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Thesis

SENSORIMOTOR INTEGRATION AND PAIN PERCEPTION: MECHANISMS INTEGRATING NOCICEPTIVE PROCESSING

by

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SENSORIMOTOR INTEGRATION AND PAIN PERCEPTION: MECHANISMS INTEGRATING NOCICEPTIVE PROCESSING

CINDY GOMBAUT

ABSTRACT

Chronic pain continues to be a prevalent condition in the U.S. costing the healthcare system billions of dollars annually with little success in treatment modalities. The goal of this study was to review nociceptive processing in the context of sensory and motor disorders where chronic pain often appears as a common symptom. An activation likelihood estimate (ALE) meta-analysis was performed on brain coordinates from articles containing sensory disorders (spinal cord injury and amputation) with or without pain performing a movement execution and movement imagery task and motor disorders (Parkinson's disease and dystonia) performing a movement execution task. Aberrations found in the cortical activity of sensorimotor regions of both sensory and motor disorders suggests these disorders should be studied and treated as a dysfunction of sensorimotor integration instead of solely sensory or motor. Alterations of sensorimotor integration could be the necessary trigger for reorganization of cortical maps that alters nociceptive processing. Furthermore, abnormal activity found in the brain regions of both sensory and motor disorders involved in the cognitive and attentional modulation of pain suggests a once voluntary response has transitioned to a conditioned response that perpetuates the experience of pain.

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LIST OF ABBREVIATIONS

ALE ……... Activation Likelihood Estimate

Amp ……...…… Amputee

BU ……...…… Boston University

CDC ……..… Centers for Disease Control

CNS ……...… Central Nervous System

DAN ……...…… Dorsal Attention Network

Dys ……..…… Dystonia

fMRI …… functional Magnetic Resonance Imaging

FNIRT ……..…… FMRIB's Nonlinear Image Registration Tool

FSL ……...… FMRIB Software Library

HC …… Healthy Controls

IASP ……..… International Association for the Study of Pain

L …… Left

M1 …….. primary motor cortex

MD …… Motor Disorders

ME …… Movement Execution

MI …… Movement Imagery

MNI ……...…… Montreal Neurological Institute

NP ……...…… No Pain

PET …… Positron Emission Tomography

PD …… Parkinson's Disease

PLP ……...…… Phantom Limb Pain

R ……..…… Right

S1 ……..… primary somatosensory cortex

SCI …….…… Spinal Cord Injury

SD ……...… Sensory Disorders

VPL ……...…… ventral posterolateral nucleus of thalamus

w/P …… with Pain

INTRODUCTION

The CDC reported an estimated 20.4% (50.0 million) of adults in the U.S. suffered from chronic pain and that 8.0% (19.6 million) of adults had high-impact chronic pain that limited their daily activity from a 2016 National Health Interview Survey (Dahlhamer 2018). Using the Medical Expenditure Panel Survey, in 2008 health economists from Johns Hopkins University estimated the annual U.S. health care cost due to pain ranged from $560 to $635 billion dollars (Gaskin and Richard 2012). They found pain was a greater annual cost than heart disease, cancer, and diabetes. In addition to contributing to high healthcare costs, chronic pain is associated with severe restrictions in physical and mental well-being, reduced quality of life, and dependence on opioids (Rosenblum et al. 2008). Treatment approaches for pain have been traditionally largely pharmaceutical and continue to be a major challenge for clinicians who can rarely offer solutions for the complete elimination of pain. We continue to struggle to pinpoint the cause of chronic pain and effective treatments for patients who suffer from it.

What is pain?

Pain is an unpleasant sensory, emotional, and cognitive experience that occurs when a stimulus induces real or perceived tissue damage that sends signals to the brain through nerve fibers for interpretation ("IASP Announces Revised Definition of Pain - IASP" 2020). A stimulus that imposes extremes of temperature, pressure, or causes the release of injury-related biochemicals will signal specialized peripheral first order neurons called nociceptors to fire an electrical signal (Dubin and Patapoutian 2010; "Pain

Pathways - The General Pain Pathway - Activation of First Order Neurons" 2021). The first order neurons therefore transduce a signal from the periphery to the dorsal horn located in the spinal cord via the peripheral nervous system (Yam et al. 2018). These signals are further transmitted by second-order neurons of the central nervous system (CNS) whose cell bodies are located within the spinal cord or in the nuclei of the cranial nerves within the brain stem. Second-order neurons will ascend to transmit the signal to third-order neurons whose cell bodies lie within the ventral posterolateral (VPL) nucleus of the thalamus. These neurons terminate in the ipsilateral postcentral gyrus known as the primary somatosensory cortex (S1) ("Pain Pathways - The General Pain Pathway - Activation of First Order Neurons" 2021). Figure 1 displays a simplified pathway of nociceptive processing demonstrating the three orders of neurons transmitting action potentials in response to a painful stimulus in the lateral spinothalamic tract. The S1 is somatotopically organized therefore, areas of this region are specifically dedicated to represent sensations in the hand, foot, or other body parts. See Figure 2 for an electrostimulation study performed by Roux et al. to demonstrate the somatosensory homunculus in the human body (Roux, Djidjeli, and Durand 2018). A signal transmission carrying sensory information via the spinal cord route going upwards towards the brain is called the ascending pathway whereas the spinal cord route of nerves going downward from the brain to the peripheral is called the descending pathway. Pain is also a subjective experience influenced by psychological and social factors. It would be incorrect to assume pain is merely a reflection of a nociceptive stimuli as it is shaped by emotional and cognitive factors that make the experience unique for every individual. Due to many

interconnections between brain regions processing sensory, emotional, and cognitive information, factors such as anxiety, anger, or anticipation can increase or decrease pain perception (Peters 2015). Researchers have begun to question if these factors have altered pain circuits in individuals suffering from chronic pain via a shift to a negative cognitive and emotional processing of pain. Without taking this into account, treating chronic pain as solely a submodality of a sensory experience would be insufficient since we would be ignoring the contributions of individuals' unique experiences.

Acute to Chronic Pain

Acute pain is our physiological alarm system that is intended to be short-lived following tissue damage to prevent further harm and promote actions directed towards healing ("What Is Pain?" 2020). However, the transition to chronic pain can be a product of changes to the central nervous system. Chronic pain disorders such as neuropathic pain and fibromyalgia are characterized by disturbances to the somatosensory nervous system that cause widespread pain. Episodes of pain in these conditions are not always triggered by a traumatic event or injury and are often treated with prescription medication. It follows that sensory disorders with a traumatic injury to the nervous system such as a complete spinal cord injury (SCI) or limb amputation often present with symptoms of chronic pain. Pain in these conditions typically arise in body parts distal to the site of injury despite sensory deafferentation to that body part or body parts that no longer physically exist, referred to as phantom limb pain (PLP). This suggests that the origin of chronic pain may be due to central mechanisms. Following the loss of transmission of

somatosensory information from a certain body region to the brain is an example of a traumatic injury that can cause reorganization of cortical maps that further affects connectivity and functionality of brain regions including those responsible for pain perception. Since recent research has indicated how deficits in sensorimotor integration in these sensory disorders may be contributing to pain, treatment approaches have begun to implement mental imagery and mirror therapy to correct the sensorimotor mismatch in these individuals. Motor performance can therefore play a rehabilitative role during a state of somatic disperception and introduces the effects the motor system can have on the neurophysiological processing of sensory information including pain. This brings into question what role the motor cortex as well as other brain regions play in the instigation and chronification of pain.

Movement and Pain

Movement disorders are traditionally diagnosed and treated with the obvious appearance of aberrant motor activity, but pain is an important comorbid symptom that greatly contributes to patient disability and decreased quality of life. Undoubtedly a motor reaction is expected in response to a painful stimulus, but research continues to explore how exactly pain and the motor system interact. In an electroencephalography study performed by Postorino et al., pain was shown to reduce movement-preparatory activity in the brain (Postorino et al. 2017). Pain has also been implicated in the context of motor learning, Dancey et al. suggesting the presence of pain can enhance motor learning acquisition (Dancey et al. 2016), while Bouffard et al. observed pain during a

new motor task had a negative impact on the retention of motor memories (Bouffard et al. 2014). The frequent prevalence of pain amongst some of the most common movement disorders, such as Parkinson's disease (PD) and dystonia (Relja and Miletić 2017; Gandolfi et al. 2017; Chaudhuri, Healy, and Schapira 2006; Skogar and Lokk 2016), calls into question whether the experience of pain can provide insight into the pathophysiology of these disorders. Although pain can occur or be exacerbated by abnormal movements or postures, pain has been reported to occur independently and precede the onset of motor symptoms in PD by several years (Pont-Sunyer et al. 2015; Lin et al. 2013). Additionally, pain is not reported equally amongst patients with similar degrees of dystonia, and pain relief is not directly correlated with improvement of motor symptoms in either dystonia or PD (Relja and Miletić 2017; Gandolfi et al. 2017). Since pain is predominantly a sensory experience, it is insightful to note if there are any changes to the mechanisms of sensory processing in movement disorders. Indeed, deficits to central somatosensory processing determined by electrophysiological and neuroimaging studies have been observed in PD and dystonia (Relja and Miletić 2017; Berardelli et al. 2012; Tinazzi, Rosso, and Fiaschi 2003), as well as central abnormalities of sensorimotor integration (Kanovský 2002; Rossini, Filippi, and Vernieri 1998; Abbruzzese and Berardelli 2003). It is therefore of interest to investigate what changes are occurring in the CNS that are contributing to the production of pain in motor disorders.

Research Focus

Routinely classified and treated as a dysfunction of the somatosensory system, our knowledge of chronic pain disorders remains limited. However, looking at both motor and sensory disorders together in the context of pain may pave the way for understanding what changes are occurring to the central nervous system and how these changes are influencing the perception of pain. The goal of this study is to analyze what functional changes are taking place in a selected group of sensory and motor disorders that could be contributing to changes of nociceptive processing. We predict that along with the expected alterations of activity to regions involved in sensorimotor integration, we will also see changes in regions responsible for the cognitive and emotional aspect of pain.

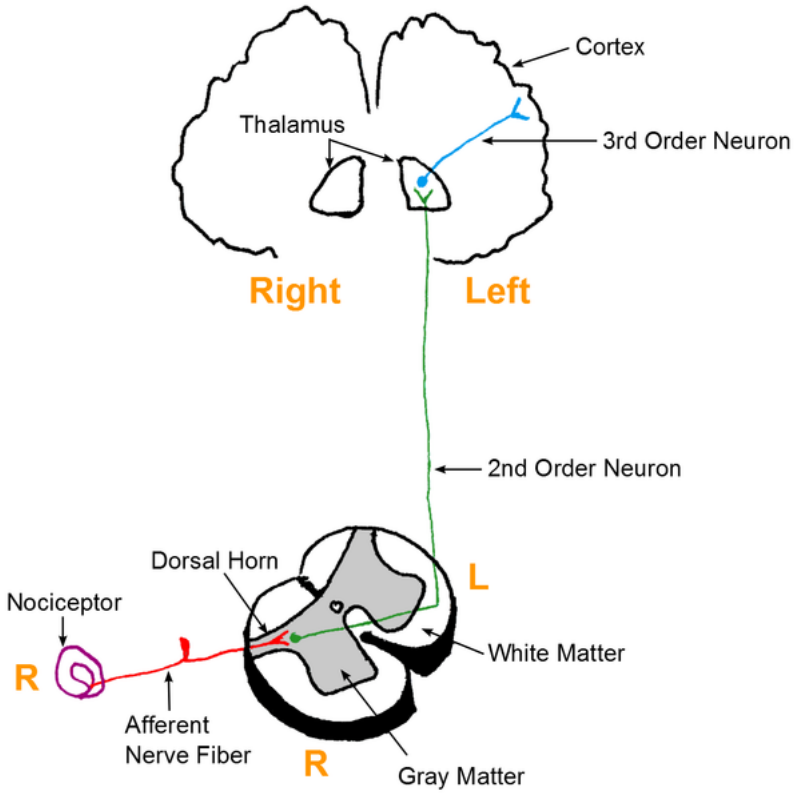

Figure 1: General Pathway of Nociceptive Processing

Simplified pathway of pain demonstrating a first-order neuron (red) with a peripheral branch and central branch extending centrally within the dorsal horn, a second-order neuron (green) extending centrally into the spinothalamic tract to the VPM of the thalamus, and a third-order neuron (blue) projecting into the S1. Image provided by "Pain Pathways - The General Pain Pathway - Activation of First Order Neurons" 2021.

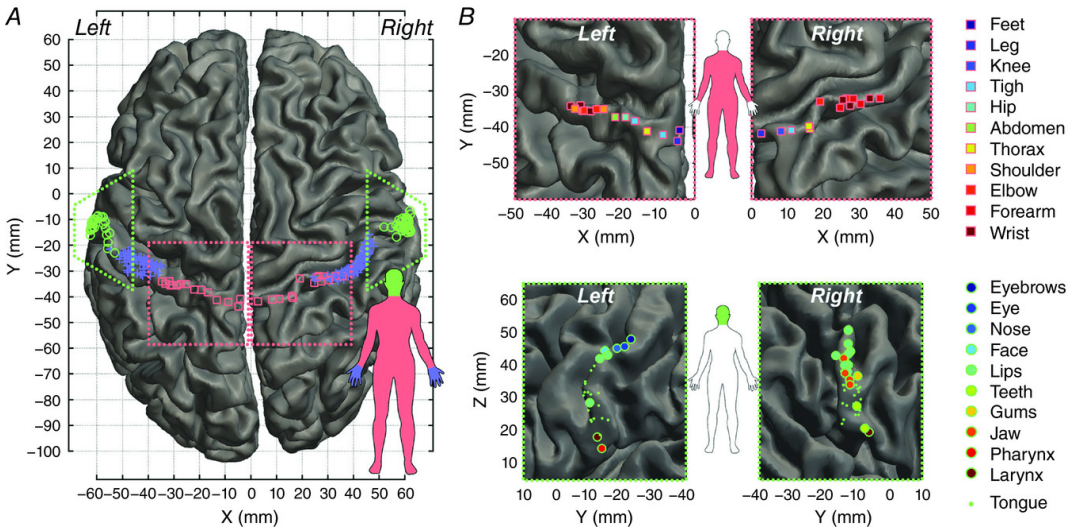

Figure 2: Somatotopic Organization of the Body

A: Overall somatotopic organization of the head (green), hands (purple), and body (pink). B-Top: Medial-to lateral somatotopic organization of the body and limbs. B-Bottom: Medial-to lateral somatotopic organization of the head and face. All coordinates reported in standard MNI space. Image provided by Roux, Djidjeli, and Durand 2018

METHODS

Database Search

Searches were performed in the following databases presented with their respective timelines: Pubmed (1950-2021) and Google Scholar (1950-2021). Database searches were organized according to: Populations, Neuroimaging Methods, and Task Specification. These search terms were combined using the operator "AND" reflecting between parameter combinations and "OR" reflecting within parameter searches. If the Pubmed database was being used, key words were first searched through the Pubmed MeSH database to include additional subheadings or quantifiers within the same context of the key word. See Figure 3 for an example of the of search methodology. *Population* key terms (see Table 1) searched were "*spinal cord injury", "SCI", "amputees", "phantom limb pain", "pain"*. *Neuroimaging Methods* key terms searched were "*MRI", "fMRI", "task-based fMRI", "cerebral activation"*. *Task Specification* key terms searched were "*movement execution", "movement imagery"*. Manual searches were completed through the reference lists of the included articles. All studies that met the inclusion criteria were reviewed in full whereas others were reviewed solely by abstract.

The inclusion criteria were: the study provided stereotaxic coordinates of cortical activity averaged within-group comparisons or a single representative subject during a movement imagery or movement execution task in the sensory and motor disorders listed in Table 1 with or without pain. Criteria for sensory disorders were: complete spinal cord injuries defined as loss of sensory and motor function below the point of injury and amputees defined as amputation of all or part of an arm or leg. Motor disorders included

(1) Dystonia: characterized by involuntary and sustained muscle contractions leading to twisting, repetitive movements and abnormal postures ("Dystonia - Symptoms and Causes" 2020) and (2) Parkinson's disease: defined as a progressive disease of the nervous system characterized by muscular rigidity and tremor ("Parkinson's Disease - Symptoms and Causes" 2020). Participants with Parkinson's disease were all studied during the "OFF" period which was defined as withdrawal of antiparkinsonian medication for 12+ hours. The criteria for pain in sensory disorders was defined as the perception of a localized or generalized unpleasant bodily sensation that caused physical discomfort or mental distress. Phantom limb pain was defined as pain that is perceived as originating from an amputated limb. Movement imagery was defined as a mental execution of a movement without any muscle activation of the limb imagined to be moved that may, or may not, involve a visual cue. Movement execution task was defined as muscle activation of a limb while performing a task. Studies were excluded from analysis if: (1) stereotaxic coordinates were only reported as between-group comparisons; (2) stereotaxic coordinates included subjects with incomplete spinal cord injuries; (3) stereotaxic coordinates included Parkinson's disease subjects actively taking antiparkinsonian medications; (4) stereotaxic coordinates reported did not differentiate between the two groups of subjects with pain and subjects without pain.

Stereotaxic coordinates were extracted and placed into one of the following groups: *healthy controls* from studies evaluating sensory disorders - movement execution, *healthy controls* from studies evaluating sensory disorders – movement imagery, *sensory disorders without pain* - movement execution, *sensory disorders*

without pain - movement imagery, *sensory disorders with pain* - movement execution, *healthy controls* from studies evaluating motor disorders - movement execution, and *motor disorders* - movement execution. Due to lack of articles studying movement imagery in motor disorders and limited by articles reporting of within-group stereotaxic coordinates, movement imagery was solely analyzed in sensory disorders.

Table 1: List of Included Sensory and Motor Disorders

Sensory Disorders		Motor Disorders	
Spinal Cord Injury		Dystonia	
	Complete thoracic SCI; Complete lumbar SCI		Cervical dystonia; Focal upper limb dystonia; Generalized idiopathic torsion dystonia; multifocal idiopathic torsion dystonia
Amputees	Unilateral upper limb amputees; Bilateral upper limb amputees; Unilateral lower limb amputees	Parkinson's Disease	Probable PD; Akinetic-rigid PD; Tremor-dominant PD; Mixed type PD; PD with freezing of gait

ALE / Statistical Analysis

If stereotaxic coordinates were reported as Talairach coordinates, the BioImage Suite 2.0 MNI 2 Talairach Converter web application ("BioImage Suite MNI<->TAL" 2020) was used to convert to MNI space. A single dataset analysis via the software program GingerALE was performed on each of the groups listed in Table 2. Contrast dataset analyses were then performed for sensory disorders without pain (SD NP ME > HC ME SD) and motor disorders to evaluate movement execution (MD ME > HC ME MD), sensory disorders without pain to evaluate movement imagery (SD NP MI > HC MI SD), and sensory disorders with and without pain to evaluate movement execution (SD NP ME > SD w/P ME). Reciprocal analyses were also performed. The single dataset analysis had a cluster forming threshold of $p=0.005$. The contrast threshold was set to $p=0.05$ with a minimum cluster volume of 200 mm^3. Brain regions reported in Tables 5, 6, and 7 used the Harvard-Oxford Cortical Structural Atlas and the Cerebellar Atlas in MNI152 space after normalization with FNIRT from the FSL program, reporting the label with the highest probability.

Table 2: List of Groups and Abbreviations for Single Dataset Analysis

	Group	Abbreviation
Sensory Disorders	Healthy controls – movement execution	HC ME SD
	Healthy controls – movement imagery	HC MI SD
	Sensory disorders without pain – movement execution	SD NP ME
	Sensory disorders without pain – movement imagery	SD NP MI
	Sensory disorders with pain – movement execution	SD w/P ME
Motor Disorders	Healthy controls – movement execution	HC ME MD
	Motor disorders – movement execution	MD ME

RESULTS

Of the included studies, stereotaxic coordinates were extracted from 33 experiments, totaling 841 subjects and 968 coordinates. An example of the search methodology is included in Table 3 to demonstrate how keywords were used to find related articles. Additionally, Figure 3 displays the screening process of the database search as articles were excluded or kept for the meta-analysis.

Table 3: Example of Keyword Search Methodology Used to Identify Studies for Meta-Analysis

Search Stage	Search Terms	Number of Hits
1	"Spinal Cord Injuries" [Mesh]	58,950
2	"Magnetic Resonance Imaging" [Mesh]	576,654
3	Movement Execution	14,101
4	Spinal Cord Injuries AND Magnetic Resonance Imaging AND movement execution	7

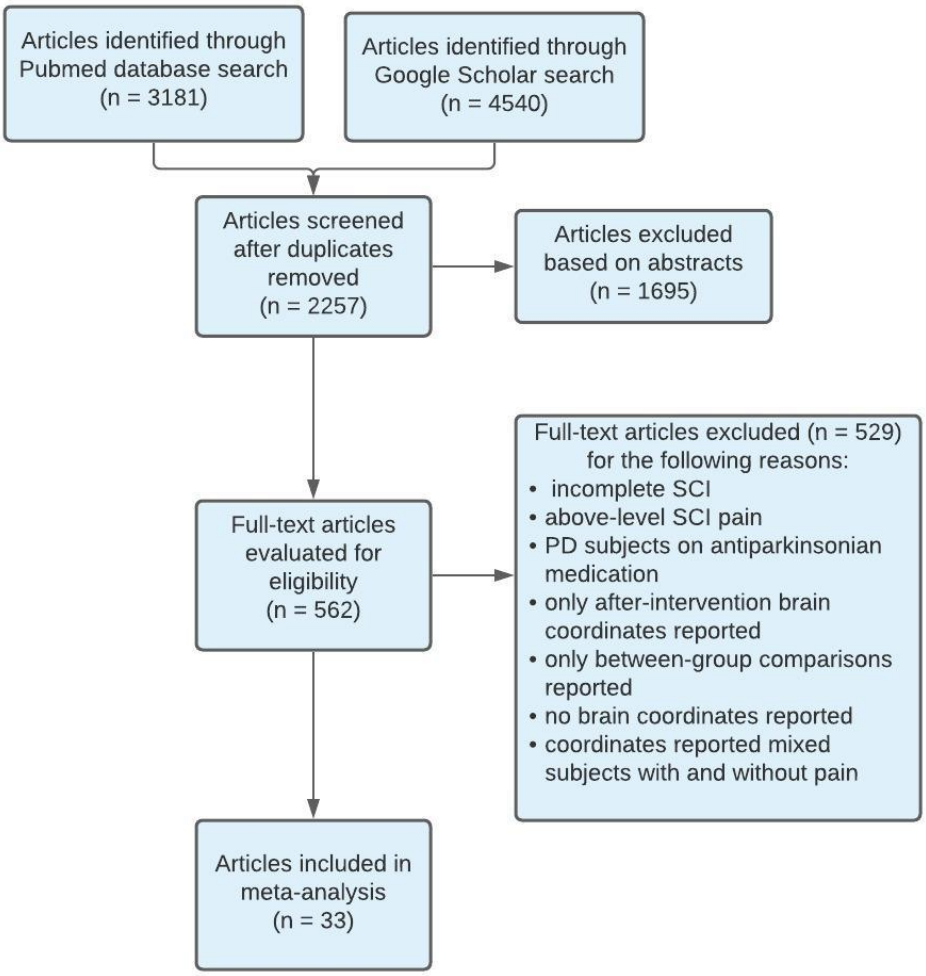

Figure 3: Flow Diagram of Search Methodology for Articles Included in Meta-Analysis

SCI = Spinal Cord Injury, PD = Parkinson's Disease

Studies used for sensory disorders included SCI and amputee participants with or without pain and healthy controls performing a movement execution or movement imagery task. The tasks performed ranged from simple (plantar flexion) to moderate

(hand movement tasks) difficulty. Imaging modalities used were either PET or fMRI. See Table 4 for characteristics of studies for sensory disorders.

Table 4: Characteristics of Studies Included in the Meta-Analysis Measuring Cortical Activity during Movement Imagery and Movement Execution in Sensory Disorders

	Study	Imaging Modality	Participants	Task Performed
Sensory Disorder				
SCI	Curt et al. (2002)	PET	SCI NP, HC	Exec: R wrist extension
	Cramer et al. (2005)	fMRI	SCI NP, HC	Exec: R plantar flexion MI: R plantar flexion
	Hotz-Boendermaker et al. (2008)	fMRI	SCI NP, HC	Exec: R dorsal and plantar flexion MI: R dorsal and plantar flexion
	Alkadhi et al. (2005)	fMRI	SCI NP, HC	Exec: R dorsal and plantar flexion MI: R dorsal and plantar flexion
Limb Amputation	Roux et al. (2003)	fMRI	Amp PLP, HC	Exec: R and L flexion and extension of fingers or toes
	Diers et al. (2010)	fMRI	Amp PLP, Amp Non-PLP, HC	Exec: R and L make a fist MI: R and L make a fist
	Lotze et al. (2001)	fMRI	Amp PLP, Amp	Exec: R and L make a fist

		Non-PLP, HC	MI: R and L Make a fist
Maclver et al. (2008)	fMRI	Amp PLP, HC	Exec: R and L opening and closing of a fist MI: R and L opening and closing of a fist
Raffin et al. (2012)	fMRI	Amp Non-PLP	Exec: R and L opening and closing of a fist MI: R and L opening and closing of a fist
Zheng et al. (2020)	fMRI	Amp PLP, Amp Non-PLP, HC	Exec: R and L movement of big toe MI: R and L movement of big toe
Romero-Romo et al. (2010)	fMRI	Amp Non-PLP, HC	Exec: R and L flexion and extension of toes MI: R and L flexion and extension of toes
Duarte et al. (2020)	fMRI	Amp PLP	Exec: R and L dorsal and plantar flexion
Foell et al. (2013)	fMRI	Amp PLP	Exec: Lip pursing and R and L hand movement tasks
Jing Yu et al. (2014)	fMRI	Amp Non-PLP	Exec: R and L tapping toes

SCI = Spinal Cord Injury, Amp = Amputee, PLP = Phantom Limb Pain, Non-PLP = Non-Phantom Limb Pain, HC = Healthy Controls, NP = No Pain; fMRI = functional Magnetic Resonance Imaging, PET = Positron Emission Tomography; R = right, L = left

Studies used for motor disorders included participants with Parkinson's disease and dystonia without pain and healthy controls performing a movement execution task. The tasks performed ranged from simple (finger tapping) to complex (writing). Imaging modalities used were either PET or fMRI. See Table 5 for characteristics of studies for motor disorders.

Table 5: Characteristics of Studies Included in the Meta-Analysis Measuring Cortical Activity during Movement Execution in Motor Disorders

	Study	Imaging Modality	Participants	Task Performed
Motor Disorder				
Dystonia	de Vries et al. (2008)	fMRI	Dys, HC	R wrist flexion/extension, fist clenching
	Kadota et al. (2010)	fMRI	Dys, HC	R and L hand tapping
	Preibisch et al. (2001)	fMRI	Dys, HC	R writing
	Lerner et al. (2004)	PET	Dys, HC	R hand tapping, writing
	Ibanez et al. (1999)	PET	Dys, HC	R hand tapping, writing, fist sustained contraction
	Ceballos-Baumann et al. (1995)	PET	Dys, HC	R hand joystick movement
	Playford et al. (1998)	PET	Dys, HC	R hand joystick movement
Parkinson's Disease	Baglio et al. (2011)	fMRI	PD, HC	R finger button press

Cerasa et al. (2006)	fMRI	PD, HC	R finger tapping
Haslinger et al. (2001)	fMRI	PD, HC	R hand joystick movement
Katschnig et al. (2011)	fMRI	PD, HC	R and L ankle dorsiflexion
Kraft et al. (2009)	fMRI	PD, HC	R and L hand button press
Maillet et al. (2012)	fMRI	PD	R hand joystick movement
Mallol et al. (2007)	fMRI	PD, HC	R and L hand movements
Sabatini et al. (2000)	fMRI	PD, HC	R finger to thumb opposition, making and clenching fist
Yu et al. (2007)	fMRI	PD, HC	R thumb button Pressing
Zhao et al. (2014)	fMRI	PD, HC	R finger tapping
Yan et al. (2015)	fMRI	PD, HC	R and L finger to thumb opposition
Schwingenschuh et al. (2012)	fMRI	PD, HC	R and L ankle dorsiflexion

Dys = Dystonia, PD = Parkinson's Disease, HC = Healthy Controls; fMRI = functional Magnetic Resonance Imaging, PET = Positron Emission Tomography; R = right, L = left

Meta-Analysis

See Table 6, 7, and 8 for significant results found in activated brain regions with stereotaxic coordinates in MNI space identified by the ALE meta-analyses.

Table 6: Activated Brain Regions within each Between-group Contrast for Sensory Disorders Performing a Movement Execution Task

	Cluster #	Volume mm^3	P-value	Z-value	x, y, z	Brain Region
Execution						
HC > SD NP	1	2752	.0076	2.43	49.8,2.9,13.4	R Precentral Gyrus
	2	2040	.0033	2.72	-9.6,0,45	L Juxtapositional Lobule Cortex
SD NP > HC	1	800	.0041	2.64	9.4,-6,68.8	R Juxtapositional Lobule Cortex
	2	384	.0052	2.56	-36,-22,56	L Precentral Gyrus
SD NP > SD w/ P	1	888	.0094	2.35	6.8,-6.5,70.8	R Juxtapositional Lobule Cortex
SD w/ P > SD NP	1	936	.0312	1.86	-28,-40,54	L Superior Parietal Lobule

MNI coordinates (x,y,z) of brain regions surviving a cluster threshold of $p<0.05$ for contrast studies and a cluster forming threshold for $p<0.005$ for single studies. HC = Healthy Controls, SD = Sensory Disorders; NP = No Pain, w/ P = with Pain; L = Left, R = Right; ALE = Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

Table 7: Activated brain regions within each between-group contrast for sensory disorders performing a movement imagery task

	Cluster #	Volume mm^3	P-value	Z-value	x, y, z	Brain Region
Movement Imagery						
HC > SD NP	1	3224	.0024	2.82	0,0,60	L Juxtapositional Lobule Cortex
SD NP > HC	-	-	-	-	-	-

MNI coordinates (x,y,z) of brain regions surviving a cluster threshold of $p<0.05$ for contrast studies and a cluster forming threshold for $p<0.005$ for single studies. HC = Healthy Controls, SD = Sensory Disorders; NP = No Pain; L = Left, ALE = Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

Table 8: Activated Brain Regions within each Between-group Contrast for Motor Disorders Performing a Movement Execution Task

	Cluster #	Volume mm^3	P-value	Z-value	x, y, z	Brain Region
Movement Execution						
HC > MD	1	1552	.0018	2.91	-12,2,60	L Superior Frontal Gyrus
	2	1360	.003	2.75	-20,-22,-4	L Thalamus
	3	816	.0058	2.52	-42,-4,8	L Insular Cortex
	4	560	.0045	2.61	58,-36,22	R Planum Temporale, R Supramarginal Gyrus, posterior division
	5	312	.0193	2.07	-42,-36,60	L Postcentral Gyrus
MD > HC	1	608	.0273	1.92	30,-68,-32	R Cerebellum Crus I
	2	448	.0234	1.99	39,-46,41	R Supramarginal Gyrus, posterior division
	3	360	.0039	2.66	30,-18,50	R Precentral Gyrus
	4	208	.0231	1.99	-8,-50,-26	L Cerebellum I-IV

MNI coordinates (x,y,z) of brain regions surviving a cluster threshold of $p<0.05$ for contrast studies and a cluster forming threshold for $p<0.005$ for single studies. HC = Healthy Controls, MD = Motor Disorders; L = Left, R = Right; ALE = Activation Likelihood Estimate. Brain labels automatically generated in GingerALE using the MNI space.

Sensory Disorder Analysis Results

See Table 6 and 7 for more detailed information of activation clusters. A peak activation was found in the right precentral gyrus and the left juxtapositional lobule cortex for the movement execution contrast HC > SD NP. A peak activation was found in the right juxtapositional lobule cortex and the left precentral gyrus for the movement execution contrast SD NP > HC. One activation peak was found in the right juxtapositional lobule cortex for the movement execution contrast SD NP > SD w/ P. One activation peak was found in the left superior parietal lobule for the movement execution contrast SD w/ P > SD NP. One activation peak was found in the left juxtapositional lobule cortex for the movement imagery contrast HC > SD NP. No activations were found in the movement imagery contrast SD NP > HC.

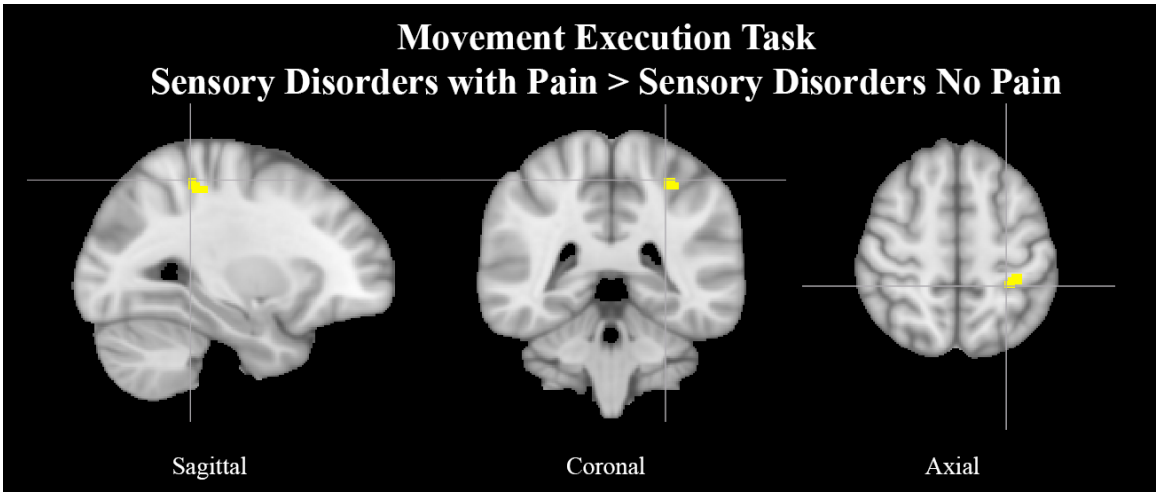

Figure 4: Left Superior Parietal Lobule Activation in Sensory Disorders with Pain

Exemplar of a between-group activation peak of the movement execution contrast SD w/P > SD NP. Yellow-colored regions show increased brain activity in the left superior parietal lobule (cross-hairs reflect peak activation peak x=-28,y=-40,z=54).

Motor Disorder Analysis Results

See Table 8 for more detailed information of activation clusters. Five activation peaks were found in the movement execution contrast HC > MD. Four activation peaks were found in the movement execution contrast MD > HC.

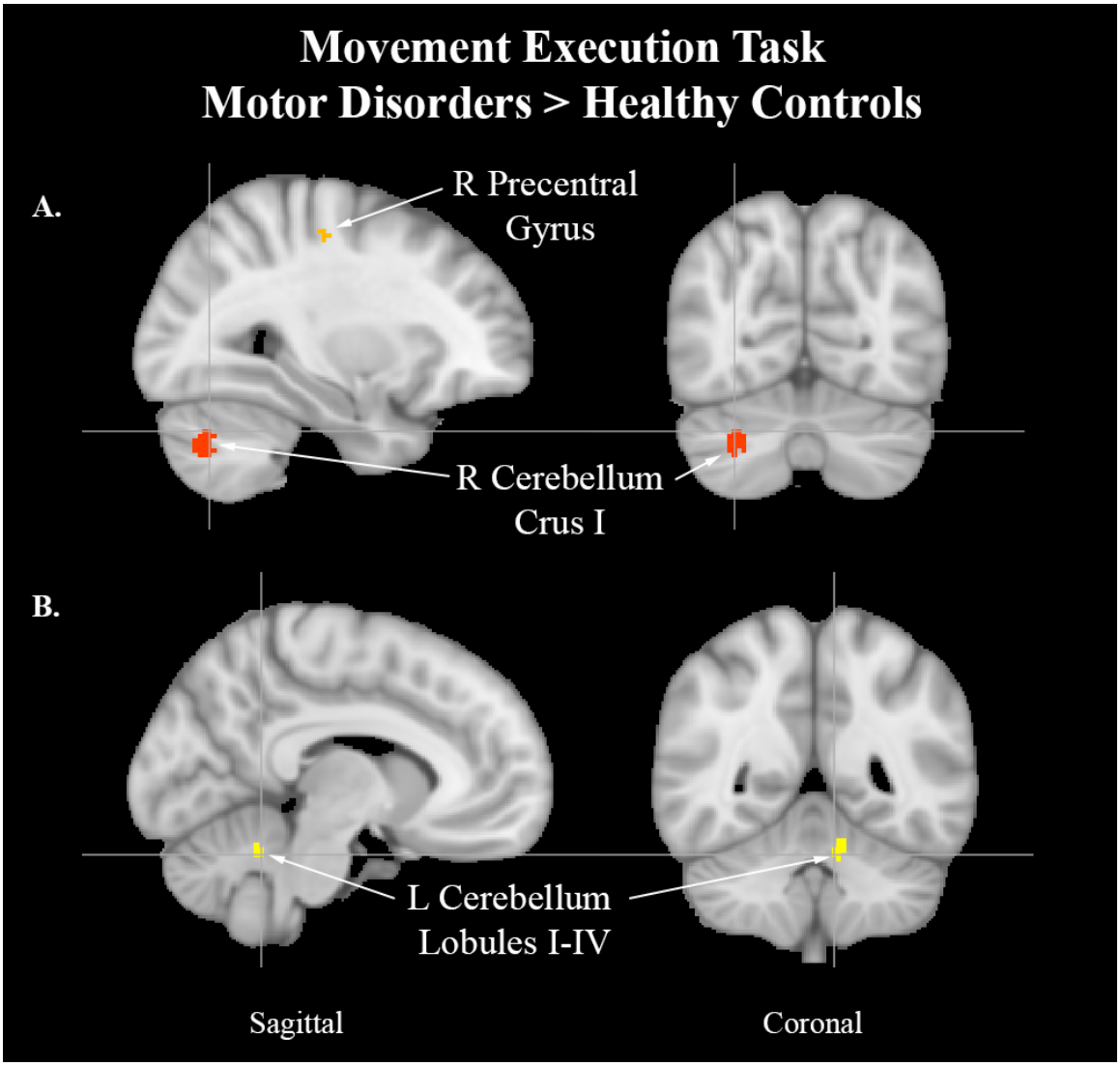

Figure 5: Cerebellum Activation Peaks in Motor Disorders

Exemplar of between-group activation peaks of the movement execution contrast MD > HC. A. Orange-colored region shows increased brain activity in the right precentral gyrus. Red-colored regions show increased brain activity in the right cerebellum Crus I (cross-hairs reflect activation peak x=30,y=-68,z=-32). B. Yellow-colored regions show increased brain activity in the left cerebellum lobules I-IV (cross-hairs reflect activation peak x=-8,y=-50,z=-26).

DISCUSSION

Sensorimotor integration and its relationship to nociceptive processing is a poorly explored avenue of research. This study analyzed cortical activity in disorders traditionally characterized as solely sensory or motor to evaluate if disturbances to sensorimotor integration causes shifts of activity in other brain regions that influence nociceptive processing. An increased activation of the left superior parietal lobule in subjects with sensory disorders with pain while performing a movement execution calls into question how a conditioned anticipation of pain can influence nociceptive processing. Similarly, an increased activation of the right cerebellum Crus I in subjects with motor disorders during a movement execution further questions how disturbances to sensorimotor integration can contribute to changes in the attentional modulation of pain. Finally, a decrease of activity in motor disorders of regions involved in somatosensory processing along with increases of activity in areas responsible for voluntary movement and sensorimotor processing will challenge the traditional classification of motor and sensory disorders as solely a dysfunction of sensory or motor processing respectively and introduce a possible origin for the development of central sensitization.

Sensory Disorders

Sensory disorders occur when there is damage along the afferent nerve pathways thereby causing a disturbance to sensory processing. Sensory discrimination and thresholds may be severely altered or completely abolished in conditions such as what is seen in SCI's and limb amputations. Reorganization to cortical maps following sensory

deprivation is hypothesized to contribute to a common symptom of many sensory disorders: deafferentation pain, or the sensation of burning, tingling, or pain in a limb that no longer exists or has suffered total sensory loss. Deafferentation pain symptoms are believed to originate from a central mechanism, specifically the result of cortical reorganization following an assault to sensory processing. Interruptions to sensory processing leads to further aberrations in the activity of other brain regions involved in sensorimotor integration which influences limb proprioception and the planning and execution of intended movements.

The ALE meta-analysis revealed a significant cluster over the left superior parietal lobule in subjects with sensory disorders with pain which could be indicative of conditioned pain expectations. This region functions as part of the fronto-parietal dorsal attention network (DAN) involved in the top-down allocation of attention (Lanssens et al. 2019) and when triggered by nociceptive stimuli has led to its more recently recognized role in pain chronification. As a sensory orienting system, regions within the DAN such as the left superior parietal lobule can influence the attentional modulation of pain. Ptak et al. found that the DAN's voluntary orienting of attention is done via a mechanism that either temporarily amplifies the significance of behaviorally relevant sensory information or suppresses irrelevant distractors (Ptak and Schnider 2010). Aberrations in the activity and functional connectivity of the DAN have previously been reported in chronic pain disorders, such as fibromyalgia (Napadow et al. 2010) and chronic back pain (Hashmi et al. 2013). The temporary amplification of stimuli is a necessary innate response of attentional bias towards pain to identify and form a goal-driven behavior to escape the

source of pain. Although increased activity in this region was relevant to accomplish a goal at a certain point in time, continued increased activity within the left superior parietal lobule could lead to a "voluntary" amplification of pain. One's attentional bias towards a painful stimulus is modulated by factors such as its perceived threat value, personality traits of the individual experiencing pain, and the situational circumstance when the pain occurs (Ahmad and Aziz 2014). A perceived threat value is assigned to a noxious stimulus which will modulate how much attention is necessary and therefore the expectation of pain. The anticipation of a highly painful stimuli can exacerbate the perception of experienced pain (Kong et al. 2008), whereas the expectation of a low noxious stimuli can reduce the perception of pain (Wager et al. 2004; Koyama et al. 2005). A study done by Zeidan et al. investigated the brain activity of an individual whose experienced pain did not match their anticipated pain, or in other words the study performed violated expectations of pain. This notably produced activity in the left superior parietal lobe (Zeidan et al. 2015). Higher activity in the left superior parietal lobule in sensory disorders with pain could indicate the subjects had anticipated pain from a motor execution task that produced no noxious stimuli. This could be especially true for subjects suffering with chronic pain conditions that are constantly in pain from mundane daily tasks. The expectation of pain became a learned condition in which any activity can act as a pain-predictive cue that leads to the attentional modulation of pain and a learned pain perception. This learned attention to pain via hypervigilance to pain-predictive cues that have been assigned a higher threat value could lead over time to pain chronification. Increased white matter connectivity has been reported from the superior

parietal lobule to the hippocampus, an important region for fear conditioning, in patients with chronic pain (Bishop et al. 2018). Additionally, an over attentiveness to pain found in traits such as pain catastrophizing and an avoidant personality type are typically associated with chronic pain conditions (Poppe et al. 2011). Individuals with these personality traits could be more susceptible to pain chronification through a conditioned over attentiveness and exacerbation of pain-predictive cues with involuntarily assigned high threat values which similar to a learned muscle memory need to be unlearned and disengaged from pain.

The activation of the left superior parietal in subjects with sensory disorders with pain suggests that disturbances to sensory processing can lead to changes in the activity of other brain regions responsible for the attentional modulation and learned expectation of pain. Since pain does not occur in every subject with sensory deafferentation, individual differences such as personality type or situational events likely influences the process of cortical reorganization and therefore the susceptibility to the development of chronic pain. This supports the importance of integrating a psycho-social approach into treatments following a disruption to sensory processing in an attempt to shape the inherited and/or acquired psychological factors that influence the perception of pain.

Motor Disorders

Motor disorders are characterized by aberrant muscle movements caused by pathological changes within the brain ("Movement Disorders - Symptoms and Causes" 2017). Because a large array of brain regions are able to influence movement execution

through anticipation, planning, or proprioception, it is plausible that changes in the functional or structural organization of these regions in the cortex could contribute to the progressive worsening of movement disorders such as Parkinson's disease and dystonia's. The common co-occurrence of pain in movement disorders (see Relja and Miletić 2017; Gandolfi et al. 2017; Chaudhuri, Healy, and Schapira 2006; Skogar and Lokk 2016) suggests other regions are often altered and that non-motor symptoms are significant in the diagnosis and treatment of movement disorders.

The ALE meta-analysis revealed activation of an important region with a potential role in the attentional modulation of pain and sensorimotor integration: the cerebellum. Motor disorders have typically been studied and treated as a dysfunction of the firing rate and firing pattern of central motor regions such as the basal ganglia. However, in light of findings that show the experience of pain involves activity in many regions of the brain (Coghill 2020), more thought has shifted towards the involvement of other brain regions as contributing to the appearance of motor and non-motor symptoms, such as pain. Chronic pain has been reported as a common non-motor symptom in motor disorders such as Parkinson's disease (Borsook 2012) and dystonia's (Kutvonen, Dastidar, and Nurmikko 1997). Whether the instigator of pain is induced through peripheral or central mechanisms, aberrant activity across many brain regions could be responsible for the perpetuation of chronic pain. Two ALE clusters activated in subjects with a motor disorder that may contribute to sensorimotor dysfunction and pain were the right cerebellum crus I and left cerebellum lobules I-IV (See Table 8).

Functional subregions within the cerebellum have been identified where the anterior lobe (lobules I-V) is involved with sensorimotor integration (Stoodley, Valera, and Schmahmann 2012) while the Crus I is thought to be involved in higher level processing of cognitive and emotional states (Mehnert and May 2019). Therefore, the cerebellum has the ability of integrating sensory information and modulating the motor response. Welman et al. discovered Crus I to be one of the two regions of the cerebellum activated by a painful stimulus and the anticipation of a painful stimulus (Welman et al. 2018). It is well accepted that anticipation or attention directed towards a nociceptive stimulus influences the perception of pain. The increased activity of the Crus I in motor disorders could indicate a susceptibility to a learned anticipation of pain while performing a movement execution that further disrupts sensorimotor processing and causes a worsening of symptoms. In line with this theory, a study found increased regional homogeneity of the right Crus I was positively correlated with symptom severity in cervical dystonia subjects (Wei et al. 2021). In addition, the Crus I has been reported to be activated during the acquisition, extinction, and recovery of a conditioned fear in response to abdominal pain (Kattoor et al. 2014). This emphasizes once more the role of this region in the cognitive processing of nociceptive information and its direct role in learned behavioral expectations of pain.

The activation of the right cerebellum Crus I and left cerebellum lobules I-IV suggests alterations in cognitive processing and sensorimotor integration in subjects with movement disorders. These findings highlight the occurrence of disturbances in regions that could perpetuate the severity of motor and non-motor symptoms. Disturbances could

cause individuals with motor disorders to become more susceptible to changes in the processing of nociceptive stimuli and alter learned behavioral responses to pain.

How do we characterize pain conditions: Should we be treating sensory and motor disorders differently?

Communication between the S1 and primary motor cortex (M1) via intracortical connections or through thalamocortical connections is essential for interpreting peripheral afferent inputs and executing goal-driven behavior. Information is gathered and shared between these two regions simultaneously so that somatosensory processing and movement execution are rarely processed independently of each other. A study by Umeda et al. found that the S1 not only integrates information from M1 and peripheral stimuli during active movement, but also receives information prior to movement initiation from the M1 suggesting a short path efference copy of anticipated actions directly to S1 (Umeda, Isa, and Nishimura 2019). Furthermore, sensory stimuli have been shown to increase M1 excitability (Matur and Öge 2017) which demonstrates how sensory feedback has a critical role during the acquisition and formation of motor memories. Therefore, disruptions to sensorimotor integration could originate from abnormalities in the processing of incoming sensory information or disturbances in the motor planning and execution system.

Abnormal activity in the M1 and also sensory processing regions of the brain in subjects with motor disorders argues against the traditional categorization of motor and sensory disorders as solely one or the other. Instead, we should be studying and treating

these as disorders of sensorimotor integration in the context of pain. The S1 and M1 are undeniably integrated, therefore disruption of communication between these two regions may be a cause for a cascade of sensory and motor symptoms and for the chronification of pain. The study by Wei et al. found an increased regional homogeneity in the right precentral gyrus of cervical dystonia patients (Wei et al. 2021), a region more commonly recognized as the primary motor cortex (M1) responsible for the initiation and control of voluntary movement (Papale and Hooks 2018). Increased activity in the right precentral gyrus of the motor disorder group when compared to healthy controls during movement execution was similarly reported in this ALE analysis. The M1 is connected to many other motor-related regions such as the basal ganglia (Papale and Hooks 2018). This hyperactivity could be a compensation mechanism for the basal ganglia dysfunction in an attempt to maintain motor function. However, increased activity from motor regions such as the M1 and the anterior cerebellum such as what was observed in the analysis could cause further disruptions in motor, sensory, and cognitive function due to their dynamic connectivity to other brain regions (Takakusaki 2017). Indeed, decreased activity was found in the motor disorder group performing a movement execution in brain regions involved in sensory processing, such as the left superior frontal gyrus, left thalamus, and left postcentral gyrus and decreased activity in the left insular cortex, a region that links sensory experience with emotional value. The left superior frontal gyrus also plays a vital role in the executive processing of working memory (du Boisgueheneuc et al. 2006), or a short-term memory system that influences decision making and goal-driven behavior. Research has implicated an interaction between motor and cognitive networks in working

memory processes (Marvel, Morgan, and Kronemer 2019), which suggests how a disturbance to the M1 can impact both sensory and cognitive processing. These results caution against treating a disorder as solely motor since this approach could ignore the significant contributions of aberrations in sensory and cognitive regions to the origins of pathology and pain.

Incongruence between the sensory and motor cortex due to injury to the nervous system leads to an impairment in sensorimotor integration. Reorganization of the functional connectivity within the cortex following an impairment in sensorimotor integration provide the undesired changes that causes hyperactivation of pain circuits. A traumatic event, recurring irritation, or imbalances of neurotransmitters act as the trigger that causes a change in ascending signaling that disturbs sensorimotor integration and begins the process of cortical reorganization. The ability of the brain to make functional changes throughout an individual's life and experiences to adapt to stimulus changes has been well accepted (Kolb and Gibb 2011; Markham and Greenough 2004). In a study done by Melgari et al., an uncoupling of S1-M1 functional communication was observed in dystonic patients during a movement execution thus supporting the presence of abnormal sensorimotor integration (Melgari et al. 2013). Cortical reorganization may occur in an attempt to improve the disrupted communication and maintain appropriate activity. However, when reorganization brings about negative consequences such as further disturbances in activity with other regions then this is termed maladaptive neuroplasticity (Li et al. 2016). Upon development of new pathways or synapses, alterations to the ratio of excitatory and inhibitory activity may contribute to an

imbalance in these cortical circuits, including those of nociceptive pathways (Potter et al. 2016). Progressive central sensitization, a mechanism which involves increases in excitability and synaptic efficiency coupled with reduced inhibition of neurons in the central nervous system, especially within the pain connectome (Coghill 2020; Kucyi and Davis 2015), could leave an individual susceptible to increased sensitivity to pain (Latremoliere and Woolf 2009). An impaired processing of pain generated as a consequence of maladaptive neuroplastic changes to the CNS could change the sensorimotor response to normal stimuli that progresses into a conditioned pain response.

As alterations of transmission and processing of nociceptive stimuli occur, we begin to question if there is a loss of the top-down regulation of pain. Once a protective mechanism to detect and initiate a behavioral response to escape a noxious stimulus**,** acute pain becomes maladaptive as it transitions into chronic pain with involvement of the cognitive system of pain perception that contributes to misinterpretation of incoming sensory information. Treatments focus on addressing the more obvious pain symptoms, but alterations in these cognitive systems that may perpetuate and chronify the pain are often ignored. Although the functional architecture of cognitive systems is largely preserved, individual experiences that shape differences in personality make the various connections in one's cognitive system relatively unique (Adelstein et al. 2011). Differences in the experience of pain could therefore be explained by individuals using different connections or components of the distributed nociceptive system. Coghill introduces the idea of a distributed nociceptive system that involves a wide range of

regions involved in the processing of nociceptive information that, while highly resilient to injury, suggests the possibility of differential activations from one person to another (Coghill 2020). Comparable to a muscle memory which reproduces a motor action without any conscious thought (University 2017), the repetitive differential activation of the distributed nociceptive system could become an involuntary skill. While an early, acute back pain group activated brain regions well-recognized for acute pain, a fMRI study found a chronic back pain group activated regions in an emotion-related circuitry, such as the amygdala and the medial prefrontal cortex (Hashmi et al. 2013). This indicates that nociceptive processing in sensorimotor disorders can transition to a more affective-emotional processing of pain that allows involuntary factors such as attention, catastrophizing, and learning to further influence sensory processing and motor execution.

We need to integrate our knowledge from motor and sensory disorders in pain based on four key findings: (1) the hyperactivity of the M1 of subjects with motor disorders, (2) the decreased cortical activity in sensory processing regions, such as the left superior frontal gyrus, left thalamus, and left postcentral gyrus of subjects with motor disorders, (3) increased activity of cognitive and sensorimotor regions of the cerebellum of subjects with motor disorders, and (4) increased activity of regions involved in the anticipation and expectation of pain in both sensory and motor disorders. The first and second key findings support the strong integration between sensory and motor systems, which introduces studying and treating aberrations in one system as a disruption to sensorimotor integration altogether. Indeed, the third key finding of abnormal activity in

a region with a role in sensorimotor integration, the anterior cerebellum, was found in motor disorders. Adjusting our approach to these disorders as a dysfunction of sensorimotor integration can be especially revealing in the context of pain as the high prevalence of pain as a symptom in both sensory and motor disorders could point towards a common pathophysiology. Finally, the third and fourth key findings of abnormal activity in cognitive-motivational brain regions in both sensory and motor disorders suggests a similar automatic anticipation of pain that further disturbs motor and sensory processing, including nociceptive processing.

Limitations

There are several limitations that require mention. As an ALE meta-analysis is a composite of individual studies, the associated limitations of each investigation, including sample size, hemisphere-specific brain activation dependent on task, and effects of patient medications are important. For this investigation, there is a relatively low number of studies, 33 overall. Furthermore, there was limited data available to extract from studies performed due to articles not reporting within-group stereotaxic coordinates, the lack of differentiation between subjects who were experiencing pain or those that were pain-free, and publication bias.

Conclusion

A multi-layered approach is required when studying central nervous system contributions to the origin and perpetuation of chronic pain. We first consider how interruptions to sensory and motor processing can initiate cortical reorganization that further alters the activity and function of other brain regions in relation to nociceptive processing. We then propose how these alterations can make these regions more susceptible to changes in the cognitive and attentional modulation of pain. This multiple system approach of pain modulation suggests the evolution from a sensory and motor dysfunction to a conditioned cognitive expectation and perpetuation of pain. Therefore, an interruption to sensorimotor integration suggests a susceptibility to maladaptive changes to nociceptive processing mechanisms.

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