



Delineating conditions and subtypes in chronic pain using neuroimaging

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Abstract

Differentiating subtypes of chronic pain still remains a challenge—both from a subjective and objective point of view. Personalized medicine is the current goal of modern medical care and is limited by the subjective nature of patient self-reporting of symptoms and behavioral evaluation. Physiology-focused techniques such as genome and epigenetic analyses inform the delineation of pain groups; however, except under rare circumstances, they have diluted effects that again, share a common reliance on behavioral evaluation. The application of structural neuroimaging towards distinguishing pain subtypes is a growing field and may inform pain-group classification through the analysis of brain regions showing hypertrophic and atrophic changes in the presence of pain. Analytical techniques such as machine-learning classifiers have the capacity to process large volumes of data and delineate diagnostically relevant information from neuroimaging analysis. The issue of defining a “brain type” is an emerging field aimed at interpreting observed brain changes and delineating their clinical identity/significance. In this review, 2 chronic pain conditions (migraine and irritable bowel syndrome) with similar clinical phenotypes are compared in terms of their structural neuroimaging findings. Independent investigations are compared with findings from application of machine-learning algorithms. Findings are discussed in terms of differentiating patient subgroups using neuroimaging data in patients with chronic pain and how they may be applied towards defining a personalized pain signature that helps segregate patient subgroups (eg, migraine with and without aura, with or without nausea; irritable bowel syndrome vs other functional gastrointestinal disorders).

Keywords: Chronic pain, Migraine, IBS, Machine learning

1. Introduction

Chronic pain is one of the most frequently encountered medical conditions and still remains an enormous clinical, behavioral, and social challenge.¹⁶ Understanding how elements of pain differ between individuals is critical towards optimizing medical care. Attempts at differentiating subtypes of chronic pain, even within a particular disease state, may evaluate several features. For example, a person’s phenotype can be indexed to evaluate the behavioral or clinical evaluation of pain symptoms, whereas their biotype can provide information relating to the expression of genetic markers, or by evaluating brain data, how pain information is processed differently between individuals. Phenotypic analyses have dominated clinical and research investigations to date and commonly group patients experiencing

chronic pain symptoms under a single identifier to understand the etiology of pain symptoms. Routinely, clinical evaluation has depended on factors such as psychosocial factors, pain variability and quality, sleep and fatigue, quantitative sensory testing and sensory profiling (notably, pain intensity), and conditioned pain modulation to define a pain condition.¹⁹ Phenotypic evaluations are inherently subjective and can have a high degree of temporal variability,⁵² intersubject variability,²⁷ and be susceptible to factors such as observational bias, as noted by Cowen et al.¹⁵ who argue for more objective tools when evaluating pain. This variability in symptom reporting can place limitations on developing techniques such as genome-wide association studies^{30,76} and research aimed at resolving pain mechanisms and outlining therapies. New methods that use objective criteria may provide critical insight to improve how chronic pain is understood.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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1.1. Neuroimaging of chronic pain

Chronic pain is a complex process that integrates brain networks implicated in a myriad of behavioral, affective, cognitive, and motor functions. Thus, aside from sensory measures, psychological factors such as depression² and anxiety³ can significantly influence pain levels and are associated with discrete brain networks.⁵⁰ Other processes such as cognitive domains implicated in pain include attention and emotional circuitry²⁵ that alone integrate frontal, temporal, and subcortical brain structures.²⁸ Brain imaging of these networks provides a potentially integrative and objective measure that is intended to be

independent of factors such as observer bias and provide more stable metrics of pain in patient groups (see Ref. 17 for discussion). In other words, behaviors are defined by brain networks. Techniques such as voxel-based morphometry, as well as resting-state functional neuroimaging use static or non-task-related images of the brain, and therefore are (in theory) removed from certain forms of bias because they rely on statistical methods for quantifying anomalous data in pain cohorts.

Clinical evaluation of pain has proved difficult to segregate subtypes in many disease states. For example, in persons with Parkinson's disease, attempts have been made to create subtypes from clinical features such as the extent of motor symptoms⁵⁸; however, the extensive variability both in symptom breadth and in their temporal presentation represent formidable barriers because they present as overlapping spectral, rather than categorical, features.⁴⁶ Similar findings are observed in persons with headache⁶⁹ and gastrointestinal disorders⁶⁵ that rely heavily on patient-reported symptoms. The concept of overlapping pain conditions and associated pain symptom reporting adds further complexity to the clinical diagnosis, which may be informed by brain imaging of pain-relevant brain networks that occur on a subliminal level.⁸ For example, the insula is a region implicated in pain salience in patients with migraine whose structural morphology and functional activity are clinically related.⁷ As well, subcortical brain structures including the amygdala, brainstem, and cerebellum are involved in the processing of emotional elements of a painful stimulus such as fear of pain condition.⁴ Notably, because pain is an "experience" and therefore tied to perception,⁵⁶ it remains to be determined how brain imaging can be applied towards defining pain subtypes and whether insights are best applied either independently or cooperatively to inform patient diagnostics.

1.2. Two clinical conditions

Delineating pain groups using phenotypic criteria is fundamentally limited in its ability to resolve group differences in patients with chronic pain. It remains to be determined if neuroimaging can provide additional data and extend knowledge on a group of patients who share similar pain phenotypes. Two chronic pain conditions that share phenotypic features and are often evaluated in tandem for their shared etiology and clinical presentation are irritable bowel syndrome (IBS) and migraine. Notably, we refer to a patient's phenotype as it relates to pain symptomology and specifically the evolution and characteristics of how pain symptoms present over the course of an individual's life. For example, both conditions begin in childhood, involve intermittent attacks, female predisposition, have autonomic components that include nausea and vomiting,¹⁰ and commonly both conditions occur in the same patient.⁵³ Migraine has been associated with functional gastrointestinal disorders and other bowel disease, including colic, gastroparesis, celiac disease, and inflammatory bowel disease.^{18,29}

2. Neuroimaging comparisons between migraine and irritable bowel syndrome

The aim of this review is to evaluate the potential of structural neuroimaging to inform the clinical divisions between 2 chronic pain conditions. We focus on the objectives of (1) comparing patient groups with migraine and IBS by outlining changes in brain structure in the 2 cohorts, (2) providing a meta-analysis of stereotaxic data reported from the 2 conditions, and (3) providing a review of research evaluating machine learning on structural

neuroimaging data in these cohorts. Reports of brain regions can be found in **Tables 1 and 2**, as well as in **Figure 1**.

2.1. Brain regions

Data extracted from neuroimaging studies reflected average thickness and volume from cortical and subcortical regions of the brain. White matter integrity was evaluated using diffusion-weighted imaging¹ and measures reflecting water diffusion along the axial (AD = sensitive to axonal damage), radial (RD = sensitive to myelin level), and a mean (MD = measure sensitive to edema) of all directions, as well as a measure anisotropic water diffusivity (fractional anisotropy; FA = nonspecific marker of neuropathology). The patient data reflect individuals with IBS and migraine from approximately 20 to 60 years of age. Patient cohorts ranged in size from 8 to 110 and reflected mainly comparisons between patients and healthy controls.

2.1.1. Frontal cortex

Although structural brain changes are reported in both cohorts, more diffuse abnormalities are presented within persons with migraine than IBS within the frontal cortex. In IBS cohorts, evidence of decreased cortical thickness within the middle frontal gyrus^{13,62} as well as the DLPFC and DMPFC³³ was observed. For persons with a migraine diagnosis, an increase in surface area of the left suborbital gyrus was observed in one study,⁴⁹ whereas a decrease in brain volume was reported in regions including the right middle frontal lobe, left superior frontal sulcus, and left precentral sulcus.³⁷ In the migraine cohort, an increase in FA was found²⁰ and an increase in gray matter density in the orbitofrontal cortex⁶² and a decrease in brain volume was reported by 4.^{13,33,41,62} A review on persons with migraine supports a general decrease in brain volume within the frontal cortex.³⁵

2.1.2. Visual cortex

The visual cortex does seem to be impacted in migraine subjects in a manner that was not observed those with IBS. A decrease in brain volume in the visual cortex has been reported for migraine³⁷ as well as IBS.^{13,62} In patients with IBS, a small cluster of cortex within the occipital cortex was found to show decreased thickness relative to healthy controls⁶² and a small region within the cuneus.¹³ In migraine cohorts, an increase in brain volume is reported within the visual cortex in the lateral occipital-temporal cortex⁷⁴ and broadly across the visual cortex when associated with visual aura.²³ As such, differences in pain conditions within the visual cortex seem to be related to the visual symptoms associated with migraine patients.

2.1.3. Somatosensory cortex

Similar trends are reported across structural brain data within the somatosensory cortex in patients with IBS and migraine. In persons with IBS, an increase in cortical thickness^{36,41,62,70} was reported with only one study reporting a decrease in cortical thickness.²⁰ Specifically, female patients with IBS have been reported to have greater cortical thickness in the postcentral gyrus than healthy female,^{36,41} as well as in the secondary somatosensory cortex.⁶² Healthy controls have been reported to have increased cortical thickness in the somatosensory cortex relative to persons with migraine³² as well as an increased gyrification index (ie, increased folding) in left postcentral gyrus.⁷⁴ Relative to controls and patients without aura, patients with aura

Table 1**Structural brain changes in patients with IBS.**

Principle author	Year	Cohort	Age	Sex	Duration	Frontal		Visual		Sensory		Parietal		Temporal		Motor		Limbic		Sub-cortical	
						Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec
Blankstein	2010	IBS (11) HC (16)	IBS (30.2 ± 8.45) HC (31.5 ± 9.4)	IBS (11F) HC (16F)	2–20 years (mean 9.1)													X		X	
Seminowicz	2010	IBS (55) HC (48)	IBS (31.0 ± 12.3) HC (32.2 ± 10.1)	IBS (55F) HC (48F)	11.1 ± 7.7 years	X	X		X	X			X				X	X			X
Piche	2013	IBS (14) HC (14)	IBS (31.6 ± 8.3) HC 29.8 ± 6.9)	IBS (14F) HC (14F)	12.7 ± 2.6														X		
Chen	2011	IBS (10) HC (16)	IBS (32.8 ± 10.4) HC (29.1 ± 7.9)	IBS (10F) HC (16F)	2–20 years														X		
Irimia	2015	IBS (33) HC (56)	IBS (38.7 ± 10.4) HC (38.6 ± 11.51)	IBS (14F/19M) HC (33F/23M)	13.68 (SD 10.66)																
Chua	2017	IBS (29) HC (39)	IBS (36.2 ± 7.2) HC (37.2 ± 8.3)	IBS (29F) HC (39F)			X		X			X							X		X
Hubbard	2016	IBS (17) HC (17)	IBS (16.44 ± 1.73) HC (16.29 ± 1.83)	IBS (13F/4M) HC (13F/4M)	3.62 (SD 2.52)		X					X							X		
Hong	2014	IBS (11) HC 41)	IBS (31.6 r 21–47) HC (28.2 r 19–48)	IBS (9F/2M) HC (25F/16M)	—														X		
Labus	2014	IBS (82) HC (119)	IBS (32.2 (SD 9.6) HC 29.9 (SD 10.3)	IBS (82F) HC (119F)	12.7 (SD 8.9)		X			X				X					X		X
Jiang	2013	IBS (90) HC (176)	—	IBS (70F/20M) HC (155F/21M)	11.5					X					X				X		
Ellingson	2013	IBS (33) HC (93)	IBS (33.2 ± 10.8) HC (30.4 ± 10.4)	IBS (21F/12M) HC (72F/21M)	11.5 ± 1.53 SEM	X					X					X			X	X	X

An overview of reported brain changes is provided from studies evaluating patients with IBS.

"—" = data not reported; Dec = decrease; HC = healthy control; IBS = irritable bowel syndrome; Inc = increase; r = range.

Table 2**Structural brain changes in patients with migraine.**

Principle author	Year	Cohort	Age	Sex	Duration	Frontal		Visual		Sensory		Parietal		Temporal		Motor		Limbic		Sub-cortical	
						Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec	Inc	Dec
Rocca	2006	M (16) HC (15)	M (42.7 r 28–58) HC (38.6 r 24–50)	M (15F/1M) HC (13F/2M)	24.8 r 2–48		x								x						x
Kim	2008	M (20) HC (33)	M (33.7 ± 11.3) HC (33.8 ± 10.5)	M (17F/3M) HC (29F/4M)	9.8 ± 6.0		x					x				x					x
Schmidt-Wilcke	2008	M (35) HC (31)	M (32.4 ± 9.2) HC (32.3 ± 12.6)	M (32F/3M) HC (31F)																	x
Schmitz	2008	M (28) HC (28)	M 43.50 (SD 8.21) HC 42.50 (SD 9.31)	M (28F) HC (28F)	30.50 (SD 11.43)		x					x		x							x
Valfre	2008	M (27) HC (27)	M (34.9 ± 8.4) HC (34.9 ± 8.6)	M (21F/6M) HC (20F/7M)	20.6 ± 8.9									x		x					x
Maleki	2013	M—HF (10) M—LF (10) HC (10)	M—HF (43.9 ± 3.4) M—LF (40.2 ± 3.6) HC (39.1 ± 3.2)	M (14F/6M) HC (7F/3M)	—					x				x		x					x
Jin	2013	M (21) HC (21)	M (31.2 ± 11.3) HC (30.7 ± 10.5)	M (16F/5M) HC (16F/5M)	10.6 ± 6.6		x		x												x
Hougaard	2016	M (60) HC (60)	M (33.36 r 18–59) HC (33.39 r 18–59)	M (42F/18M) HC (42F/18M)	med MA attack frequency 12 per year (r of 2–96/ year)																x
Zhang	2017	M (32) HC (32)	M (38.3 ± 10.16) HC (38.8 ± 10.02)	M (24F/8M) HC (24F/8M)	9.5 ± 6.23				x		x			x							x
Gaist	2018	M (166) HC (137)	M (48.0 ± 6.6) HC (48 ± 7.7)	M (166F) HC (137F)	23.04 ± 10.8																x
Messina	2013	M (63) HC (18)	M (36.9 r 22–63) HC (37.2 r 22–56)	M (42F/21M) HC (13F/5M)	17 y (r 1–49)		x	x						x							x
Schmitz	2008	M (24) HC (24)	M 45.50 (SD 9.31) HC 41.50 (SD 12.90)	M (24F) HC (24F)	30.62 (SD 12.23)		x						x								

An overview of reported brain changes is provided from studies evaluating patients with IBS.

“—” = data not reported; Dec = Decrease; HC = healthy control; HF = high frequency; IBS, irritable bowel syndrome; Inc = increase; LF = low frequency; M = migraine; r = range.

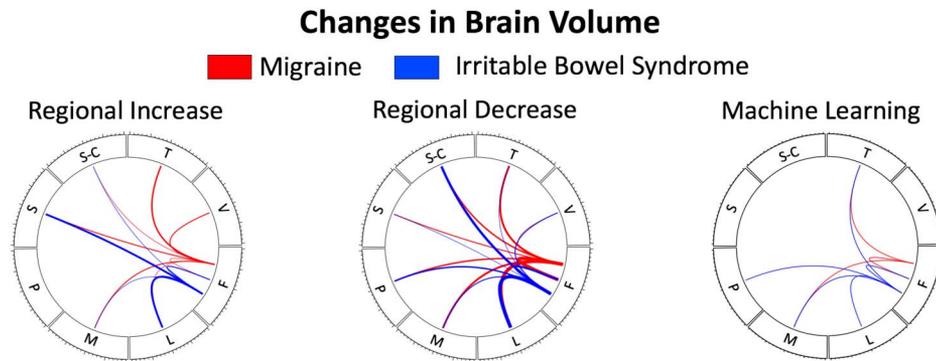


Figure 1. Regional structural changes in IBS and migraine cohorts presented using chord diagrams. Chords represent reported changes with the center of each chord being the frontal (F) cortex presented for convenience. The machine-learning diagram presents both increases and decreases together. Line weights are proportional to the number of studies reported. IBS, irritable bowel syndrome.

had decreased cortical thickness of the right central sulcus.⁴⁹ Together, findings suggest that similar trends are reported within the somatosensory cortex, even when considering subtypes of patients with migraine who may experience aura.

2.1.4. Parietal cortex

Structural neuroimaging data from patients with IBS and migraine within the parietal cortex were similar between cohorts. No evidence of increased cortical thickness from the reviewed studies was found for the parietal regions in either the IBS or migraine cohorts. In patients with IBS, there are consistent reports of a decrease in the posterior parietal cortex,^{13,33,62} and a similar decrease is found in migraine patients in both the posterior parietal cortex³⁹ as well as the inferior parietal lobe.⁶¹ As such, similar regions and trends are reported within the parietal cortex.

2.1.5. Temporal cortex

Differences in how brain structure is implicated between patients with IBS and migraine are found within the temporal cortex. In the context of IBS, evidence to support a structural change is limited, with only one study identifying lower volumes in bilateral hippocampi.⁴¹ Alternatively, in migraine, there is evidence to support a decrease in gray matter volumes^{57,61,67} including gray matter density in the parahippocampal area⁶¹ as well as increases^{45,49,74} in regions such as the left inferior temporal cortex.³⁵ Therefore, differences in pain groups within the temporal cortex are found where persons with migraine may demonstrate gray matter changes external to the hippocampus and parahippocampus.

2.1.6. Motor cortex

In migraine and IBS cohorts, similar changes in brain structure are observed. Findings in persons with IBS support the presence of an increase in the primary motor cortex in female relative to male IBS patients³⁶ and a decrease in brain volume within the premotor cortex⁶² as well as lower FA in motor regions.²⁰ In patients with migraine, an increase in cortical thickness around the central gyrus^{35,45} as well as a decrease in motor and premotor regions^{35,39,49,67} are reported.

2.1.7. Limbic regions

The limbic regions of the brain experience similar changes in brain structure between IBS and migraine cohorts. Several studies

report an increase in brain volume in persons with IBS within the anterior cingulate cortex and posterior cingulate cortex, insula, as well as increased FA in the fornix and external capsule next to the right posterior insula.^{11,33,54,62} Patients also reported a decrease in the anterior midcingulate cortex and right caudal anterior cingulate cortex, and female patients seem to have higher MD in the cingulate white matter than male patients with IBS do.^{5,13,20,31,36,42,70} In patients with migraine, a decrease in gray matter volume within the left cingulate gyrus, right anterior cingulate cortex, and bilateral insular cortex is reported.^{32,37,39,45,60,67,74} No significant increases within limbic regions were reported in the migraine cohort.

2.1.8. Subcortical regions

In terms of brain regions, group trends were largely similar in terms of how subcortical regions were impacted structurally. However, it seems that distinct subcortical structures are impacted in each clinical cohort. In persons with IBS, Ellingson et al.²⁰ reported higher MD in regions in the internal capsule and thalamus and a lower FA and MD in the globus pallidus. An increase in gray matter density in the hypothalamus⁵ and decreased gray matter density were found in the thalamus⁶² and left cuneus¹³ have also been observed, thus focusing attention largely on the thalamus within IBS cohorts. In migraine cohorts, an increase in the gray matter of cerebellar regions⁷⁴ and the periaqueductal gray (PAG)⁵⁷ and a decrease in gray matter volume of the cerebellum³⁷ were found. The former (PAG) has previously been implicated in having a role in descending pain modulation⁴⁴ and is a notable difference between groups. That is, contrary to reports in IBS, the volume expansion¹² as well as atypical functional activity have been reported within the PAG in persons with migraine, which has been proposed as generator for migraine attacks.⁷¹ As such, subcortical structures may provide novel insight into specific pain conditions.

2.1.9. Sex differences and psychometrics

Biological sex has been shown to influence changes in brain morphology. As shown in **Table 1**, a significant portion of subjects evaluated were female. In persons with IBS, Jiang et al. found that brain changes were most observant in female subjects. Females with IBS were found to have lower cortical thickness within the bilateral subgenual anterior cingulate cortex and greater cortical thickness within the precentral gyrus and postcentral gyrus relative to female healthy controls.³⁶

Alternatively, in migraineurs, an ALE analysis comparing 191 migraine patients and 199 healthy controls found no effect of sex.³⁵ It has been reported that changes in brain morphology in persons with IBS correlate with patient health variables such as sex, anxiety, depression, IBS bowel subtype, and early-life trauma.⁷⁰ In persons with migraine, an ALE analysis found that estimated frequency of attack has been reported to correlate with changes in the GM volume of the right claustrum, left cingulate gyrus, right anterior cingulate, amygdala, and left parahippocampal gyrus.³⁵ Thus, the influence of biological sex and clinical features seems to influence IBS and migraine in distinct manners.

2.2. Meta-analysis

To further examine the brain regions implicated in the 2 evaluated cohorts, a meta-analysis of reported stereotaxic coordinates was performed. Of the included studies (limited by author reporting of coordinates), stereotaxic coordinates were extracted from 9 experiments (5 from migraine and 4 from IBS), totaling 473 subjects and 107 coordinates (**Fig. 2**). Only studies that reported coordinates comparing the sample population relative to healthy controls were included. One cluster of stereotaxic coordinates was found in the combined data set and was located within the inferior frontal gyrus of the right hemisphere (Montreal Neurological Institute [MNI] coordinates: 62, 14, 10; extrema value: 0.0167). This cluster contained only studies from the migraine cohort.^{39,57,67} Notably, changes within this region are not reported in the IBS literature from our review (see above). However, reported clustering in the right hemisphere aligns with prior literature suggesting a right hemisphere focus for pain processing.⁶⁶ As outlined in the current review, a large number of brain regions are found to display altered morphology within the frontal cortex in both groups, and altered changes within the inferior frontal gyrus have been specifically implicated in pain processing.⁴⁰ The right hemisphere inferior frontal gyrus has been implicated in cognitive processes such as attentional switching²⁶ and response inhibition.²² As such, the current meta-analysis findings suggest that group differences may be observed within the frontal lobe between groups in relation to factors that may influence motor tasks.

2.3. Defining pain signatures and subgroups using higher level classification tools

The availability of large-scale data has instigated the use of more mathematically driven techniques to understand data emerging from brain imaging. One of the most popular forms of this is

machine learning where regression-based analyses (for example) can be applied to understand data trends in ways that either reinforce a priori knowledge or provide data-driven knowledge (see Ref. 51 for review of machine learning in neurological disorders). In the former, called supervised learning, knowledge regarding group designations may be supplied (eg, designating if a participant is a healthy control or migraine patient) to determine how well-evaluated metrics (eg, functional Magnetic Resonance Imaging fMRI BOLD data) are able to predict group membership. Unsupervised learning is where data are submitted without a priori knowledge, which enables a more data-driven approach to evaluate trends emerging from that data set. Accordingly, machine learning has the capacity to be applied as a classification tool in persons with pain to aid in the delineation of variables that may be used to differentiate existing group membership, or to supply novel data that extend current pain-group knowledge.

Research evaluating patients with IBS and migraine using structural neuroimaging data and machine learning has been minimal. Regions delineating patients with IBS from healthy controls using morphological criteria can achieve an accuracy of 70%. Although this level of accuracy is low, it provides a list of regions that help distinguish healthy from IBS persons: the horizontal ramus (R), subcallosal area (L), intraparietal sulcus (L) and transverse parietal sulci (L), fusiform gyrus (L), transverse temporal sulcus (R), superior precentral gyrus (L) and primary interoceptive cortex (L), posterior segment of the lateral sulcus (L), and posterior insula/inferior parietal sulci (L).⁴² Evaluating migraine patients without aura using gray matter data, the top 10 brain regions that classified patients relative to controls (accuracy of 71.43%) included the hippocampus (L/R), parahippocampus (L/R), precentral gyrus (L/R), superior frontal gyrus (L/R), supplementary motor area (L), superior frontal gyrus (R), and inferior frontal gyrus (R) (opercular part). Notably, these patients had elevated depression and anxiety scores that may also have impacted structural brain data.⁷⁵ Using a support vector machine model, Garcia-Chimeno et al.²⁴ found that they could correctly classify controls vs patients (chronic migraine) at a level of 94% using diffusion tensor imaging from the left uncinate, and left cingulate gyrus that also integrated patient reports of pain and their analgesic use. Accordingly, the value of using brain imaging data is best exemplified when used in conjunction with patient-related data.

In patients with chronic pain, the use of machine-learning classifiers has been yielding results that are at times strong but

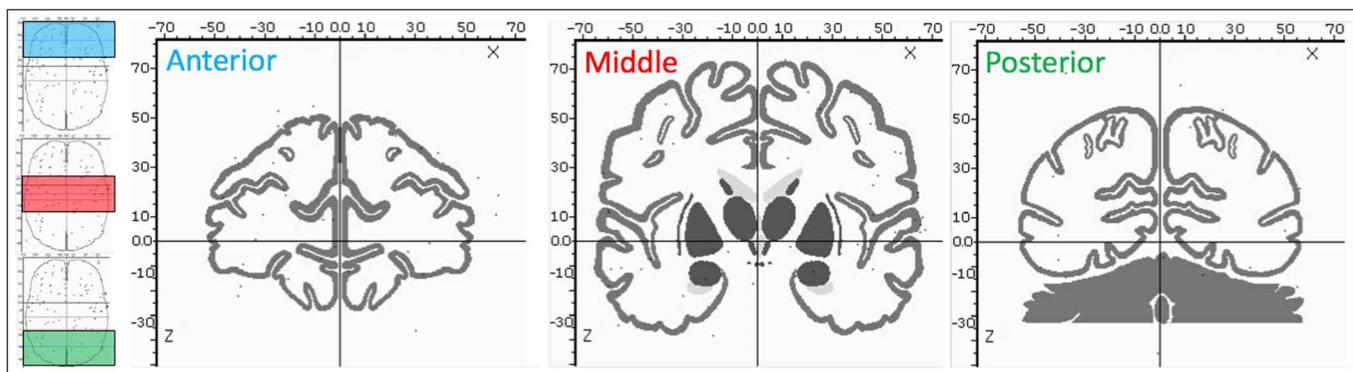


Figure 2. Coordinate evaluated in meta-analysis. Three sections are presented going from the anterior (blue) through the middle (red) and posterior (green) aspects of the brain. Black dots represent stereotaxic coordinates reported in the included studies within the window presented on the left. Image is presented in MNI space.

largely variable between studies. The accuracy of such classifiers ranges from approximately 50% to 90% and only addresses the differentiation between pain and nonpain groups, and not addressing the diversity in underlying pain subtypes. Although research has shown in both IBS and migraine cohorts that distinct brain regions can be identified through structural metrics to classify patients relative to healthy controls, no research has evaluated these 2 conditions in tandem. Despite this, evidence suggests that a relatively high level of accuracy can be obtained in relation to healthy populations (approximately 70%–90%). Comparing results from the above investigations with those shown to contribute towards subliminal pain processing (see Ref. 8), it is interesting to note that only cortical structures are observed. The prefrontal cortex is inherently involved in the conscious awareness of pain, and temporal lobe structures such as the hippocampus are involved with conscious and unconscious memories. Both of these regions were identified through the above machine-learning studies in the IBS and migraine cohorts and align with a neuronal basis of pain chronification. Pursuing future research that directly compares pain cohorts with machine-learning algorithms is likely to yield highly valuable clinical information.

3. Discussion

In this review, 2 highly phenotypically related pain conditions were chosen to evaluate and compare how structural neuroimaging data can distinguish the 2 groups. Findings highlight unique differences between these patient groups that may be exploited in future work attempting to delineate pain subtypes using single study or advanced classification tools.

3.1. Are differences in pain groups observable and relevant?

In the current review, a comparison was performed between 2 chronic pain conditions with similarities in terms of their clinical phenotype. Interestingly, a large number of regions displayed similar trends between groups that align with those reported in prior work on the “pain matrix,”^{47,48} consistent with a core set of brain regions being implicated in the pain response. However, beyond these regions, the 2 populations diverged. Group differences were observed mainly within the visual, temporal, and subcortical regions, and findings from the meta-analysis highlighted a difference in the inferior frontal gyrus. An increase in cortical thickness within the visual cortex was observed in the migraine and not IBS group, which may align with the visual component of migraine symptoms.⁶⁸ Although both groups showed decreases in temporal lobe volumes, only the migraine cohort showed evidence of an increase in brain volume. The finding of hippocampal changes in patients with migraine has been attributed towards stress³⁸ but is also suggested to play an important role in the pathophysiology of migraine.⁴⁵ Interestingly, a very pain-relevant area was found in the migraine but not IBS cohort (PAG), which plays a role in descending pain modulation.⁴⁴ Finally, findings from the inferior frontal gyrus may relate to a loss of motor control for patients with migraine,⁷³ the extent of the pain (right sided), or how the pain influences nearby motor structures such as speech perception (Brodmann Area 44: Broca’s area). Together, findings from the review and meta-analysis support an identifiable difference between conditions that share very similar phenotypic presentations.

Findings from the reviewed machine-learning studies highlighted unique features. That is, in the IBS group, dominant regions were reported that included frontal, parietal, motor, and

limbic regions. Alternatively, in the migraine group, frontal, temporal, and limbic regions of the cortex were reported. In both cases, only cortical regions were reported as features to the associated algorithms. This is a novel finding and contrasts with findings from single studies (Fig. 1) that report both cortical and subcortical structures as being active, as well as prior findings that implicate subcortical structures in pain processing.⁸ Reasons for this may include low variability in subcortical volumes, inconsistent labeling of subcortical structures, and a lower relative contribution to pain symptoms in comparison with cortical structures. The precise nature of this will be the subject of future research. Notably, the output from such algorithms produced varying degrees of success, ranging from 50% to 90% in accuracy,^{6,9,55,64} and suggests that the performance of pain-group classifiers may currently be limited in terms of reproducibility or stability. Changes in brain regions highlighted outside of the pain matrix have been suggested to correspond to comorbidities⁶³ such as depression⁵⁹ or anxiety²¹ and may have influenced brain morphology. This would align with higher ratings of depression and anxiety found in the migraine cohort and may account for findings in the limbic (eg, insula) and prefrontal (eg, orbitofrontal cortex) regions. Considering that the currently referenced work is at the level of differentiating pain conditions from healthy control cohorts, comparing pain subtypes is likely to present even greater instability.

3.2. Integrating neuroimaging to improve pain classification

It has been previously argued by our group that pain processing continues, even if it does not reach conscious awareness.⁸ To this point, analysis of neuroimaging data would provide invaluable knowledge that could not be addressed using existing phenotypic evaluation criteria. However, the delineation of brain regions implicated in specific pain cohorts has received a paucity of attention because the pain-neuroimaging field first validates the ability to distinguish regions that are implicated in the elementary response to pain.^{34,47,48}

To improve the stability and accuracy of machine-learning classifiers, future analyses should integrate multimodal data. As in phenotypic as well as biotype analyses, the isolation of a single or even a set of brain regions is not pathognomonic for a particular pain disorder.⁴³ Because each domain has limitations, the use of metadata from multiple modalities likely has a critical role in defining pain subtypes in future research. The use of phenotypic data definitely has a critical role in the evaluation of patients with chronic pain because it reflects the impact that a disease has on factors such as quality of life; however, understanding subliminal factors such as neuronal processing of pain information and genetic susceptibility will not only help delineate new pain subtypes but also improve the precision of personalized medicine. The use of large pain imaging repositories such as PainRepository.org will contribute to the development of accurate pain-group classifiers by improving their accuracy and reproducibility.⁴²

3.3. Limitations

This study has several limitations that require address. First, the literature search was not exhaustive and therefore we may have missed studies that are published. The impact of missing a publication on findings from this review is likely minimal as our findings integrated prior reviews. Second, the performed meta-analysis is limited in terms of the number of studies that were included. We were constrained in terms of how many studies we

could extract reported stereotaxic coordinates from as not all studies reported coordinates from statistical comparisons. Similar to other reviews, we chose to align our reporting with the brain regions reported by study authors. Third, a lack of investigations examining the age effects of chronic pain conditions constrained our ability to comment on the impact of age in the evaluated clinical conditions. Although prior research has shown age-dependent effects in terms of the clinical presentation of migraine,⁷² as well as the functional organization of the brain,¹⁴ this is an area that requires greater attention from researchers. Due to the limited nature of the available literature, investigations evaluated in this review were focused on young adults. Finally, our choice of pain conditions for evaluation was based on prior literature examining both IBS and migraine both independently and in tandem. If different pain conditions were chosen, it is possible that study findings may have been marginally different, although we are confident that conclusions would remain the same.

4. Conclusion

The capacity to identify subgroups of patients and achieve personalized medical practice will require the integration of a person's brain type. Information retrieved from brain imaging is likely to play a significant role in this process because it offers a bridge that connects the variance in a person's innate biology with their presenting phenotype and can provide insight into mechanisms of pain perception and persistence. The specific delineation of pain subgroups is likely to be best fulfilled by integrating metadata from diverse modalities and using higher level computing to discern trends using supervised and semi-supervised techniques. Future research will be required to determine the optimal integration of each technique to define pain subtypes.

Disclosures

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