0.37Hz on the ICA data, which was interpolated to detect sub TR condition-level differences in hemodynamic delay. All within-condition pairwise combinations were computed via the maximal lagged correlation algorithm, and tested using a one-sample t-test ($p < .05$). Between-condition differences in FNC were examined using a two-tailed paired-samples t-test ($p < .05$) and corrected for multiple corrections [False Discovery Rate (FDR)[17] = .05].

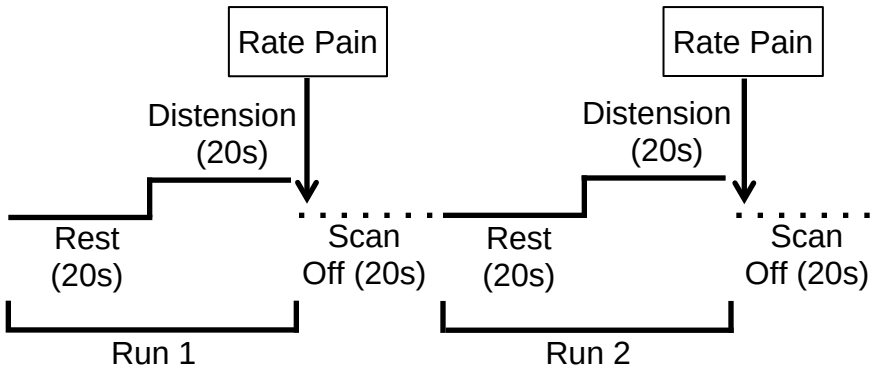

Figure 2-1.The fMRI scanning session consisted of seven 40 sec runs, with 20 sec of rest and 20 sec of rectal balloon distension. Pain ratings were collected at the end of each run, and participants were given 20 sec before the start of the subsequent run. An example of the first two runs is portrayed above.

CHAPTER 3
RESULTS

Pain Ratings

To examine whether the lidocaine gel resulted in the reduction of pain, we conducted a two-tailed paired-samples t-test of the patients' pain ratings collected during the fMRI sessions. There was a significant difference between pain ratings in the NH (M = 47.82, SD = 13.212) compared to the RL (M = 32.55, SD = 17.489) condition [$t(10) = 2.235$, $p < .05$]. Results confirm that rectal lidocaine significantly decreased the patients' average pain ratings in response to rectal distension.

Lidocaine-Related Changes in DMN Connectivity

Among the ICs identified by the GIFT toolbox, the default mode network (DMN) was readily detectable by its high correlation with the GIFT template of the DMN in both the NH and RL conditions (r = .36 and r = .40, respectively). A paired-samples t-test of the DMN spatial maps (i.e., Z score maps) revealed significant condition-level differences of the DMN spatial patterns (Figure 3-1). In comparing the NH and RL spatial maps of the DMN, significantly different regions were included in the map ($p \leq 0.05$, FDR ≤ 0.05, cluster threshold = 30 voxels). These significant differences imply more functional connectivity between the DMN and regions listed in Table 3-1. Compared to the RL condition, the spatial map of the DMN for the NH condition showed significant activity of the insula and precentral gyrus. Conversely, patients showed increased functional connectivity of the DMN with the superior temporal gyrus, middle temporal gyrus, angular gyrus, and inferior parietal lobule in the RL condition compared to NH.

Functional Network Connectivity of the Default Mode and Pain-Related Networks

In addition to the DMN, three ICs associated with discrete dimensions of pain (i.e. sensation, affect, and cognition) were identified in each condition. Specifically, we identified ICs representing: 1) a Sensorimotor Network (SMN), 2) an Insular Salience Network (ISN), and 3) a Cognitive Control Network (CCN). We included all four networks in subsequent FNC analyses to better understand how pain-related processes potentially interact and influence the coherence of the DMN. Tables 3-2 through 3-7 list the regions contained in each IC, based on condition, and each IC's time course can be seen in Figure 3-2.

Results of the FNC analyses showed significant within- and between-condition correlations for the four networks, demonstrating temporal relationships between these networks during pain processing. Figure 3-3 shows the overall pattern of the FNC within- and between-condition results. The arrows symbolize networks with significantly correlated temporal relationships, where A→B represents a relationship showing that network A precedes network B by a certain amount of time. In NH, significant temporal correlations emerged between DMN and all three pain-related networks (SMN, $p \leq .001$; ISN, $p \leq .001$; CCN, $p \leq .001$), with activity in pain-related networks preceding DMN activity (Figure 3-3a). Additionally, there were significant temporal relationships among the pain-related networks, so that SMN preceded ISN ($p < .001$) and CCN ($p < .001$), and ISN preceded CCN ($p < .001$). In the RL condition, significant relationships with similar lag times to NH were found between SMN→DMN ($p < .001$) and ISN→DMN [($p < .001$), Figure 3-3b)]. Although similar patterns were evident under RL, there were notable differences in the amount of temporal lag between multiple network pairs. Among pain-related networks, however, overall lag times in the RL condition were

longer compared to NH, with a significant difference in the lag time for the SMN→ISN relationship ($p < .001$). Additionally, the FNC analysis revealed that there was an overall difference in the temporal order of interactions among the networks in the RL condition compared to NH. Specifically, under RL, neural activity in the CCN preceded that of the DMN ($p \leq .001$) and the SMN ($p \leq .001$). Figure 3-3c represents the significant between-condition differences among the networks' temporal correlations. When overall lag times between conditions were directly compared, the only significant difference was between ISN→CCN ($p = .007$), with a significantly longer lag time for this relationship in the RL condition.

Table 3-1. Significant differences in functionally connected regions to the DMN, based on condition ($p \leq .05$, FDR ≤ .05).

Condition	Region	Brodmann Area	TAL Coordinates			Peak Z-score	Cluster size
			X	Y	Z		
NH > RL	Left Insula	13	-47	12	6	3.64	52
	Left Precentral Gyrus	43	-54	-7	13	2.82	7
RL > NH	Right Superior Temporal Gyrus	39	42	-58	27	5.66	81
	Right Middle Temporal Gyrus	39	48	-66	26	3.53	9
	Right Angular Gyrus	39	56	-63	31	4.33	12
	Right Inferior Parietal Lobule	40	47	-46	40	4.72	23

Table 3-2. Regions comprising the Sensorimotor Network in the NH condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Postcentral Gyrus	43	-53	-10	22	3.07	56
Right Postcentral Gyrus	2	39	-25	39	3.06	67
	43	65	-16	14	3.85	34
Right Insula	13	45	-15	19	2.93	156
Right Precuneus	7	7	-45	51	3.20	17
	19	33	-71	36	3.42	24
L. Inferior Parietal Lobule	39	-36	-63	38	2.88	40
R. Inferior Parietal Lobule	40	39	-36	51	3.09	45
Right Thalamus		12	-18	7	3.28	39
Right Declive		34	-58	-7	3.12	15
Right Culmen		0	-36	-19	3.55	28
Right Caudate		20	-2	28	3.04	16
Left Middle Frontal Gyrus	6	-4	-15	62	2.70	31
	8	-22	22	47	3.02	18
R. Middle Frontal Gyrus	8	15	31	44	2.97	17
Left Cingulate Gyrus	24	-7	-14	41	2.87	46
Right Cingulate Gyrus	32	18	14	39	3.07	23
L. Superior Temporal Gyrus	13	-34	-46	13	2.96	15
	41	-42	-29	14	2.81	24
R. Superior Temporal Gyrus	22	51	-14	6	3.14	643
	41	50	-32	16	3.00	41
Right Inferior Frontal Gyrus	9	53	5	30	3.21	46
Left Paracentral Lobule	5	-19	-32	50	3.21	46
Left Precentral Gyrus	3	-33	-28	45	2.85	68
	4	-36	-17	37	2.99	207
Right Precentral Gyrus	4	28	-29	44	2.92	35
	6	10	-18	65	3.02	53
Left Substania Nigra		-11	-23	-6	3.25	16
Right Cuneus	17	19	-72	8	2.70	35
R. Parahippocampal Gyrus	19	27	-43	-1	3.07	16

Table 3-3. Regions comprising the Sensorimotor Network in the RL condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Postcentral Gyrus	3	-41	-20	35	3.22	933
	43	-53	-13	15	3.81	27
Right Postcentral Gyrus	2	40	-22	31	3.38	925
	3	62	-14	26	4.32	79
Left Insula	13	-42	-15	17	3.17	105
Right Insula	13	48	-18	19	3.44	151
Right Precuneus	7	25	-41	43	3.06	40
	19	36	-66	37	3.05	19
R. Inferior Parietal Lobule	40	42	-40	38	2.98	34
Left Thalamus		-19	-23	18	2.89	21
Left Declive		-19	-68	-9	2.92	34
Right Declive		21	-59	-12	2.99	21
Right Culmen		0	-34	-17	3.80	29
Left Caudate		-20	8	24	2.90	26
Left Middle Frontal Gyrus	6	-28	16	49	2.92	24
R. Middle Frontal Gyrus	6	7	-18	50	2.96	97
Left Cingulate Gyrus	24	-7	-11	39	3.06	21
L. Superior Temporal Gyrus	41	-40	-34	14	3.44	24
Left Inferior Frontal Gyrus	45	-44	35	4	2.70	36
	47	-41	16	-14	2.34	32
Left Paracentral Lobule	6	-3	-29	58	2.90	25
Left Middle Temporal Gyrus	39	-31	-67	28	2.75	19
R. Middle Temporal Gyrus	39	45	-66	22	3.04	55
Left Superior Frontal Gyrus	6	-8	8	55	2.81	31
R. Superior Frontal Gyrus	6	18	22	65	2.97	20

Table 3-4. Regions comprising the Insular Salience Network in the NH condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Insula	13	-42	-17	14	3.84	85
Right Insula	13	34	-7	17	3.96	746
Left Cingulate Gyrus	32	-4	12	36	3.98	59
L. Superior Temporal Gyrus	22	-55	-46	14	3.98	18
Right Superior Temporal Gyrus	22	56	-46	13	3.84	29
Right Precentral Gyrus	44	46	-2	9	4.40	69
Left Postcentral Gyrus	40	-58	-27	23	3.92	80
Left Inferior Frontal Gyrus	44	-60	7	14	4.10	645
Left Inferior Parietal Lobule	40	-57	-38	25	3.50	20
Right Inferior Parietal Lobule	40	58	-36	24	4.00	118
R. Superior Parietal Lobule	7	15	-51	61	3.94	56
Left Claustrum		-34	-5	8	4.27	159
Right Claustrum		32	8	-3	5.45	18
R. Transverse Temporal Gyrus	41	40	-20	12	4.22	39
R. Middle Temporal Gyrus	19	45	-58	15	3.81	48

Table 3-5. Regions comprising the Insular Salience Network in the RL condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Insula	13	-38	-3	13	4.25	858
Right Insula	13	40	-13	3	4.39	1121
Right Cingulate Gyrus	24	3	12	31	4.24	223
L. Superior Temporal Gyrus	22	-59	-3	6	5.97	26
R. Superior Temporal Gyrus	13	53	-44	20	4.34	20
	22	61	-52	9	3.97	27
	39	45	-52	22	3.78	29
Left Precentral Gyrus	13	-48	-9	13	5.23	36
Left Postcentral Gyrus	40	-50	-24	16	4.21	101
Right Postcentral Gyrus	43	51	-12	17	4.03	116
Right Inferior Frontal Gyrus	44	52	0	16	5.15	29
Right Inferior Parietal Lobule	40	56	-33	22	4.56	33
Right Precuneus	31	9	-69	18	4.05	71
Right Lentiform Nucleus		31	-4	1	5.02	30

Table 3-6. Regions comprising the Cognitive Control Network in the NH condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Superior Frontal Gyrus	6	-2	8	58	3.75	137
	8	-2	37	44	5.64	23
	9	-19	43	38	5.10	41
Right Superior Frontal Gyrus	6	15	25	52	4.38	26
	9	19	46	35	3.87	29
	10	29	49	27	4.07	44
Left Middle Frontal Gyrus	6	-47	8	43	4.07	198
	8	-4	46	38	4.19	1044
	9	-45	11	35	3.99	35
Right Middle Frontal Gyrus	6	15	14	57	4.27	52
	8	15	34	44	3.78	21
	9	54	18	30	3.76	50
Left Insula	13	-47	9	3	3.44	20
R. Superior Temporal Gyrus	22	44	-55	15	3.53	30
Left Precuneus	31	-3	-46	30	3.83	32
Left Inferior Frontal Gyrus	44	-53	13	16	3.89	27
Left Middle Temporal Gyrus	39	-48	-63	25	3.94	20
Left Inferior Parietal Lobule	39	-41	-63	40	3.88	43
	40	-55	-54	38	3.83	156
Left Supramarginal Gyrus	40	-53	-52	25	4.02	27
Right Supramarginal Gyrus	40	53	55	37	3.53	37
Right Uvula		29	-71	-23	4.46	44

Table 3-7. Regions comprising the Cognitive Control Network in the RL condition ($p \leq .05$, FDR ≤ .05)

Region	Brodmann Area	TAL Coordinates X	Y	Z	Peak Z-score	Cluster size
Left Superior Frontal Gyrus	6	-19	22	52	5.20	166
	9	-4	47	30	5.30	710
Right Superior Frontal Gyrus	6	7	20	54	5.26	65
	10	23	46	55	4.88	45
Left Middle Frontal Gyrus	6	-50	8	49	5.18	23
	8	-41	9	43	5.11	89
Right Middle Frontal Gyrus	6	15	13	42	4.37	45
Left Precuneus	31	-3	46	30	4.13	71
Left Insula	13	-42	12	0	3.98	151
Left Superior Temporal Gyrus	39	-47	-60	30	4.04	193

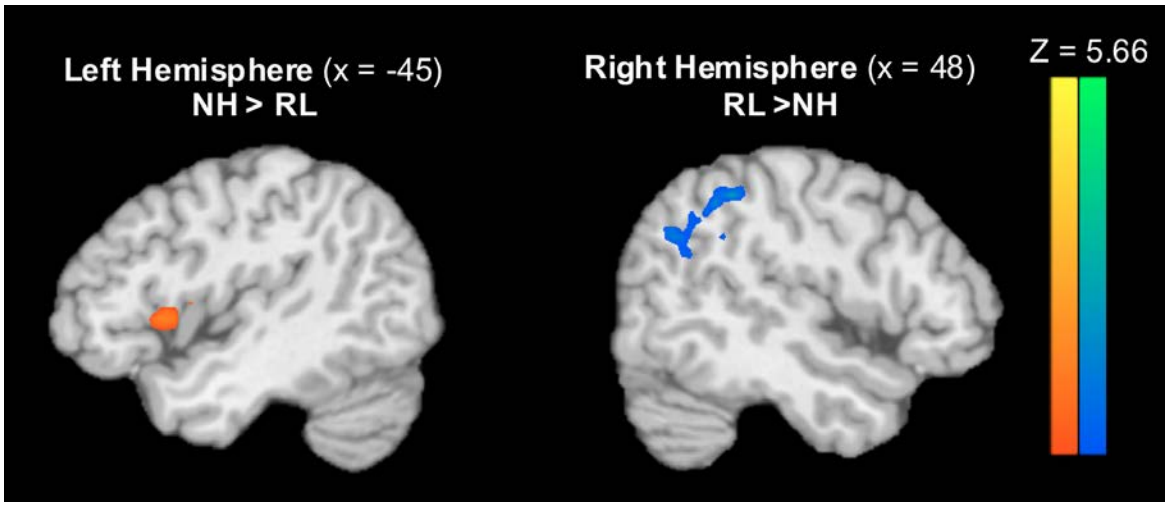

Figure 3-1. Significant differences ($p \leq .05$, FDR ≤ .05) between the NH and RL conditions emerged in the regions functionally connected with the DMN. Regions identified as significantly more connected with the DMN in NH include the insula and (orange, pictured left) precentral gyrus (not shown), whereas the superior and middle temporal gyri (blue, pictured right), angular gyrus (not shown), and inferior parietal lobule (blue, pictured right) were significantly more connected with the DMN in RL.

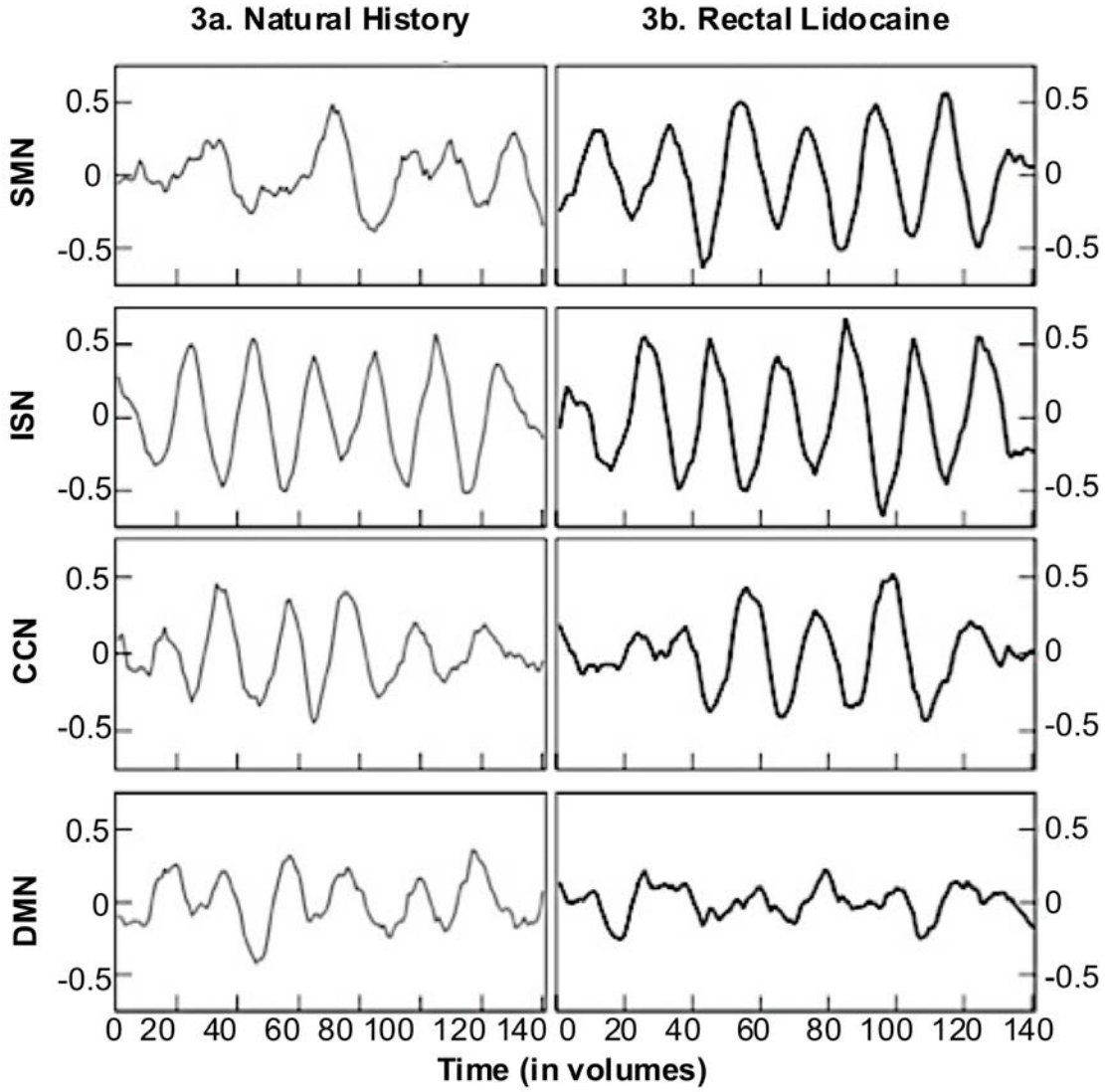

Figure 3-2. Lag times reported in the FNC analyses were calculated based on the time course, or temporal waveform, of the DMN and three pain processing networks. Time courses from the ICs in the NH condition are shown on the left, and time courses from the ICs in the RL condition are shown on the right.

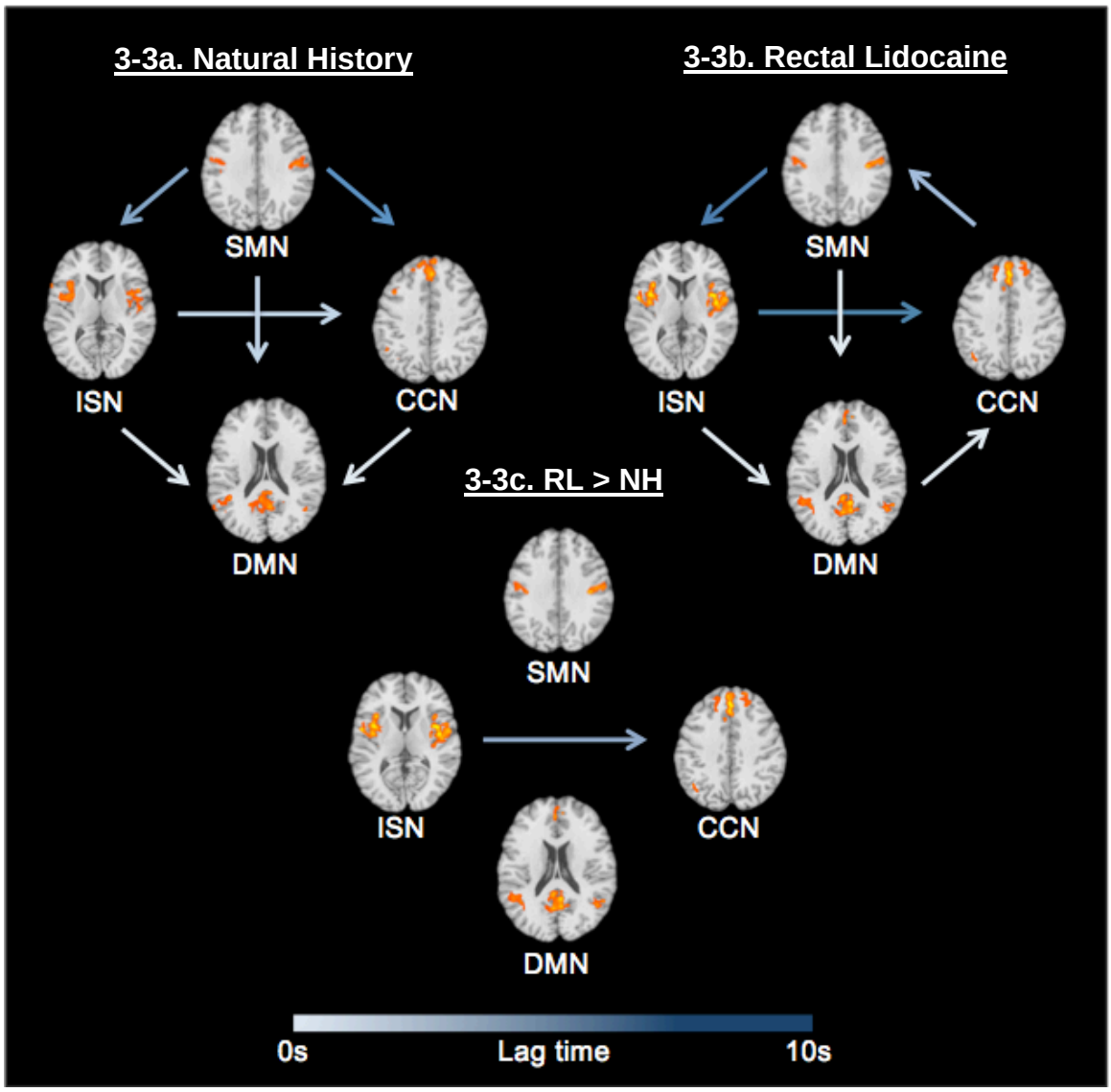

Figure 3-3. The temporal relationships between the DMN and pain-related neural networks (i.e. independent components) are represented above, with A → B denoting that network A precedes network B. Longer lag times are shown in arrows with darker colors. The only significant condition-level differences were found for the ISN→ CCN relationship. In the RL condition, the CCN lagged the ISN significantly more than in the NH condition ($p \leq .05$, FDR ≤ .05). All images are in radiological convention, and Z-plane coordinates for each network are located at: SMN = 32, CCN = 38; ISN = 7, DMN = 18.

CHAPTER 4
DISCUSSION

Rectal lidocaine has been shown to significantly reduce visceral pain in irritable bowel syndrome patients (IBS).[48] This study examined the effects of rectal lidocaine on: 1) the coherence of the default mode network (DMN) in patients with IBS, and 2) the dynamic interactions between the DMN and pain-related networks via functional network connectivity (FNC) analysis. Overall, the results showed that, compared to a natural history (NH) baseline condition, rectal lidocaine produced a significant change in the functional and spatial patterns of the DMN in patients with IBS. Additionally, although the application of rectal lidocaine did not have a significant condition-based effect on the FNC between the DMN and pain-related networks, the analgesic significantly altered the temporal characteristics defining the synergy between two discrete pain-related networks.

DMN Functional Connectivity Under Lidocaine

Although the IC representing the DMN was easily identifiable in patients with IBS under both conditions, our results suggest that this network is functionally connected with a number of brain regions not typically seen in the DMN of healthy individuals without rectal lidocaine administration. Specifically, we found that the insula and precentral gyrus were incorporated into the DMN during the NH condition. Both the insula and precentral gyrus have been associated with acute and chronic pain processing in IBS patients.[31] Previously described functions of the insula related to pain processing include self-reflection,[33] bodily arousal,[19] and bodily awareness.[26] Our results of greater DMN connectivity with the insula during NH compared to RL are consistent with findings comparing DMN connectivity between healthy controls and

other chronic pain populations, including fibromyalgia[36] and diabetic neuropathy patients.[7] Napadow and colleagues[36] suggested that their findings in fibromyalgia patients demonstrate an association between increased spontaneous pain in patients and increased DMN connectivity to the insula; this association supports our results of increased pain ratings during NH. Further, increased interconnection of the DMN with the insula has been suggested as demonstrating increased cognitive-emotional components of pain processing.[6] Because these areas were significantly more connected to the DMN during NH compared to RL, our results suggest that increased nociceptive pain sensitivity contributes to chronically active pain-related brain structures. Thus, the disruption of "normal" DMN connectivity may represent one possible mechanism by which pain transitions from an acute to chronic state.

Following the administration of RL, we identified several regions that showed increased functional connectivity within the DMN. Compared to NH, there was higher coherence among the middle temporal gyrus, angular gyrus, and inferior parietal lobule. These regions have previously been described as key nodes of the DMN among healthy individuals, and have been associated with mental exploration[4] and episodic memory retrieval.[16] Thus, the increased coherence of these regions in the DMN under RL suggests that as pain sensation is lowered, somatic focus also decreases, which in turn facilitates a pattern of DMN connectivity more consistent with pain-free individuals.

Functional Network Connectivity

The results from this study also suggest that in addition to the changes in DMN connectivity, the pain relief provided by rectal lidocaine was associated with changes in the temporal characteristics, or functional network connectivity (FNC), of the DMN and other pain-related networks. In this study, we identified three ICs representing networks

associated with discrete pain-related processes. The Sensorimotor Network (SMN) contained subcortical structures including the thalamus, declive, substantia nigra, and culmen. These structures have been associated with receiving sensory and nociceptive input.[30, 43] The Insular Salience Network (ISN) was comprised of regions associated with determining the salience of stimuli that threaten homeostasis, including the insula,[22] temporal, and somatosensory regions.[34]

The Cognitive Control Network (CCN) contained structures associated with attention and cognitive processing of pain and included: 1) the left superior frontal gyrus, which has been linked to self-reflections in decision making[13] and working memory,[15] 2) the dorsolateral prefrontal cortex, which is associated with attention to pain and pain catastrophizing,[18] and 3) the inferior parietal lobule, which is associated with active, cognitive evaluation of pain sensation.[28]

During the NH condition, patients with IBS manifested high levels of neuronal coherence among network combinations. Examination of the temporal characteristics between the DMN and the pain-related networks were consistently negatively correlated and had short lag times. Specifically, the neural activity among the pain-related networks preceded that of the DMN and, as expected, the DMN deactivated almost instantly when activity in the pain-related networks increased. These results suggest that upon feeling visceral stimulation from the rectal balloon distension, neuronal resources are allocated to pain-related structures and superfluous processes (such as DMN activity) are suppressed, which is consistent with prior work showing the deactivation of the DMN during acute pain sensation.[42]

However, when sensory information related to chronic pain was attenuated via rectal lidocaine, there was a significant decrease in individual's behavioral pain ratings. Additionally, the FNC results revealed that the attenuated sensory input was associated with changes in the temporal characteristics (i.e., longer lag times) between pain-related network pairs. For example, the SMN→ISN relationship was slower during the RL condition, suggesting longer response time between stimulus detection and determination of salience. Because the intensity, and thus salience, of the visceral stimulus was diminished by the rectal lidocaine, the immediate attention and decision-making resources were less pertinent. Interestingly, the changes in temporal relationship between the ISN→CCN emerged as the only significant difference between the conditions, with rectal lidocaine showing a longer lag time between the two networks compared to natural history. This result suggests that although rectal lidocaine resulted in longer lag times among pain-related network pairs compared to the NH condition, perhaps the crucial neural mechanism underlying the reduction of behavioral pain ratings occurs in the ISN → CCN relationship. Future studies are needed, however, before an assumption about causality can be made.

Strengths and Limitations

To the best of our knowledge, this study is the first to examine the effect of lidocaine, or any active analgesic, on DMN functional connectivity in patients with IBS. The DMN has previously been suggested as a potential neural marker of treatment efficacy in chronic pain[2] and our findings demonstrate that this network's plasticity is sensitive to treatment effects. However, the data provide correlational rather than causational information, thus more research is needed on mechanisms behind these analgesic-related DMN changes (e.g. neurotransmitters affected, influence of

expectation). A second strength of the study is that it appears to be the first to explore functional network connectivity between the DMN and pain-related networks in patients with IBS and in response to an analgesic.

Limitations to the present work are important to note. First, although the block design of our study proved valuable in understanding the temporal relationships between the DMN and pain-related networks, it is possible that patterns of DMN connectivity reflect anticipatory anxiety to painful stimuli or residual pain from the prior distension block. To address whether these processes confounded patterns of DMN connectivity, future studies could examine the effects of analgesics under pure resting-state conditions. Second, our study did not use a healthy control group, but rather a within-subjects design. Although this design was ideal for addressing the goals of the original study for which data were collected,[11] the current study would have benefitted from a mixed design to better determine the degree to which lidocaine restored "healthy" DMN connectivity. Finally, because the exact function of the DMN is still unclear,[10] future studies should address how treatment influences behavioral variables during fMRI data collection (such as mood and level of anxiety), and the result of these changes on DMN functional and functional network connectivity.

Conclusion

In conclusion, our results support evidence of aberrant DMN functional connectivity under increased pain intensity, and demonstrated that this network has the potential to show within-patient changes in plasticity as a result of an analgesic. Additionally, analgesic administration altered the temporal relationship between the DMN and networks related to sensory, salience, and cognitive processing of pain, suggesting slowed temporal relationships between pain-related networks. However,

caution is advised in assuming that the DMN could be a potential “biomarker” for chronic pain, because neither sensitivity nor specificity of DMN activity has been established.

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BIOGRAPHICAL SKETCH

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