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Chronic Pain in Children: Structural and Resting-State Functional Brain Imaging Within a Developmental Perspective

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Abstract

Chronic pain is a major public health problem in the United States costing \$635 billion annually. Hospitalizations for chronic pain in childhood have increased almost tenfold in the last decade, without breakthroughs in novel treatment strategies. Findings from brain imaging studies using structural and resting-state fMRI could potentially help personalize treatment to address this costly and prevalent health problem by identifying the underlying brain pathways that contribute, facilitate, and maintain chronic pain. The aim of this review is to synthesize structural and resting-state network pathology identified by recent brain imaging studies in pediatric chronic pain populations and discuss the potential impact of chronic pain on cortical development. Sex-differences, as well as treatment effects on these cortical alterations associated with symptom changes, are also summarized. This area of research is still in its infancy with currently limited evidence available from a small number of studies, some of which suffer from limitations such as small sample size and suboptimal methodology. The identification of brain signatures of chronic pain in children may help to develop new pathways for future research as well as treatment strategies.

Introduction

Chronic adolescent pain is estimated to cost society \$19.5 billion (1), and insufficient funding for prevention, care, education, and research is likely to escalate this cost even more (2). Prevalence rates of chronic pain in children differ across numerous epidemiological studies relative to diagnosis, duration of pain, early adversity, and age (3). Coffelt et al (4) reported that between 2004–2010 the number of children admitted to a hospital for chronic

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pain increased 831%, with a significant portion presenting with comorbid conditions such as depression, anxiety, and/or a change in bowel habits. Many of these chronic pain conditions involve multiple systems and show comorbidity with each other (5,6), with girls exhibiting a greater prevalence of chronic pain conditions, and even more pain with increased age (3,7). If left untreated, the development of chronic pain and psychiatric comorbidities can persist (8–11), while early targeted interventions have the potential to prevent the pain from continuing into adulthood.

Chronic pain can be characterized as somatic (musculoskeletal and cutaneous) and visceral (hollow or solid organs and smooth muscle). These two classes of pain have similarities and differences in underlying anatomical composition, organization, and cellular processes (12–14) that can be represented as different neurological signatures (e.g. brainstem connectivity patterns) (13). Pediatric pain brain imaging studies have provided insight into supraspinal pathologies, their relationship to observed behaviors, and treatments that can change chronic pain-induced alterations. This review will synthesize structural and resting-state network pathology from brain imaging studies in pediatric chronic pain populations. We discuss the potential interaction of chronic pain with cortical development, the possible role of microglia activation in this process, and suggest how treatments targeted at these cortical pathways show promise in treating this debilitating condition. The PubMed database was searched in November 2018 using the keywords “children”, “pain” and “brain.” Only studies investigating structural and resting-state functional connectivity between children with chronic pain and healthy controls were used due to the lack of studies using diffusion tensor imaging (DTI). The age limit for the children was set at 18 years old. A total of 11 neuroimaging studies were found that met review criteria. Limitations and advantages of each of the studies are discussed, highlighting areas for future research.

Investigating Cortical Mechanisms in Pediatric Chronic Pain using Brain Imaging

The limited brain imaging studies in children compared to adults makes it difficult to provide conclusive statements about interacting structural, connectivity, and neurochemical abnormalities. However, recent studies in children with complex regional pain syndrome (CRPS), migraine, sickle-cell disease, and functional abdominal pain (FAP)/irritable bowel syndrome (IBS) have produced findings analogous to that in adults. Multimodal imaging refers to the use of different brain imaging techniques to detect and quantify different aspects of brain structure, function, and molecular signaling. Two of the most common methods are 1) structural MRI - determining properties of gray matter - and 2) functional MRI – assessing cortical activation through changes in local concentration of paramagnetic deoxyhemoglobin (blood-oxygen-dependent imaging [BOLD] imaging). Diffusion-tensor imaging (DTI), an imaging modality measuring white matter microstructure, has been investigated in adults with chronic pain but not in children.

Gray matter is mainly measured using two approaches, voxel-based morphometry (VBM) and surface-based analyses (SBA). VBM quantifies the amount of gray matter in each voxel and allows for comparisons across subjects and groups. In SBA, various morphometric measures are derived from geometric models of the cortical surface. Cortical thickness is defined as the distance between the white matter surface and the pial surface. Volume is a

quadratic function of distances in the surface and a linear function of thickness. Surface area and the mean curvature, which is a measure of folding patterns (how sharply the cortex is folded), are also metrics derived from SBA (15,16). During resting-state, “functional networks” are groups of brain regions connected by their spatiotemporal configuration and function (17). The most common network alterations reported in chronic pain include the default-mode network (DMN), sensorimotor network (SMN), salience network (SN), emotional regulation network (ERN), central executive network (CEN), and central autonomic network (CAN) (Table 1, Figure 1). The DMN consists of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), inferior parietal cortex, lateral temporal cortex, and hippocampal formation. It is responsible for emotional processing, self-referential mental activity, and recollection of prior experiences (18–20). The SMN consists of the basal ganglia, thalamus, posterior insula, and the primary/secondary motor and somatosensory cortices. It receives input from the periphery and is important for the awareness of bodily sensations and the generation of appropriate motor responses (21). The SN consists of the mPFC, orbitofrontal cortex (OFC), anterior insula (aINS), and anterior mid-cingulate cortex (aMCC). It responds to a wide range of sensory stimuli or expectations of such stimuli, computes the subjective salience of such stimuli and, accordingly, coordinates appropriate behavioral, affective, and bodily responses aimed to assure homeostasis of the organism (21–23). The SN plays the major role in switching from the DMN to the engagement of the CEN, the ERN, and the CAN whenever the homeostasis of the organism is perturbed or the brain is expecting such a perturbation in the future. The CEN encompasses the dorsolateral prefrontal cortex (dlPFC) and posterior parietal regions and is related to working memory, attentional processes, planning and response selection (21). The ERN is comprised of the amygdala, the locus coeruleus, hippocampus (Hipp), amygdala, subgenual ACC (sgACC), pregenual ACC (pgACC), mPFC and ventrolateral prefrontal cortex (vlPFC). The ERN is an important link between stimulus appraisal and autonomic output (21). Finally, the CAN includes the brainstem, amygdala, hypothalamus, sgACC, aINS, aMCC, mPFC, and OFC and is responsible for central control and modulation of the autonomic nervous system (ANS) (21,24).

Below is a summary of disease-related structural and resting-state brain-imaging findings across networks and chronic pain conditions in children (see Table 2). Sex-differences within each pain condition are discussed.

Complex Regional Pain Syndrome (CRPS)

CRPS is characterized by chronic pain, typically affecting an extremity but not exclusively, and associated with allodynia, hyperpathia, changes in skin color, temperature and/or swelling in the affected areas (25). It may or may not be associated with an injury.

Children with CRPS compared to normal controls—Children with CRPS type I (absence of identified peripheral neuropathy) have less gray matter (GM) and higher resting-state functional connectivity (RS-FC) within the SN than healthy controls (HCs) (26,27). They also have less GM and higher RS-FC in the cortical areas of the SMN, lower RS-FC in the basal ganglia of the SMN (26,27), less GM and higher RS-FC in the ERN (26,28), less GM and higher RS-FC in the CEN (26,27), less GM in the CAN (26), and less GM and

higher RS-FC in the DMN than their HC counterparts (26). These findings suggest that much of the brain involved in regulating chronic pain may be hyperactive in children with CRPS and are responsible for consistent chronic pain with no obvious peripheral abnormalities and mediated by the central nervous system.

Headaches: Migraines

Migraines are defined as an intense pulsing or throbbing pain most often in the head, although other sensory and motor systems can be involved, with some clinicians labeling recurrent bouts of severe abdominal pain as “abdominal migraines” (29,30). However, physiological evidence supporting the diagnosis of “abdominal migraine” is minimal (31,32). Additional symptoms can include nausea, vomiting, as well as sensitivities to light and sound. For some individuals, the onset of migraines can be predicted with the occurrence of an aura, described as visual disturbances of flashing lights and/or temporary loss of vision or some other premonitory symptom.

Findings of children with migraines associated with headaches compared to HCs indicate that children with migraines have less GM in the SN (33); mixed results regarding GM in the SMN (33,34); less GM in the ERN (33,34); less GM in the DMN (33,34). This suggests that children with migraines have excess gray matter loss, synaptic pruning and cortical reorganization throughout the brain, which could potentially contribute to hyperconnectivity and chronic pain. From a developmental perspective, this indicates that children with migraines may be undergoing cortical processes that represent sped up cortical development/aging and/or atrophy compared to healthy children. We later discuss plausible cellular mechanisms that may underlie these processes. No RS-FC studies have been conducted in this population.

Disease – Sex Interaction in Children with Migraines associated with severe headache

Sex differences have also been observed in GM trajectories throughout development. Specifically, GM volume reaches the highest levels in females 1–3 months earlier than in males throughout all structures. As there are sex GM trajectory differences (35), it is important to look at sex differences in the brain for children in chronic pain to understand potential sex-related developmental pathologies. Such differences have only been investigated in children with migraines.

Boys with migraines have lower GM in regions of the ERN compared to girls with migraines, and lower RS-FC compared to girls and HCs (33,34). Boys with migraine have shown lower GM in regions of the ERN compared to male HCs; Girls with migraines have greater GM in regions of the SMN compared to boys with migraines and HCs of both sexes; Girls with migraines have greater GM and greater RS-FC in regions of the DMN compared to boys with migraines and HCs of both sexes (34). This suggests that the underlying circuits in networks affecting sensory processing may be different in boys (ERN) vs girls (DMN) with migraine. Further research in other chronic pain conditions can determine sex-dependent changes and differences that can direct targeted treatments. No RS-FC studies have been conducted in this population.

Puberty Stage Effects in Children with Migraines

GM changes during puberty, a period of significant brain development, has only been studied in children with migraines (36). In children with migraines, during early puberty boys show more GM in the SMN compared to girls, yet at mid-puberty, girls show more GM in the SMN compared to boys. At early puberty, boys exhibit more GM in the ERN compared to girls, but at mid-puberty, the opposite sex finding occurs (girls show more GM in the ERN compared to boys (34). Thus girls may be more vulnerable to gray matter atrophy during early puberty, while boys may be more vulnerable in mid-puberty. As girls start puberty at an earlier age compared to boys, the development of these networks may be associated with cortical development due to age (i.e lower overall GM in boys compared to girls), as well as due to the effect of migraine. Future multisite studies are needed to determine the degree to which puberty and biologic sex impact the effects of migraine on brain development.

Irritable Bowel Syndrome (IBS)/Functional Abdominal Pain (FAP)

IBS is the most common disorder of brain-gut interaction (traditionally referred to as a functional gastrointestinal disorder), defined by recurrent abdominal pain associated with altered bowel habits. Patients often suffer from other GI symptoms such as nausea, diarrhea, constipation, and bloating. IBS remains defined by symptom criteria and by the absence of identified gastrointestinal structural, inflammatory, immunologic, or biochemical pathology (21).

Children with IBS/FAP compared to HCs have less GM in regions of the SN (37–39), less GM in the SMN (with decreases over time), as well as greater RS-FC within the SMN (37,38); they have less GM, as well as lower RS-FC between areas of the CEN (37,39); and mixed results regarding GM and RS-FC within the DMN (37,39). Similar conclusions can be made for children with CRPS, as less GM being associated with accelerated development and altered resting-state functional connectivity, including greater SMN processing associated with hyperactive cortical circuits contributing to central pain. However, only one longitudinal study has been conducted to date and more studies are needed to prove this hypothesis. It has been shown that in adults, GM loss is the consequence of chronic pain (40), suggesting that cortical hyperactivity, or other cortical cellular processes - which may be causing or be a consequence of chronic pain - may be a contributor to this phenomenon, but future studies are needed to address this hypothesis, especially in children.

Sickle Cell Disease (SCD)

Vaso-occlusive pain crises are considered the hallmark symptom in SCD, a condition caused by a genetic defect in the β -globin chain and polymerization of HbS, and children with SCD may have repeated pain crises often requiring hospitalization (41). Over time, many children with SCD develop chronic pain (42). The impact of SCD on cognitive function may have salience in terms of cognitive-focused interventions and thus is mentioned here.

Children and adolescents with SCD are susceptible to mini-silent strokes that can impact brain structure and function and may contribute to chronic pain and cognitive dysfunction (43–47). Children with SCD compared to HCs have been found to have less GM in the

DMN (48), ERN and SMN (49), as well as greater RS-FC in the DMN, a finding associated with lower cognitive performance (50). These results run parallel to the GM loss and greater RS-FC observed in other chronic pain conditions in children. Lower GM and greater RS-FC in the DMN suggest that this key network involved in regulating chronic pain is hyperactive and contributing to symptoms. This may also be associated with accelerated development/aging of the brain and heightened neural connectivity associated with chronic pain and other neurological deficits.

Efficacy of Treatments and Associated Brain Changes

Treatment effects concerning neuroimaging findings in CRPS—Longitudinal studies have shown that with appropriate therapy, chronic pain can be reduced, and these clinical improvements are associated with supraspinal changes. Following an intensive three-week, eight hours/day, five days/week psycho/social/physical treatment regimen (51), decreased RS-FC in the SMN was associated with decreased pain (27). GM volume in the SMN increased following the intervention (26). This growth in GM was also associated with lower pain scores (26,27). Previously lower GM in the ERN increased and higher RS-FC in the ERN decreased (27,28). GM in the CAN increased (26). RS-FC within the DMN decreased and was associated with decreased pain (26). Additionally, increases in RS-FC between the dlPFC and periaqueductal gray were observed following treatment (26), reflecting an enhanced ability to engage in top-down inhibitory mechanisms (52,53). However, all of these studies were conducted in one institution and one condition (CRPS), and more research is needed as validation.

Discussion

Children across all chronic pain conditions studied were found to have lower gray matter (GM) and greater resting-state functional connectivity (RS-FC) within the major pain-associated networks. Some of these differences between children with and without pain were associated with altered pain perception. Reduced chronic pain was associated with normalized pathologic brain connectome differences associated with non-pharmacological, pain-focused interventions.

Data from neuroimaging studies in children with chronic pain (Table 2) indicate generally lower GM throughout the brain across diagnoses compared to healthy controls, with one longitudinal study showing decreased GM in the sensorimotor network in children with IBS from ages 7–9 years compared to that in controls (37). Most studies have found that children with chronic pain exhibit higher RS-FC compared to healthy controls. However, longitudinal studies will be needed to replicate these findings in larger samples across chronic pain conditions, age, puberty, and between sexes.

The Developing Brain – A Primer

The *structure* of the developing brain is a product of variable regressive (e.g. synaptic pruning) and progressive (e.g. increased myelination) cellular processes occurring simultaneously, which correspond to brain shrinkage and growth (54). Between the ages of 7 and 30 years, as the brain grows in an evolutionarily relevant sequence, there is a reduction

in the density of gray matter, but an increase in white matter (54,55). Moreover, it has been established that trajectories that take both brain size and age into consideration are more likely to predict functional characteristics (e.g., intellectual ability (56), or neurodevelopmental disorders, such as autism, attention-deficit/hyperactivity disorder, and schizophrenia (36,56–58)) compared to absolute GM density (56,59,60).

The developing *functional* brain exhibits pronounced “small-world” characteristics (61). This means the brain is organized into local networks that are not as communicative as more densely connected networks found in adults. Early in development, functional hubs are largely confined to sensory and motor regions, and, with age, shift to the PCC and insula. Developmentally, the most important networks are regarded to be the central executive network, salience network, and default mode network. These networks are identifiable at an early age and undergo significant change until the age of about 20 years. Deficits in these networks are often seen in neurodevelopmental disorders and chronic pain (26–28,33,34,37–39,50,61,62). Thus, even as most imaging studies to date in pediatric pain populations have been cross-sectional, we will discuss these findings in the context of the developing brain.

The Developing Brain During Childhood and Adolescence and its Role in Pain

Neuroplasticity in infancy and childhood underlies the tremendous nociceptive brain development before adulthood (63). Neuroplasticity plays an essential role in the development of neonatal brain circuits and gray matter (GM) and white matter development (WM) throughout adolescence (62). The human brain undergoes extensive changes in GM and resting-state functional connectivity (RS-FC) throughout development into adolescence and young adulthood (55,59,62,64–69). The effect of nociceptive stimuli on the developing, infant human brain has been studied using electroencephalography (EEG) and event-related potentials (ERPs). Larger nociceptive ERPs, but not tactile ERPs have been found in preterm infants who were exposed to many invasive, skin-breaking, painful procedures and morphine (70), suggesting that pain experienced in the neonatal intensive care unit (NICU) affects brain networks involved in pain processing but not in perception of non-painful tactile stimuli. Up to 68.4% of children who spend time in the NICU can develop chronic pain by age 10, and greater pain-related stressors, painful procedures, and morphine in the NICU are associated with lower global brain volumes and lower gray matter throughout the brain during childhood (71,72). Abnormalities in WM microstructure are associated with greater numbers of invasive procedures by age 7 and lower cognitive function (73). Cortical abnormalities associated with chronic pain can continue into adulthood and are manifest by both physical and psychological symptoms (10,37,74). These results suggest that the developing brain is plastic and vulnerable and that changes in pain processing circuits in response to nociceptive stimuli can result in longlasting anatomical and functional changes contributing to lifelong chronic pain.

As children age their GM decreases and their RS-FC increases (61,62). Pain during childhood may magnify and hasten these neurodevelopmental changes. Along these lines, the rapid These neurological changes as a consequence of GM loss during synaptic pruning and associated myelination could lead to increased RS-FC connectivity. We hypothesize that this neural developmental “speed-up process” involving microstructural processes such as

the production of more myelin, selective synaptic pruning, and the development of subcortical-cortical connectivity (61,68,75,76) could be a cortical facilitator of chronic pain symptoms in children, facilitating exacerbated communication between brain regions. In adults, a reduction of cortical GM, specifically in the cingulate, orbitofrontal cortex, insula, dorsolateral prefrontal cortex, thalamus, and somatosensory cortex, has been associated with chronic pain and linked to premature aging (40,77–81). Longitudinal studies in adults with chronic pain, compared to controls, have shown decreases in GM in the somatosensory cortex, motor cortex, throughout the striatum, and in the insula (82,83), a finding that is a consequence and not the cause of chronic pain (40). Just as overall greater RS-FC was found in most cortical networks in children with chronic pain, increased RS-FC has been observed in adults with chronic pain longitudinally. Specifically, decreased GM and increased sensorimotor-mPFC functional connectivity found in both cross-sectional and longitudinal studies predict pain chronification (83,84), and hyperconnectivity has been associated with the intensity of chronic pain (85). High mPFC-nucleus accumbens (subcortical-cortical) connectivity in adults with chronic pain plays a significant role in reorganizing and decreasing the GM in the cortex and increasing the emerging WM tracts in pain modulatory regions (86). As the mPFC is involved in the salience network, emotion regulation network and central autonomic network, increased activity in mPFC in children with chronic pain can be heavily impacted by increasing activity throughout multiple cortical networks involved in pain, thus increasing pain focus and amplifying pain signaling (84,87,88).

Formation of pain-associated pathologic neural networks is also influenced by genetic and epigenetic factors (89–91). Atypical pain sensitivity and sensory integration issues are common in children with developmental disorders (e.g., autism) (92,93). These developmental brain alterations could leave children with chronic pain vulnerable to the development or exacerbation of chronic pain and psychiatric pathologies at later times during childhood and adolescence (8,94,95), and may even “set the stage” for pain problems throughout the lifespan.

The possible role of microglial activation in chronic pediatric pain—In the last decade, many mechanistic studies have focused on the role of microglia and neuro-glial interactions in the spinal cord and brain in chronic, persistent pain. Using PET imaging, greater brain glial activation has been observed in brains of adults with chronic low back pain and fibromyalgia, specifically within the sensorimotor and executive control networks (96,97). These findings suggest a plausible mechanism underlying hyperconnectivity of the SMN in low back pain patients (98) and other patients with chronic pain, including children. (27,83,99–104). Microglia continuously monitor the interstitial fluid for extracellular signals and consequently respond to maintain homeostasis via a multitude of highly diverse processes. These activities affect both grey and white matter, including neuronal plasticity, synaptic pruning, programmed cell death, and phagocytosis (105). Additionally, phenotypic characteristics of aging and activated microglia have been associated with an elevation in pro-inflammatory cytokines and proliferative capacity, while showing a decrease in phagocytosis and motility, a phenomenon that is known as “microglia priming” (106). The effects of microglia priming (e.g. exaggerated neuroinflammatory response) are known to have a vital role in excitation of lamina I neurons in the central nervous system, which are

crucially involved in chronic neuropathic pain. Additionally, excess glial activation and synaptic pruning can be observed as gray matter loss, as glial cells are known to remove synapses in an activity-dependent manner via inflammatory-mediated neurodegeneration and reactive microgliosis (107–109). Future research focusing on imaging microglia, central nervous system function, and intrinsic brain connectivity may help provide a mechanistic explanation underlying the observed cortical changes (i.e. decreased GM and greater RS-FC) and hypothesized accelerated aging (81,110–112) in children with chronic pain.

Treatments and Cortical Mechanisms—Non-pharmacological treatments for chronic pain, such as cognitive-behavioral therapy (CBT), have proved efficacious (113–116) and provided insight into cortical mechanisms that could be targeted to improve symptoms. For example, an intensive day-hospital treatment program, consisting of physical, occupational, and CBT therapies (51), decreased previously higher amygdala connectivity in the sensorimotor, salience and central executive networks in adolescents with chronic pain compared to controls at a matched time interval before and after the patients were discharged. This decrease in connectivity was associated with a decrease in self-reported pain (28). CBT on its own has also proved efficacious for children with chronic pain in reducing activity limitations and pain intensity (117). Changes in neural connectivity associated with CBT effectiveness in children with chronic pain are yet to be explored, but have been shown to change RS-FC in adults with chronic pain and are associated with symptom improvement (104,118).

Results from other therapies in adult chronic pain patients have shown the effectiveness of such interventions and should be evaluated in children. Non-invasive treatments such as transcranial magnetic stimulation (TMS) and brain-computer interfaces (119) have shown promising results in adults with chronic pain. Pharmacological treatments such as SSRIs, SNRIs, and pregabalin are effective in reducing abnormally higher RS-FC which was associated with clinical improvement, across multiple networks in adults with chronic pain (120–122). Such pharmacological management of chronic pain and associated brain changes in children has yet to be investigated. Greater neuroplasticity in children compared to adults suggests that brain-targeted interventions may be more potent with effects longer-lasting when taking place during childhood before irreversible brain changes have occurred. This hypothesis is consistent with the clinical efficacy of neuromodulatory treatments such as hypnosis in children with chronic pain (123).

Limitations and Advantages—Neuroimaging studies have been known to have flexibility regarding analysis pipelines and statistical methodology. Many small changes can have a large effect on the results produced so that analysis parameters are crucial to the final results (124,125). We compiled study scanner parameters and methodology to examine how differences in study design and analysis parameters may influence final results (Supplementary Tables). Small sample size may lead to false positives and need to be replicated in larger samples, such as twenty subjects are for MRI data replicability (126). False positives can result from liberal statistical thresholding (deviating from the norm of $p < 0.001$) or using uncorrected results (127,128). Use of different analytic programs can also create risk for false positives (128). Future studies require adequate sample size,

standardized pipelines for processing data, appropriate statistical thresholding, and consideration of confounding variables such as age, sex, motion, and other cortical confounds. Surface-based approaches have also been shown to have greater sensitivity and accuracy of cortical landmarks compared to volume-based approaches (129–132). Longitudinal versus cross-sectional studies with baseline randomization is preferred for causality inferences. Data-driven methodologies can analyze data more flexibly, have the ability to detect components that may not have been regarded as important a-priori, and can generate a context for new models (133,134).

Future Directions—The current review of pediatric pain neuroimaging studies found changes in gray matter and resting-state functional connectivity networks, with findings needing replication given the paucity of studies and differing pathophysiology between chronic pain conditions. Neuroimaging has shown that a network-based approach to identifying brain alterations in chronic pain conditions can contribute to a better understanding of pathophysiology and targets for interventions aimed at affective and sensory components of pain perception (135,136). Yet abnormalities in these networks and reversal with effective treatment have been documented. Longitudinal research will help identify the subgroups of children that respond to different pain treatments consistent with a phenotypic, “precision medicine” approach. Future research on mechanisms associated with the development of pediatric chronic pain and progression into adulthood will require the integration of genetic, neonatal, familial, and historical data as well as other physiological and psychological parameters with data obtained from brain imaging. For such multimodal, integrated studies, large data sets will be needed to provide developmental pathways that explain trajectories of chronic pain in childhood and risk for progression of pain into adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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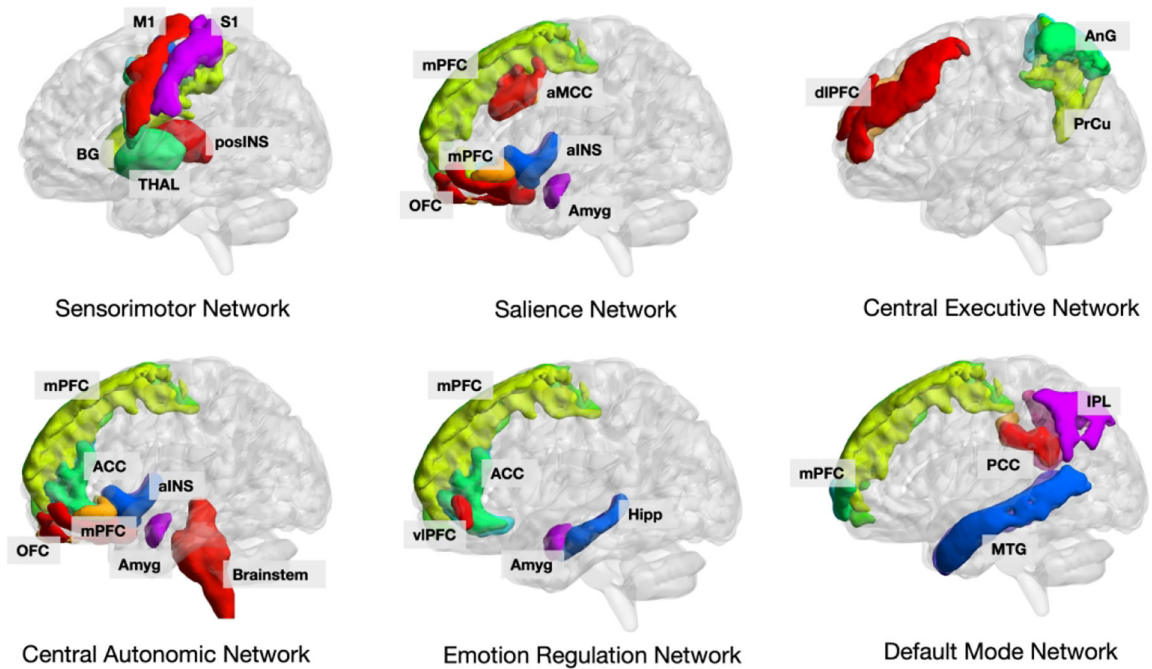


Figure 1:
Brain Networks Involved in Chronic Pain

Key:

Sensorimotor Network: M1: primary motor cortex, S1: primary somatosensory cortex, BG: basal ganglia, THAL: thalamus, posINS: posterior insula,

Salience Network: mPFC: medial prefrontal cortex, aMCC: anterior mid-cingulate cortex, OFC: orbitofrontal cortex, aINS: anterior insula, Amyg: amygdala

Central Executive Network: dlPFC: dorso-lateral prefrontal cortex, AnG: angular gyrus, PrCu: precuneus,

Central Autonomic Network: mPFC: medial prefrontal cortex, OFC: orbitofrontal cortex, ACC: anterior cingulate cortex, aINS: anterior insula, Amyg: amygdala, Brainstem: brain stem

Emotion Regulation Network: mPFC: medial prefrontal cortex, vIPFC: ventrolateral prefrontal cortex, ACC: anterior cingulate cortex Hipp: hippocampus, Amyg: amygdala

Default Mode Network: mPFC: medial prefrontal cortex, PCC: posterior cingulate cortex, IPL: inferior parietal lobule, MTG: middle temporal gyrus

Table 1:

Brain Networks involved in Chronic Pain

Brain Network	Regions	Function
Default Mode Network (DMN)	mPFC, PCC, IFC, LTC,	Responsible for emotional processing, self-referential mental activity and recollection of prior experiences.
Sensorimotor Network (SMN)	Basal ganglia, thalamus, pINS, S1, S2, M1, M2	Receives input from the periphery and is important for the awareness of bodily sensations and generation of appropriate motor responses.
Saliience Network (SN)	mPFC, OFC, aINS, aMCC, amygdala	Responds to subjective stimuli or expectation of a stimulus and coordinates appropriate behavioral, affective and bodily responses and works to maintain homeostasis
Emotional Regulation Network (ERN)	Amygdala, locus coeruleus, hippocampus, sgACC, pgACC, mPFC, vIPFC	Activated by real or perceived disturbance of homeostasis, links stimulus appraisal and autonomic output
Central Executive Network (CEN)	dIPFC, PPC	Working memory, attentional processes, planning, response selection
Central-Autonomic Network (CAN)	Brainstem, amygdala, hypothalamus, sgACC, aINS, aMCC, mPFC, OFC	Central control and modulation of the autonomic nervous system (ANS)

Key:

Default Mode Network: mPFC; medial prefrontal cortex, PCC; posterior parietal cortex, IFC; inferior parietal cortex, LTC; lateral temporal cortex

Sensorimotor Network: pINS; posterior insula, S1; primary somatosensory cortex, S2; secondary somatosensory cortex, M1; primary motor cortex, M2; secondary motor cortex

Saliience Network: mPFC; medial prefrontal cortex, OFC; orbitofrontal cortex, aINS; anterior insula, aMCC; anterior mid-cingulate cortex

Emotion Regulation Network: sgACC; subgenual anterior cingulate cortex, pgACC; pregenual anterior cingulate cortex, mPFC; medial prefrontal cortex, vIPFC; ventrolateral prefrontal cortex,

Central Executive Network: dIPFC; dorsolateral prefrontal cortex, PPC; posterior parietal cortex

Central-Autonomic Network: sgACC; subgenual anterior cingulate cortex, aINS; anterior insula, aMCC; anterior mid-cingulate cortex, mPFC; medial prefrontal cortex, OFC; orbitofrontal cortex

Table 2:

Brain Alterations Observed in Children with Chronic Pain

Default Mode Network	Brain Regions	medial frontal cortex, posterior cingulate or retrosplenial cortex, precuneus, inferior parietal cortex, lateral temporal cortex, and hippocampal formation
	Function	<ul style="list-style-type: none"> self-awareness processing self-referential mental activity and episodic memory monitoring internal thoughts, external goals, and future planning
	Alterations in IBS	<ul style="list-style-type: none"> mixed results regarding gray matter of the posterior cingulate cortex have been observed [Bhatt et al., 2019, Hubbard et al., 2016], and lower gray matter in the posterior cingulate has been associated greater abdominal pain [Hubbard et al., 2016]. mixed results regarding resting-state functional connectivity have been observed, with lower connectivity between the posterior cingulate and insula, but greater resting-state functional connectivity between the thalamus and posterior cingulate, and posterior cingulate and dorsolateral prefrontal cortex [Bhatt et al., 2019, Hubbard et al., 2016]
	Alterations in CRPS	<ul style="list-style-type: none"> lower gray matter in the lateral temporal cortex, dorsal posterior cingulate and precuneus [Erpelding et al., 2016] greater resting-state functional connectivity within the default-mode network. Following an intensive psycho-social treatment regimen, a decrease (shift towards normalization) in resting-state functional connectivity has been observed associated with decreased pain [Becerra et al., 2014]
	Alterations in Migraines	<ul style="list-style-type: none"> lower gray matter in the lateral temporal cortex, medial frontal cortex and precuneus [Faria et al., 2015, Rocca et al., 2014]
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> lower gray matter in the posterior cingulate and precuneus has been observed [Kirk et al., 2009] greater resting-state functional connectivity has been observed in the precuneus (associated with lower cognitive performance) and medial frontal cortex [Colombatti et al., 2016]
	Sex Difference	<ul style="list-style-type: none"> N/A
	Sensorimotor Network	Brain Regions
Function		<ul style="list-style-type: none"> central processing and modulation of visceral and somatic sensory information
Alterations in IBS		<ul style="list-style-type: none"> lower gray matter in the basal ganglia and thalamus [Bhatt et al., 2019] greater resting-state functional connectivity between the caudate nucleus and precentral gyrus [Bhatt et al., 2019] decreased gray matter in the somatosensory cortex, putamen and posterior insula from 7–9 years of age [Gupta et al., 2015]
Alterations in CRPS		<ul style="list-style-type: none"> lower gray matter in the primary motor cortex, supplementary motor area, caudate nucleus, putamen, nucleus accumbens, anterior thalamus, and greater gray matter in the posterior thalamus [Erpelding et al., 2016] Following an intensive psycho-social treatment regimen, increases from previously lower gray matter in the putamen, caudate nucleus, and thalamus was observed [Erpelding et al. 2016] greater resting-state functional connectivity within cortical areas of the sensorimotor network, but lower resting-state functional connectivity within the basal ganglia [Becerra et al., 2014]
Alterations in Migraines		<ul style="list-style-type: none"> greater gray matter in the putamen which was negatively associated with disease duration. Girls with migraines exhibit greater gray matter in primary sensorimotor cortex, and primary motor cortex, but lower gray matter in the caudate nucleus and

		putamen compared to girl healthy controls. Boys with migraines exhibit greater gray matter in the primary motor cortex, but lower gray matter in the primary somatosensory cortex, supplementary motor area, thalamus, pallidum, putamen and caudate nucleus compared to boy healthy controls [Faria et al., 2015, Rocca et al., 2014]
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> • lower gray matter in the thalamus, caudate nucleus, putamen, and pallidum [Kawadler et al., 2013]
	Sex Difference	<ul style="list-style-type: none"> • During early puberty, boys with migraine exhibit greater gray matter in the primary somatosensory cortex, supplementary motor area, pallidum and caudate nucleus compared to girls. At mid-puberty, girls exhibit greater gray matter in primary somatosensory cortex, primary motor cortex, caudate nucleus, putamen, thalamus compared to boys [Faria et al., 2015]
Salience Network	Brain Regions	dorsal anterior cingulate cortex (dACC), anterior insula
	Function	<ul style="list-style-type: none"> • response to subjective experience or expectation of any interoceptive and exteroceptive stimulus • coordination of the appropriate attentional, behavioral, affective, and visceral responses to such stimuli
	Alterations in IBS	<ul style="list-style-type: none"> • lower gray matter in the anterior cingulate cortex and dorsomedial prefrontal cortex [Bhatt et al., 2019, Gupta et al., 2015, Hubbard et al., 2016]
	Alterations in CRPS	<ul style="list-style-type: none"> • lower gray matter in anterior mid-cingulate cortex [Erpelding et al., 2016] • greater resting-state functional connectivity from the anterior insula to salience network and central executive network [Becerra et al., 2014] • following a psycho-social treatment regimen resting-state functional connectivity decreased in the orbitofrontal cortex, medial prefrontal cortex, and was associated with decreased pain [Becerra et al., 2014]
	Alterations in Migraine	<ul style="list-style-type: none"> • lower gray matter in the orbitofrontal cortex [Rocca et al., 2014]
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> • N/A
	Sex Difference	<ul style="list-style-type: none"> • N/A
Emotion Regulation Network	Brain Regions	amygdala, hippocampus, hypothalamus, posterior anterior cingulate cortex, subgenual cingulate cortex
	Function	<ul style="list-style-type: none"> • activated by perceived or real disruption in homeostasis • generation of rapid feedback inhibition of amygdala, thereby limiting the magnitude and duration of network activity and related activity in the central autonomic network
	Alterations in IBS	<ul style="list-style-type: none"> • N/A
	Alterations in CRPS	<ul style="list-style-type: none"> • Lower gray matter in amygdala, anterior hippocampus. Higher gray matter in the posterior hippocampus [Erpelding et al., 2016] • Following an intensive psycho-social treatment regimen, previously lower gray matter in the amygdala, hippocampus and parahippocampal gyrus increased in gray matter [Erpelding et al., 2016] • Greater resting-state functional connectivity from the amygdala to the executive control, sensorimotor and salience networks. Lower resting-state functional connectivity from the amygdala to precuneus and occipital lobe [Simons et al., 2014] • Following an intensive psycho-social treatment regimen, a decrease in resting-state functional connectivity between the amygdala various sensorimotor and salience parts of the brain have been observed [Simons et al., 2014]

	Alterations in Migraine	<ul style="list-style-type: none"> • Lower gray matter in the subgenual anterior cingulate cortex compared to healthy controls [Rocca et al., 2014] • Girls with migraines have greater gray matter in the hippocampus compared to healthy controls [Faria et al., 2015]
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> • Lower gray matter in the hippocampus and amygdala [Kawadler et al., 2013]
	Sex Differences	<ul style="list-style-type: none"> • Girls with migraines have greater resting-state functional connectivity between the amygdala and thalamus compared to boy's with migraines and healthy controls [Faria et al., 2015] • At early puberty, boys with migraine exhibit greater gray matter in the amygdala, compared to girls. At mid-puberty, girls exhibit greater gray matter in the amygdala compared to boys [Faria et al., 2015] • Girls with migraine exhibit greater gray matter in amygdala compared to girl healthy controls. Boys with migraines exhibit lower gray matter in amygdala compared to boy healthy controls [Faria et al, 2015] • boys with migraines exhibit lower resting-state functional connectivity from the amygdala to the thalamus and culmen [Faria et al., 2015]
Central Autonomic Network	Brain Regions	control centers in the pontine-medulla (including periaqueductal gray and hypothalamus), the central nucleus of the amygdala, and several cortical regions (including the anterior insula, anterior cingulate cortex, prefrontal and motor regions)
	Function	<ul style="list-style-type: none"> • central control and modulation of the autonomic nervous system • regulation of respiratory, cardiovascular, endocrine, and digestive activities during cognitive, affective, and motor tasks and sensations.
	Alterations in IBS	<ul style="list-style-type: none"> • N/A
	Alterations in CRPS	<ul style="list-style-type: none"> • Lower gray matter in the orbitofrontal cortex and anterior mid-cingulate cortex [Erpelding et al., 2016] • Following an intensive psycho-social treatment regimen, previously lower gray matter in the hypothalamus increased [Erpelding et al. 2016]
	Alterations in Migraine	<ul style="list-style-type: none"> • N/A
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> • N/A
	Sex Differences	<ul style="list-style-type: none"> • No reported sex differences in the central autonomic network to date
Central Executive Network	Brain Regions	lateral prefrontal cortices and posterior parietal cortex
	Function	<ul style="list-style-type: none"> • activated during tasks involving executive functions such as attention, working memory, planning and response selection • often co-activated with regions of the salience network, as the brain attempts to focus its limited processing capacity to only salient information via attention, working memory, planning and response selection
	Alterations in IBS	<ul style="list-style-type: none"> • lower gray matter in the dorsolateral prefrontal cortex, posterior parietal cortex, middle frontal gyrus, and superior frontal gyrus [Bhatt et al., 2019, Hubbard et al., 2016] • Lower resting-state functional connectivity between the anterior mid-cingulate cortex and posterior parietal cortex, greater resting-state functional connectivity between the thalamus and posterior parietal cortex [Bhatt et al., 2019]
	Alterations in CRPS	<ul style="list-style-type: none"> • Lower gray matter in the dorsolateral prefrontal cortex and precuneus [Erpelding et al., 2016]

		<ul style="list-style-type: none"> • Greater resting-state functional connectivity observed in the central executive network was decreased following an intensive psycho-social treatment regimen, associated with decreased pain [Becerra et al., 2014] • Lower resting-state functional connectivity within the left fronto-parietal network [Becerra et al. 2014] • Greater resting-state functional connectivity within the right fronto-parietal network [Becerra et al., 2014] • Following an intensive psychosocial treatment regimen, previously lower gray matter in the dorsolateral prefrontal cortex increased [Erpelding et al., 2016] • Reduced resting-state functional connectivity following an intensive psychosocial treatment regimen within the right fronto-parietal network was associated with decreased pain scores. Increased connectivity was associated with greater pain scores [Becerra et al., 2014]
	Alterations in Migraine	<ul style="list-style-type: none"> • N/A
	Alterations in Sickle-Cell Disease	<ul style="list-style-type: none"> • N/A
	Sex Differences	<ul style="list-style-type: none"> • no reported sex differences in the central-executive network to date

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