11 Influence of Pain on Cognitive Dysfunction and Emotion Dysregulation in Chiari Malformation Type I

James R. Houston, Jahangir Maleki, Francis Loth, Petra M. Klinge, and Philip A. Allen

Abstract

It has been well demonstrated that the cerebellum is associated with cognitive and affective processing as well as the traditionally conceptualized motor function. In the present chapter, we explore the behavioral and neurobiological implications of a common congenital cerebellar condition, Chiari malformation Type I, on cognitive and affective processing. We also emphasize the associations between Chiari-related chronic pain, cognitive dysfunction, and emotion dysregulation. Based on our review of the literature, we argue that chronic pain can account for a substantial amount of the cognitive dysfunction and emotion dysregulation in Chiari malformation Type I. Yet, there also exists aspects of Chiari-related cognitive dysfunction and emotion dysregulation that appear to be at least partially independent of chronic pain and more directly associated with abnormalities in cerebrospinal fluid flow dynamics and cerebrocerebellar communication pathways.

Keywords

Chiari malformation · Cognitive control · Attention · Emotion regulation · Chronic pain

11.1 Introduction

Chiari malformation Type I (CMI) is a radiologically defined congenital condition qualified by a descent of the cerebellar tonsils below the foramen magnum, leading to both an anatomical obstruction of the cerebrospinal fluid cisterns at the base of the skull and an anatomical distortion of the cerebellar structure (Fig. 11.1) (Milhorat et al. 1999). Symptom presentation is often unique, but pain in the form of acute pressure, chronic occipital headache, and neck/shoulder pain is the most relevant element in the clinical presentation and social impact. CMI patients frequently self-report pain levels akin to those experiencing chronic pain syndromes such as fibromyalgia, low back pain, and diabetic

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peripheral neuropathy (Dworkin et al. 2009; Houston et al. 2019a; Garcia et al. 2019). Chronic pain in CMI has also been associated with greater pain sensitivity and disruption of top-down pain modulation, further leading to deleterious biological and psychological outcomes (Garcia et al. 2019; Allen et al. 2018; Bushnell et al. 2013).

The pathophysiology of pain in CMI is purely based on mechanical assumptions. Given that patients often present with Valsalva-induced head and neck pain (Mueller and Oro' 2004), it is assumed that the pain is triggered by the anatomical obstruction of cerebrospinal fluid (CSF) flow at the base of the skull and the impaired regulation and equilibration of CSF pressure between the cranial and the spinal compartments (Alperin et al. 2015; Ibrahimy et al. 2021; Shaffer et al. 2014). This may also result in an irritation of pain receptors of the dura mater and small blood vessels at the base of the skull initiating neuropathic pain pathways and causing chronic headaches (Fontaine et al. 2018). One pathological hallmark of CMI is a reduced posterior fossa volume that may be associated with reduced venous drainage through the jugular veins (Houston et al. 2018a), furthering the altered pressure regulation at the base of the skull (Alperin et al. 2015). Mechanical intradural irritation of the C1 and C2 vertebrae nerve roots from the altered CSF dynamics at the base of the skull has also been proposed as a generator of the occipital-based headaches (Noseda et al. 2019). Animal models also support this concept. For example, nociceptors in the posterior dural area over the cerebellum are linked with neurons in the C2-C4 region of the spinal cord in rats (Noseda et al. 2019).

Critical to the present discussion, chronic pain has been proposed to account for the observed cognitive dysfunction among CMI patients, often being described as "brain fog" and concentration difficulties. Work from multiple independent groups have established an understanding that CMI is associated with cognitive deficits including, but not limited to, attentional control (Houston et al. 2019a; Allen et al. 2014; González and Campa-Santamarina 2018; Kumar et al. 2011), executive function (Allen et al. 2014; García et al. 2020a; García et al. 2020b; Klein et al. 2014), and episodic memory (Houston et al. 2019a; Allen et al. 2018; González and Campa-Santamarina 2018; García et al. 2020a). Rogers et al. (2018) provided the most comprehensive review at the time of publication of cognitive deficits in CMI. The authors reviewed both the adult and pediatric literatures and came to several important conclusions. First, attention and working memory deficits are evident in adult CMI. Second, there is also preliminary evidence of a processing speed deficit in adult CMI, though additional research using larger samples and utilizing matched controls is necessary. Third, language deficits have not been consistently identified in adult or pediatric CMI. Fourth, evidence of visuospatial deficits in adult CMI is largely lacking and evidence of developmental disruptions in visuospatial abilities is mostly confounded by intellectual disability. In concluding their review, the authors also highlighted the limited empirical research investigating the cognitive profile of CMI and encouraged the careful consideration of chronic symptoms, namely chronic pain and neuropsychiatric symptoms, that may at least partially explain the cognitive deficits exhibited by CMI patients. Since the time of publication, works from multiple independent groups have replicated the results from reviewed studies in the work of Rogers and colleagues and further established connections between domain-specific cognitive dysfunction in CMI, chronic pain, and anxious-depressive symptomatology.

Beyond its direct impact on cognitive function, chronic pain also affects person-environment (PE) interactions and informs the emotional landscape and health-related decision-making in CMI patients. For example, those who experience chronic pain are less likely to engage in physical activity, achieve success in the workplace, and enjoy leisure activities with social contacts (Duenas et al. 2016). Chronic pain in CMI has also been associated with greater pain sensitivity

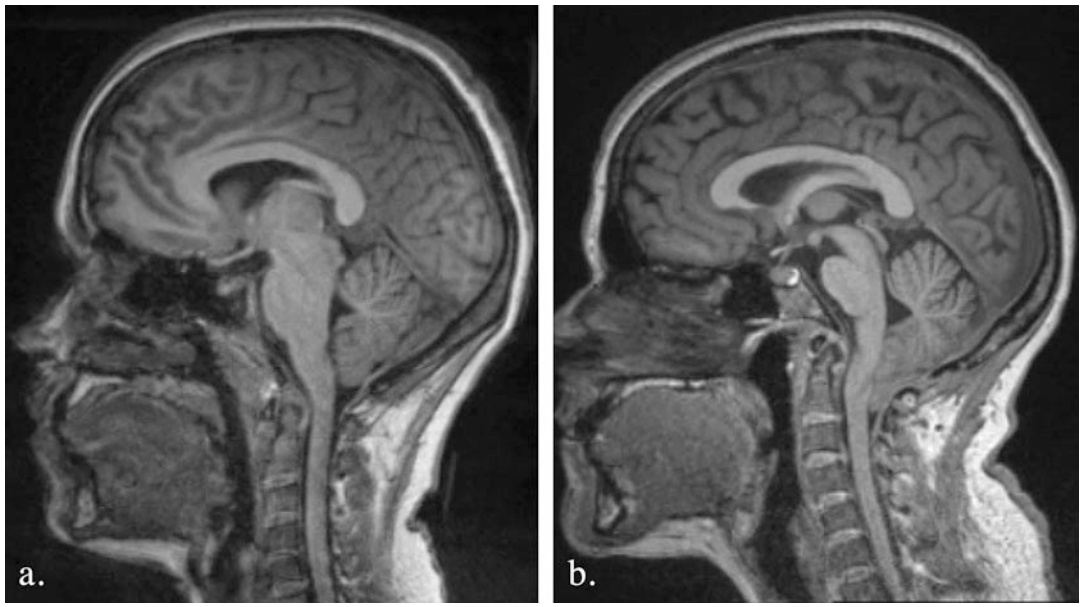


Fig. 11.1 Midsagittal radiological presentation of (**a**) a healthy control and (**b**) a patient diagnosed with Chiari malformation Type I. Image adapted from Houston et al. (2018b)

and disruption of top-down pain modulation, further leading to deleterious biological and psychological outcomes (Garcia et al. 2019; Allen et al. 2018; Bushnell et al. 2013). Duenas and colleagues (2016) provide an excellent review of the multifaceted effects that chronic pain can have on patients' lives and emphasize the need to take a biopsychosocial approach to understand the experience of individuals who experience chronic pain (see Fig. 11.2).

As such, the nature of the relationship between CMI and disruptions to cognitive and emotion function is now understood to be quite complex (Ibrahimy et al. 2021; García et al. 2021). This complexity has also been elucidated in part by recent investigations of brain microstructure and functional connectivity abnormalities in CMI. For example, in our work (Allen et al. 2018; Houston et al. 2018b, 2020, 2021), we have established a conceptual model to account for cognitive dysfunction and affective dysregulation in CMI by assuming that pain serves as a prepotent stimulus that draws limited attentional capacity. These studies have also implicated chronic pain effects on some, but not all, aspects of cerebro-cerebellar communication abnormalities (Houston et al. 2020, 2021). Thus, it remains an open question as to whether cognitive deficits are directly associated with CMI pathophysiology or whether they are secondary to developmental pain or neuropsychiatric symptom effects.

The present chapter reviews the current empirical understanding of chronic pain effects on cognitive and emotion function in CMI. Particular attention will be placed on studies focusing on controlled cognitive and emotion processing that utilized inferential statistics and representative sampling techniques. In other words, while we acknowledge the importance of clinical case reviews and scientific letters, this chapter will emphasize generalizable findings from peer-reviewed articles. Additionally, research on implicit and autonomic cognitive processing will be de-emphasized, though future investigations in this area are encouraged. We conclude the chapter with clinical care considerations and suggestions for future study.

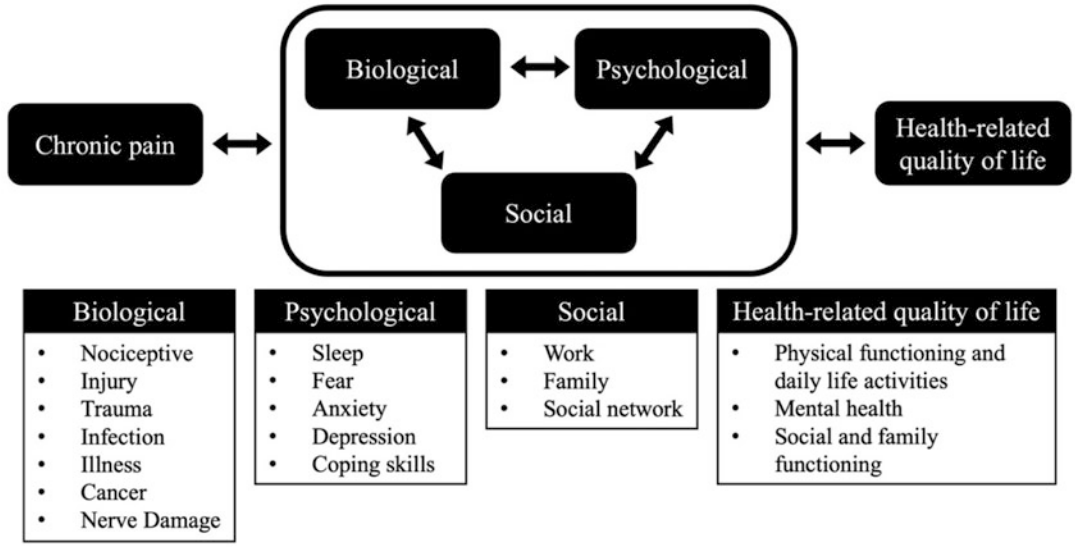


Fig. 11.2 Conceptual biopsychosocial model of pain and consequence on the quality of life. Chronic pain has reciprocal relationships with biological, psychological, and social functions, which have evocative interactions with each other and on health-related quality of life. Figure inspired by Duenas et al. (2016)

11.2 Behavioral Evidence of Pain Effects on Attention and Executive Dysfunction

Kumar and colleagues (2011) and Allen and colleagues (2014) provided two early landmark studies that demonstrated pervasive cognitive deficits in CMI patients relative to matched healthy controls. Each study had strengths but was also understandably limited given the limited research body at the time of publication. From these early studies, several considerations for future study became apparent regarding methods of assessment, treatment status of CMI patients, sample size requirements, and covariate considerations including the impact of chronic pain.

Kumar et al. (2011) utilized standardized neuropsychological tests (Trail Making Test, Figure Connection Test, and performance subset of the Wechsler Adult Intelligence Scale (WAIS) modified for the Indian population) in a sample of 10 CMI patients (presumably pre-surgical candidates) and 10 age- and sex-matched controls. Results indicated deficits in processing speed, response inhibition, and working memory. Despite the small sample size, Kumar and colleagues' work was instrumental in validating CMI patients' complaints of cognitive dysfunction and demonstrated that CMI-related cognitive deficits could be identified using comprehensive neuropsychological assessment. There were also notable limitations of the study including a small sample size, limited statistical control of false discovery, and the absence of symptom variables including chronic pain and anxious-depressive symptomatology.

Allen et al. (2014) both replicated several of the findings from Kumar et al. (2011) and rectified several of the design limitations of the earlier study. The authors examined CMI-related differences in processing speed, response inhibition, and working memory utilizing a series of laboratory tasks (computerized Digit-Symbol Coding, Stroop, and Operation Span tasks). Allen and colleagues used a considerably larger sample of 24 CMI patients and 24 age- and education-matched controls. However, unlike Kumar et al., the CMI patients had all undergone posterior fossa decompression surgery, a common surgical procedure with the purpose of

reducing compression of the cerebellar tonsils and brainstem and alleviated symptoms such as headache and chronic pain. CMI patients exhibited performance deficits on all cognitive tasks. Additionally, self-reported pain and anxious-depressive symptomatology were correlated with processing speed and working memory measures. Given these correlations, the authors re-analyzed their cognitive task data after controlling for self-report measures via analysis of covariance (ANCOVA). Results indicated that self-reported pain and anxious-depressive symptomatology could fully account for case-control differences in processing speed and working memory, though response inhibition deficits could not be accounted for by these variables.

Taken in tandem, the results from Allen et al. (2014) and Kumar et al. (2011) largely established the generalizability-focused (i.e., relying upon representative sampling and population-level inference) empirical literature on cognitive deficits in CMI. The results from these two studies also corresponded well to earlier case studies (Novegno et al. 2008; Furuya et al. 1998; Pearce et al. 2006; Riva et al. 2011) and the experiences of several physicians who frequently treated CMI patients. The two studies demonstrated case-control differences in pre- and post-surgery CMI patients, respectively. They also demonstrated that CMI-related cognitive deficits could be identified via neuropsychological testing and more targeted laboratory testing and that symptom variables could at least partially explain the cognitive dysfunction experienced by CMI patients.

Yet, several questions remained. The impact of Chiari decompression surgery on CMI-related cognitive dysfunction remained an open question. There were also several aspects of cognitive function that were not explored in these two studies, namely language, episodic memory, aspects of executive function, and social cognition. Another major lingering issue regarded the neurobiological associations of cognitive deficits in CMI. At the time of publication of these early studies, much of the research interest in CMI derived from neuroradiological research groups and focused primarily on macro-level brain structure. To our knowledge, Kumar et al. (2011) were the first to also include neuroimaging data and conduct correlational analyses between neuroimaging data (via diffusion tensor imaging-DTI) and cognitive performance. Many of these questions would be approached in the subsequent cohort of published research that would take place between the publication of Allen et al. (2014) and the present.

Expanding upon their earlier work, Allen and colleagues (2018) aimed to directly assess the relationship between chronic pain and memory in CMI patients. Further, they sought to explore the relationship between individual differences in the cognitive-affective personality process of rumination, the tendency to focus on oneself repeatedly to evaluate (often negatively) one's past actions, and reflection, the tendency to focus on oneself repeatedly to maintain a general awareness of one's feelings and mental processes (Harrington and Loffredo 2010). The researchers used the international Chiari 1000 registry project, an online database which includes demographic characteristics, symptomatology, cognitive performance measures derived from web-adapted neuropsychological assessments, and any imaging data volunteered from CMI patients. Notably, the database includes an updated self-reported pain measure similar to the measure from the researchers' earlier study (Dworkin et al. 2009). The results indicated that CMI patients with low levels of self-reported pain exhibited cognitive benefits (i.e., improved verbal memory on a modified Rey Auditory Verbal Learning Task (Schmidt 2009)) from engaging in self-focused reflection. Conversely, those with high levels of self-reported pain did not benefit from similar behaviors. Results were interpreted as suggesting that distraction due to pain can partially, but not fully, explain memory deficits in CMI.

In an effort to replicate and expand earlier neuropsychological assessment results, García and colleagues published a trio of studies that collectively comprise the most comprehensive neuropsychological testing data in the literature (García et al. 2018a, b, 2020a). Importantly, each of these studies incorporated self-report measures

of chronic pain and anxious-depressive symptomatology. García et al. (2018b) required a group of 39 CMI patients who had not undergone Chiari decompression surgery and 39 sex- and education-matched controls to complete a comprehensive neuropsychological assessment battery that targeted aspects of executive function, verbal fluency, visuospatial function, verbal memory, and processing speed. Relative to the controls, CMI patients exhibited poorer scores on all measured aspects of cognitive function. Moreover, case-control composite scores in each of the measured cognitive domains remained significant after controlling for chronic pain and symptomatology variables, suggesting that pain could not account for the observed cognitive deficits. Though, it should be noted that the effect magnitude of the case-control differences did attenuate to varying degrees, suggesting that pain and symptomatology characteristics could partially account for some of the CMI-related cognitive deficits.

García et al. (2018a) built upon the results of this study by including a sample of CMI patients who had previously undergone Chiari decompression surgery. In the study, decompressed CMI patients, non-decompressed CMI patients, and healthy controls matched for sex and education completed a highly similar neuropsychological assessment battery to that of the author's previous study. Results largely replicated the previous findings with the notable addition that case-control differences were found to be nearly identical across decompressed and non-decompressed CMI patients. That is, similar patterns of statistically significant differences and effect sizes[1] were observed between decompressed CMI patients and healthy controls and non-decompressed CMI patients and healthy controls. Moreover, the authors conducted additional analyses comparing the cognitive profiles of the CMI patients by decompression surgery status. These additional analyses yielded no significant differences between the two groups. Importantly, all the group differences observed in the study were re-tested and found to remain significant, though again somewhat attenuated in effect magnitude, after controlling for chronic pain and anxious-depressive symptomatology.

García et al. (2020a) took a more targeted approach to explore cognitive deficits in CMI. In this study, a mixed sample of 26 decompressed and non-decompressed CMI patients and 26 sex- and education-matched controls completed a battery of assessments that targeted visuospatial function, with the use of the Block Design and Visual Puzzles subtests of the WAIS IV (Drozdick et al. 2018), Benton Judgment of Line Orientation (BJLO) test (Benton et al. 1994), and the Rey-Osterrieth Complex Figure (ROCF) test (Rey 1941). CMI patients exhibited deficits on all tasks except the ROCF. Interestingly, self-reported chronic pain could account for group differences in Block Design, but not Visual Puzzles or BJLO differences. The authors interpreted this pattern of findings as suggesting that chronic pain may affect executive visuospatial capacities that are emphasized in the Visual Puzzles and BJLO tasks to a lesser degree than visuospatial attention capacities that are emphasized to a greater degree by the Block Design subtest.

In addition to working with the Chiari 1000 registry data, Allen and colleagues simultaneously collected prospective data from an independent group of 20 CMI patients and 20 age-, sex-, and education-matched controls who were recruited while undergoing decompression surgery consultation. This prospective sample completed a series of self-report measures, completed a brief neuropsychological assessment, completed a functional neurophysiological assessment in which participant engaged in a facial expression identification task while being recorded by an electroencephalogram (EEG), and submitted to a neuroimaging sequence that included structural MRI, DTI, and resting-state functional MRI (fMRI) (see Fig. 11.3).

Two of these studies, Houston et al. (2019a, 2018b), were particularly important in demonstrating the effect of pain on different aspects of cognitive dysfunction in CMI. Houston et al. (2019a) utilized a routine clinical

[1] Effect sizes estimated using mean difference and standard deviation data provided in the article.

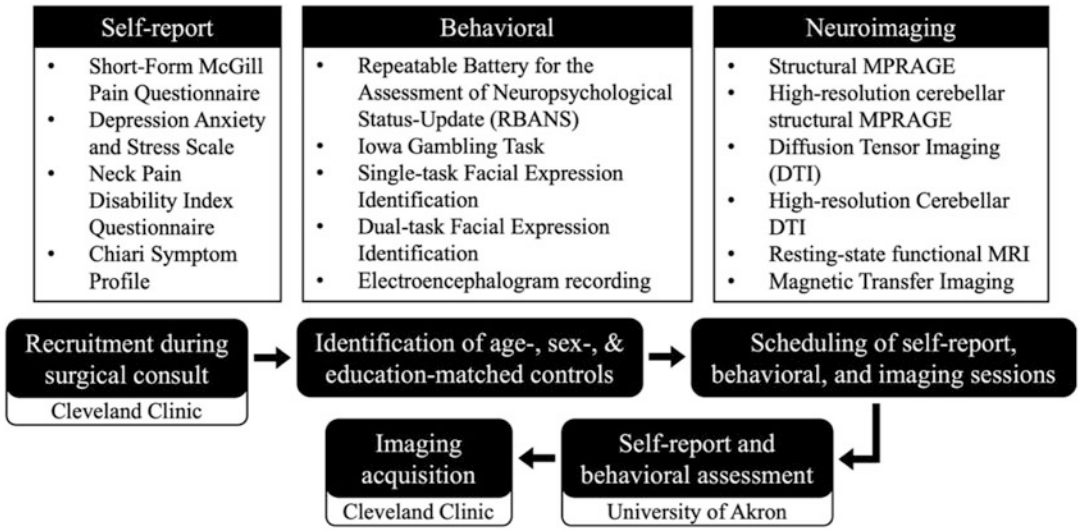


Fig. 11.3 Study protocol for the research that resulted in the publications of Houston et al. (2018b, 2019a, 2020, 2021). For more information on the self-report and behavioral measures, please see the following references: Short-Form McGill Pain Questionnaire (Melzack 1987); Depression Anxiety and Stress Scale (Henry and Crawford 2005), Neck Pain Disability Index Questionnaire (Fairbank et al. 1980), Chiari Symptom Profile (Mueller and Oro' 2013), Repeatable Battery for the Assessment of Neuropsychological Statue-Update (RBANS) (Randolph 2012), Iowa Gambling Task (Bechara et al. 1994), and Facial Expression Identification tasks and electroencephalogram recording (Pollock et al. 2012)

assessment in the form of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 2012). The assessment consists of 12 subtests assessing five cognitive domains—attention, language function, visuospatial skills, and immediate and delayed memory—and was chosen for its brevity and ease by which it could be included in a standard clinical protocol. CMI patients exhibited clinically meaningful deficits in the attention, immediate memory, and delayed memory subscales. After controlling for group differences in self-reported pain, only the case-control difference in performance on the attention subscale remained significant. Of note, the RBANS attention subscale consists of coding and span tasks that reflect aspects of selective and focused sub-domains of attention. The authors concluded that the chronic pain experienced by CMI patients could account for much, but not all, CMI-related cognitive dysfunction. More specifically, given that attention deficits persisted after controlling for chronic pain in both the Houston et al. (2019a) and the earlier Allen et al. (2014) studies, the authors interpreted this as indication that attention dysfunction may be a central feature of the cognitive profile of CMI.

Houston and colleagues (2018b) took a unique approach by examining the divided attention capacities of CMI patients using behavioral indices and event-related neurophysiological recordings from an EEG. While EEG methods lack the spatial resolution of functional MRI methods, EEG is capable of sub-millisecond temporal precision and is able to identify component neurophysiological processes using non-invasive, scalp-based electrodes. The researchers utilized a specific type of EEG analysis in which neurophysiological activity is linked to external stimulus presentation. The resultant time-locked EEG waveforms are referred to as event-related potentials (ERPs) and can be compared across conditions and groups. The underlying physiological processes that establish ERPs have been well established based on temporal and spatial waveforms characteristics. The researchers

targeted two specific waveforms, the early P1 waveform (70–170 mm post-stimulus onset) and later P3 waveform (400–600 mm post-stimulus onset). In the context of their study, the P1 waveform represents integrative visual processing and threat orienting (Dehaene and Changeux 2011; Eason et al. 1969), whereas the P3 reflects effortful cognitive control and motivational processes (Houston et al. 2018c; Krolak-Salmon et al. 2001; Rellecke et al. 2011, 2012).

In the study, participants completed two facial expression identification tasks. The first task served as a baseline and required participants to rapidly identify emotional facial expressions derived from the standardized NimStim database (Tottenham et al. 2009). The second task variant incorporated a similar facial expression identification component, but also included a preceding tone discrimination task that required a response prior to identifying the presented facial expression. The lag between the two tasks was manipulated using the psychological refractory period (PRP) paradigm, a method of assessing divided attention that is frequently used in cognitive psychology research (Pashler 1984, 1994). The PRP paradigm allows for the isolation of central processing resources, and it is generally found that response times to the second task are dependent upon the proximity of the preceding task, referred to as a lag or PRP effect (see Fig. 11.4). In individuals with deficient divided attention capabilities, the magnitude of lag effects is greater. Thus, the authors hypothesized that they would observe relatively greater lag effects in CMI patients.

Results indicated that CMI patients were slower in identifying the facial expressions compared to the matched controls in both single and dual-task conditions (i.e., a processing speed deficit). However, the magnitude of the lag effect in the dual-task variant was not different between CMI patients and controls. That is, despite slower processing speed, CMI patients did not exhibit a deficit in allocating attentional resources to identify the emotional expressions. To further explore the processing speed deficit, the authors re-analyzed their data after controlling pain and anxious-depressive symptomatology. These variables accounted for the response time difference in the dual-task variant but could not account for the processing speed deficit observed in the single-task variant. Moreover, the neurophysiological ERP analysis of the P1 and P3 ERP waveforms yielded no differences between CMI patients and controls on divided attention parameters. The second focus of Houston et al. (2018b) was to ascertain whether CMI patients also exhibited an emotion processing deficit, which is the focus of the ensuing section.

Prior to discussing evidence of pain effects on emotion dysregulation in CMI, we note one additional study provided by Lázaro and colleagues (2018) that sought to appraise verbal fluency impairments in CMI patients. The authors used a case-control design with 51 CMI patients and a control group that was approximately equivalent in age, sex, and education level. Approximately half (53%) of the CMI patients had undergone surgical intervention related to their CMI diagnosis. All participants completed the FAS Word Fluency task from the Controlled Oral Word Association Test (Ruff et al. 1996) and the Hospital Anxiety and Depression Scale, a self-report measure of anxious-depressive symptomatology (Zigmond and Snaith 1983). While the authors did not directly collect data on chronic pain symptomatology, they did include anxious-depressive symptomatology as a covariate. CMI patients exhibited deficits in both semantic and phonetic verbal fluency that could not be accounted for by anxious-depressive symptomatology. Moreover, case-control differences in the fluency measures could not be accounted for by decompression surgery status. Together, this provides indirect evidence that chronic pain, which itself is associated with both anxious-depressive symptomatology and the likelihood of undergoing Chiari decompression surgery, could not account for deficits in verbal fluency.

In sum, the data accumulated from the rigorous case-control studies to date suggest that chronic pain plays a major causal factor in the cognitive dysfunction observed by CMI patients. In particular, chronic pain appears to at least partially account for episodic memory, working memory, and processing speed deficits. However,

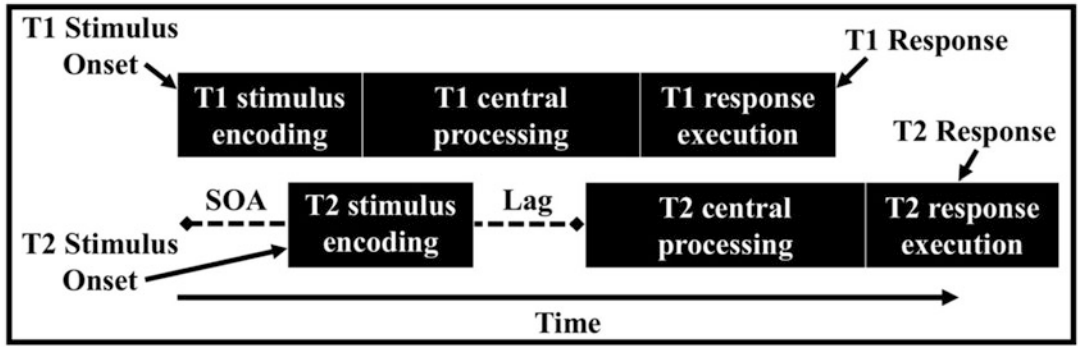


Fig. 11.4 Depiction of a single trial of the PRP paradigm as used in Houston et al. (2018b). Participant responses to the second task are generally longer when there is a shorter lag between the two tasks. T1-Task 1; T2-Task 2; SOA-stimulus onset asynchrony between the two tasks. Figure adapted from Houston et al. (2018b)

current evidence suggests that attention and executive function deficits cannot be as easily clarified by chronic pain or related anxious-depressive symptomatology. It is also unclear whether language deficits contribute to the cognitive profile of CMI. While Lázaro et al. (2018) identified fluency deficits that could not be accounted for by anxious-depressive symptomatology and García et al. (2018b) identified deficits that could not be accounted for by chronic pain or symptomatology variables, Houston et al. (2019a) failed to identify language deficits regardless of whether additional symptomatology variables were included in the analysis.

11.3 Behavioral Evidence of Pain Effects on Emotion Dysregulation

Relative to our understanding of the dynamics between pain and cognitive dysfunction in CMI, less is known regarding the relationship between the chronic pain experience of CMI patients and emotion dysregulation. For the purpose of the present review, we will reference two categories of emotion processing: (1) emotion perception/recognition and (2) emotional attributions including theory of mind/mentalizing and social cognition. Emotion recognition is generally considered to be a lower-level process and includes aspects of threat detection and other processes that are at least somewhat automatic/reflexive. By comparison, emotional attributions require the decoding of others' mental states based on observable information and comprise three overlapping abilities: the identification of emotionally relevant information in one's environment, the generation of subjective emotional experiences and one's response to the generated experiences, and the regulation of subjective emotional experiences and responses (Hoche et al. 2016; Coricelli 2005; Clausi et al. 2019; Overwalle et al. 2014). Importantly, both behavioral and neurobiological research have established these two sets of functions as distinct from one another (Oakley et al. 2016; Barbato et al. 2015; Fitzpatrick et al. 2018).

To our knowledge, there are currently four case-control studies that have investigated pain effects on emotion dysregulation in CMI, three of which also included cognitive assessments that have been previously described (Houston et al. 2018b; García et al. 2018a, b). In addition to these three, García and colleagues (2020b) contributed an additional work that specifically targeted emotion recognition and attribution capacities of CMI patients. Like their previous work, the authors relied upon a comprehensive neuropsychological assessment battery in their investigation. In a sample of 26 CMI patients and 26 sex-, age-, and education-matched controls, emotion recognition was assessed using the Facially Expressed Emotion Labelling (FEEL) Test (Kessler et al.

2002). Emotional attribution was tested using the Faux Pas test (Stone et al. 1998), Happé's Strange Stories (HSS) test (Happé 1994), and Ice-Cream Van task (Perner and Wimmer 1985). Results indicated that CMI patients performed more poorly on all measures but were particularly challenged by the three tasks requiring emotional attributions. Moreover, after controlling for self-reported anxious-depressive symptomatology, group differences in emotion recognition on the FEEL test were no longer significant. By comparison, neither self-reported chronic pain nor anxious-depressive symptomatology could account for the group differences in emotional attribution measures. The authors interpreted their findings as suggesting that CMI was associated with disruptions to the mentalizing network, while CMI-related emotion recognition deficits could be better accounted for by symptomatology variables.

As previously mentioned, the remaining studies were not primarily focused on CMI-related differences in emotion dysregulation. However, each complements the comprehensive analysis of García et al. (2020b). The most direct replications of these findings also derive from García and colleagues (2018a, b). These two studies arrived at very similar conclusions to their earlier study. CMI-related deficits in emotional attributions were identified using the HSS test in both studies and effect magnitudes were similar across decompressed and non-decompressed patients. Self-reported chronic pain and depressive symptomatology could not account for the observed deficits. In contrast, findings of CMI-related deficits in emotion recognition were less consistent. While García et al. (2018b) identified CMI-related deficits using the FEEL test and Benton Facial Recognition test (Benton et al. 1994), the effect magnitudes were approximately half the size of the emotional attribution deficits exhibited by CMI patients. Moreover, these differences could be fully accounted for by CMI-related differences in chronic pain and anxious-depressive symptomatology. Also relying upon the FEEL test, García et al. (2018a) identified small CMI-related deficits in emotion recognition for CMI patients who had undergone decompression surgery, but not those who had not undergone surgery. Once again, chronic pain and symptomatology variables could fully account for the observed differences.

Returning to the Houston et al. (2018b) EEG study, the authors had planned[2] to provide an initial investigation into potential emotion processing deficits in CMI by requiring participants to complete an emotion recognition task within the previously discussed PRP paradigm (Fig. 11.4) as well as a baseline emotion recognition task. While CMI patients did not exhibit the expected attention deficit, the authors did identify CMI-related differences in emotion recognition in the single-task, but not the PRP task variant in which happy emotional expressions elicited faster responses in controls, but not CMI patients. More importantly, distinct patterns of neurophysiological activity were identified across the groups. While CMI patients and matched controls exhibited consistency in their early perceptual responses as measured by the P1 waveform, case-control differences were identified for the P3 waveform that is believed to represent effortful control and motivational processes (see Fig. 11.5). Whereas control participants exhibited greater neurophysiological activity in response to angry emotional expressions relative to happy or neutral expressions (i.e., an expected response for normally functioning individuals (Houston et al. 2018c)), CMI patients did not exhibit distinct patterns of neurophysiological activity across angry, happy, or neutral expressions.

While not tested at the time of publication, we performed a re-analysis of this P3 data for the present chapter in which we controlled for self-reported chronic pain using ANCOVA. The re-analysis results suggest that the abnormal neurophysiological response observed in CMI patients could be fully explained by the chronic pain experiences of CMI patients. Thus, when taken in conjunction with the conclusion drawn from Houston et al. (2018b), these results suggest

[2] Project planning for the Houston et al. (2019a, 2018b) studies began in 2014 upon the completion of Allen and colleagues' initial publication.

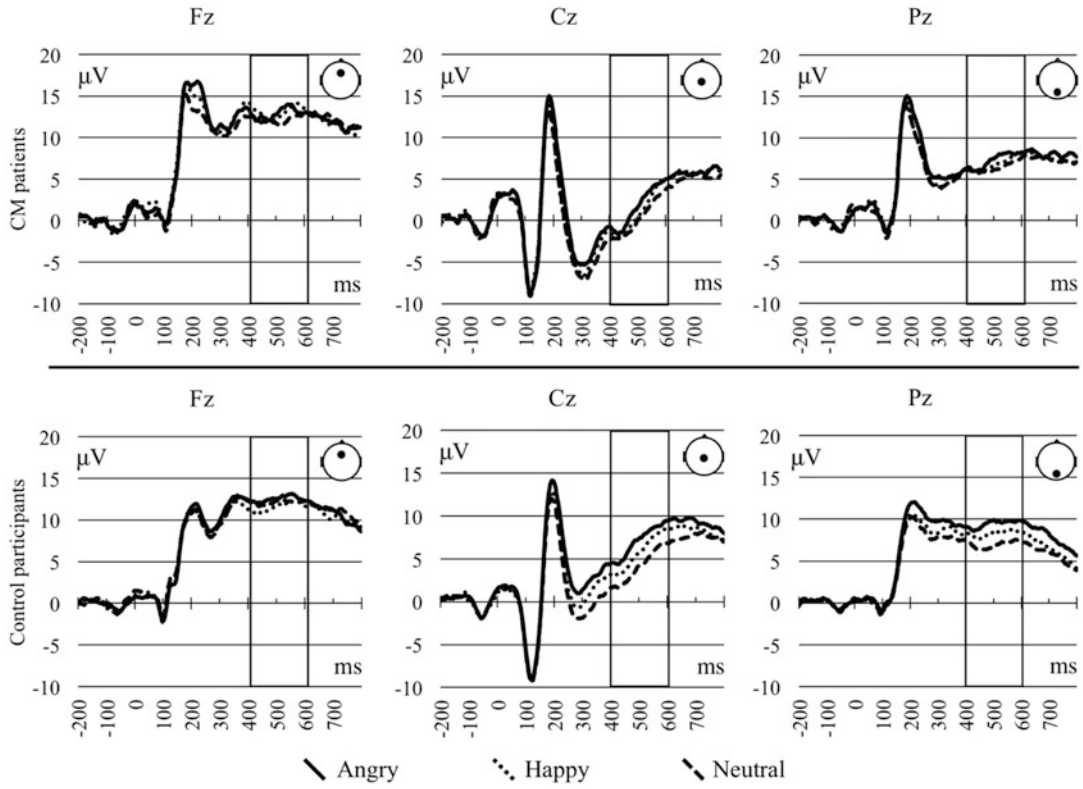


Fig. 11.5 Electroencephalogram-based P3 event-related potentials by emotion across measured channel locations for CMI and control participants in Houston et al. (2018b). Facial expression stimulus onset is represented by 0 on the x-axis. Lines represent the three emotional expression conditions derived from the NimStim database. Differences in neurophysiological responses were apparent across emotion condition in controls at both midline central (Cz) and midline parietal (Pz) channels. CMI patients did not exhibit distinct patterns of neurophysiological activity in response to the different emotional expressions at any measured channel site. μV-microvolts; ms-milliseconds. Figure adapted from Houston et al. (2018b)

that emotion recognition deficits observed in the CMI patients are due to controlled motivational processes (i.e., measurable in the P3 window), which in turn likely results from downstream effects of chronic pain.

In summarizing the evidence for CMI-related emotion dysregulation, several patterns have emerged from the nascent literature. First, there is evidence of both emotion recognition and emotional attribution deficits in CMI. Second, CMI-related emotional attribution deficits have been more reliably identified and case-control differences in emotional attribution capabilities appear to be substantially greater than emotion recognition deficits when considering effect magnitudes. Third, CMI-related emotion recognition deficits, but not emotional attribution deficits, can be best accounted for by chronic pain and anxious-depressive symptomatology. Hence, the evidence to date suggests that processes associated with forming emotional attributions, including theory of mind/mentalizing and social cognition, are part of the profile of CMI and cannot be accounted for by comorbid chronic pain and related symptomatology. These findings also indirectly speak to disruptions in the neural architecture that underlie controlled cognitive and emotion function. In the ensuing section, we review neuroscientific literature on the dynamic relationship between chronic pain and the

networks underlying cognitive dysfunction and emotion dysregulation in CMI.

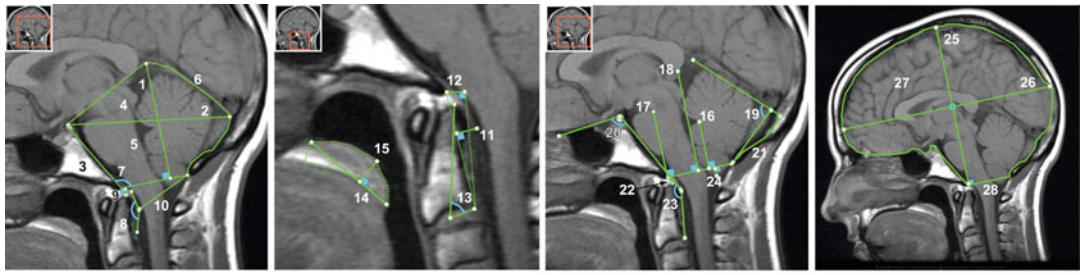
11.4 Neurobiological Foundation of Pain Effects on Cognitive Dysfunction and Emotion Dysregulation

Classically, the study of Chiari malformations can be traced to the fields of histology and, later, neuroradiology (Tubbs and Oakes 2013a, b). Largely, this work focused on establishing an understanding of the causes and the consequences of the hallmark cerebellar malformation on structures proximal to the Posterior Cranial Fossa (PCF). Through this work, it was generally assumed that the observed structural malformations to the cerebellum, along with associated disruptions to the development of midbrain and hindbrain structures, could account for the functional disturbances exhibited by patients (i.e., headache, chronic pain, motoric disturbances, numbness, brain fog, etc.), though the mechanisms were generally not empirically evaluated. This work has been influential in studying CMI specifically, with at least two dozen studies evaluating the macro-level brain morphology characteristics of the condition (Houston et al. 2018a; Sahuquillo et al. 1994; Heiss et al. 2012; Karagöz et al. 2002; Smith et al. 2013; Eppelheimer et al. 2018; Eppelheimer et al. 2019; Biswas et al. 2019; Khalsa et al. 2018). Houston et al. (2018a) summarized the findings from the structural imaging literature in indicating that CMI: (1) is associated with a reduced height of PCF structures in relation to the foramen magnum; (2) is characterized by the sharper angulation of the clivus in relation to the odontoid process; and (3) is distinguished by the retroflection of the odontoid process. Notably, in the literature, there have been few attempts to empirically identify associations between these structural abnormalities and symptom variables. For example, though unpublished in the final version of the manuscript, Houston et al. (2018a) also conducted correlational analyses between self-reported chronic pain and 29 morphometric measures on a comparatively large sample of 162 adult female CMI patients and 140 age-, sex-, and BMI-matched controls (see Fig. 11.6). There was not a single significant correlation between morphometric measures and self-reported pain in CMI patients, a finding that was later replicated in a smaller group of male CMI patients using a similar methodology (Houston et al. 2019b).

Thus, there was a long-standing gap in the CMI literature that has only recently begun to be filled by studies that are more focused on patient experience variables and symptomatology. These studies have either more explicitly analyzed the relationship between brain macrostructure and measures of patient function and symptomatology (García et al. 2020b) or utilized contemporary structural and functional imaging methods that show promise as being correlated with CMI symptomatology variables (Ibrahimy et al. 2021). Below, we review the burgeoning neuroscientific literature, emphasizing studies that sought to empirically identify the brain-based biological mechanisms that might explain the interplay between chronic pain, cognitive dysfunction, and emotional dysregulation experienced by CMI patients.

As previously mentioned, numerous studies have identified behavioral evidence of cognitive dysfunction and emotion dysregulation in CMI. Of these, several also included measures of macro-level brain morphology. For example, García et al. (2020b) measured tonsillar position in their participants in conjunction with their measures of social cognition and pain. In a secondary analysis, the authors reported on correlations between tonsillar position, headache pain, cervical spine pain, and lumbar spine pain. The authors found no significant correlations between these measures, suggesting that chronic pain was not associated with tonsillar position. Similarly, García et al. (2018b) did not identify correlations between tonsillar position, physical pain, or anxious-depressive symptomatology in a supplementary analysis of their data.

The most elaborative study that incorporated structural imaging measures comes from Houston et al. (2019a). This study, which investigated



1. Height of the posterior cranial fossa - the perpendicular distance from the most anterior portion of the tentorium to the McRae´s line.
2. Posterior cranial fossa anteroposterior diameter - a line from the top of the clivus to the internal occipital protuberance.
3. Clivus length - the distance between the dorsum sellae and the most inferior point of the clivus (basion).
4. Posterior cranial fossa area - delimited by the tentorium, the occipital bone, McRae line, and clivus.
5. Posterior cranial fossa osseous area - delimited by the occipital bone, McRae line, and the clivus.
6. Tentorium length - the distance from the most posterior aspect of the corpus callosum to the internal occipital protuberance along the dural fold.
7. Boogard angle - constituted by the clivus length and the McRae line.
8. Dural angle - the angulation of the dural reflection over the clivus, and the visualized portion overlying the dorsal aspect of the odontoid.
9. Basilar impression - the perpendicular distance from the tip of the odontoid process to McRae line.
10. Anteroposterior dura-opisthion diameter - the distance between the vertex of the dural angle and the opisthion.
11. Grabb-Oakes - measurement was defined as the perpendicular distance from a line formed by the basion to the maximum posterior-superior convexity of the odontoid to the posterior-inferior edge of the C2 vertebrae.
12. Basion to posterior axial line - the perpendicular distance from the basion to a tangential line drawn along the posterior aspect of the odontoid process.
13. Odontoid angle - formed by the top of the odontoid process, with the vertex as the midpoint between the anterior-inferior and the posterior-inferior corticated portion of the odontoid, and the posterior-inferior base of the odontoid process.
14. Soft palate length - the distance from the posterior margin of the hard palate to the tip of the uvula.
15. Soft palate thickness - the maximum thickness of the soft palate drawn perpendicular to the soft palate length.
16. Fastigium height - a perpendicular line from the fastigium of the fourth ventricle to McRae line
17. Pons height - a perpendicular line from the cephalad aspect of the pons at the mid-brain junction to McRae line.
18. Corpus callosum height - a perpendicular line from the inferior most aspect of the splenium of the corpus callosum to the McRae line.
19. Tentorium angle - formed by the tentorium and the internal occipital protuberance to the opisthion.
20. Basal angle - a line extending across the anterior cranial fossa to the tip of the dorsum sellae, and the line drawn along the posterior margin of the clivus.
21. Occipital bone length - the distance from opisthion to the internal protuberance of the occipital bone.
22. Basion-dens interval - the minimum distance from the basion to the tip of the odontoid process.
23. Wackenheim angle - formed by a line along the clivus and a line tangent to the posterior aspect of the odontoid process until the base of the C2 vertebrae.
24. Tonsillar position - the perpendicular distance between the tip of the cerebellar tonsil and the McRae line
25. Intracranial height - the maximum length of the skull perpendicular to the plane of foramen magnum.
26. Intracranial diameter - the maximum length of the skull parallel to the plane of foramen magnum.
27. Intracranial area - delimited by the outer portion of the cerebrum, the occipital portion of the occipital bone, McRae line, and the clivus connected at the dorsum sellae (excluding the sella turcica).
28. McRae line - the distance calculated from basion to opisthion.

Fig. 11.6 Common morphometric measures in the Chiari malformation literature. Figure adapted from Houston et al. (2018a), which showed no significant relationship of these measures to self-reported chronic pain

case-control differences in performance on a neuropsychological assessment battery while controlling for self-reported pain, also included 27 morphometric measures similar to those used in Houston et al. (2018a). Of the 27 included measures, only one, tonsillar position, was

correlated with self-reported pain (i.e., greater pain was associated with greater tonsillar descent). The other 26 measures were not correlated with pain. The authors concluded that despite identifying a small number of significant correlations involving morphometric measures, macro-level brain structure alone is unlikely to be a source of etiological understanding of functional outcome measures such as cognitive function and chronic pain.

A recent pair of studies by García and colleagues (2021) and Ibrahimy and colleagues (2021) also stress the relationship between brain structure and self-reported chronic pain, though in a manner unique to other structural imaging studies. Utilizing data from the Chiari 1000 registry, García et al. (2021) recorded 13 midsagittal morphometric measurements within the PCF compartment, including 4 measures of CSF space anterior and posterior to the spinal cord. The authors recorded these measurements in an effort to understand the crowding of these areas that stem from CMI-related midbrain and hindbrain abnormalities and the relationship between CSF space crowding and chronological age. The authors also included self-reported chronic pain as a covariate in their analyses and discovered that not only did narrower anterior CSF space anterior to the cerebellum in the cistern area correlate with greater self-reported pain, but it also accounted for the relationship between developmental increases in self-reported pain with age. These results were particularly interesting given that a morphometric measure of CSF space had shown to be correlated with a symptom variable, whereas direct measures of cerebellar structure were not correlated with chronic pain or other symptomatology variables. Ibrahimy and colleagues (2021) expanded upon these morphometric findings through the use of patient-specific computational fluid dynamic analysis. In their study, the authors analyzed two groups of CMI patients: those that did and did not experience cough-associated headaches. CSF motion was simulated for both groups and results indicated that a measure of CSF flow restriction, integrated longitudinal impedance, better predicted cough-associated headache than tonsillar position. Thus, when considering the results from these two studies in concert with the earlier García et al. (2018b, 2020b) and Houston et al. (2019a) studies, it appears at this time that the relationship between chronic pain and macro-level brain structure can be primarily attributed to anterior CSF space dynamics. Yet, it is still unclear as to what mechanisms are driving this relationship given the limited ability of macro-level brain analyses to draw inference on neural pathway integrity and regional communication. To approach these issues, specialized imaging techniques are required. Fortunately, there have been some initial efforts, using DTI and resting-state fMRI, to further explore some of the underlying mechanisms behind CMI and associated symptoms.

Beginning in 2011 with the work of Kumar and colleagues, there has been an interest in examining how the microstructure of communication pathways between the cerebellum and cerebrum is affected by the presence of CMI (Kumar et al. 2011; Houston et al. 2020; Kurtcan et al. 2018; Krishna et al. 2016). The majority of these studies have sought to measure structural integrity of brain white matter through the use of DTI. These studies have relied upon standard measures that capitalize on the diffusion of water along axon bundles. Healthy white matter tracts consist of a coherent organization of bundled axons of similar orientation, which results in parallel diffusion of water along the axon bundles. However, in cases of axonal degeneration and/or demyelination, there is a disruption of coherent diffusion (Peters 2002). Typical microstructure parameters used to index tissue integrity are fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, which have demonstrated associations with pathology and functional deficits (Beaulieu 2002; Bihan et al. 2001; Inglese and Bester 2010; Mori and Zhang 2006; Song et al. 2005). Of these studies, Houston et al. (2020) was the only one to include a measure of pain in their imaging analysis. The authors identified higher fractional anisotropy values in their sample of 18 CMI patients and 18 age-, sex-, and education-matched controls, a finding which replicated the earlier results of

Krishna et al. (2016) and Kurtcan et al. (2018), albeit in different brain regions (though see Kumar et al. 2011). Moreover, supplementary analyses in Appendices A and B of Houston et al. (2020) indicated several DTI parameters that were correlated with self-reported pain. Of note, fractional anisotropy in both left and right anterior corona radiata, right superior longitudinal fasciculus, and genu were correlated with self-reported pain (see Fig. 11.7). Similarly, measures of diffusivity in the right sagittal stratum, left superior longitudinal fasciculus, left and right anterior corona radiata, and genu were correlated with self-reported pain.

The authors interpreted their DTI findings as potentially reflecting an increase in inflammatory compression, a hypothesis previously stated by Krishna et al. (2016). However, the authors also considered a series of additional mechanisms that could have accounted for their DTI results. These mechanisms included decreases in axonal diameter, reductions in cortical volume, microscopic deficits of axonal structures, and reactive astrogliosis. Houston and colleagues (2020) noted that their findings of CMI-related neural microstructure abnormalities both proximal and distal to the cerebellum and PCF compartment suggest that CMI is a whole-brain phenomenon and not restricted to structures that are directly affected by cervico-medullary compression (Houston et al. 2020). The authors also conceded that their DTI-based analysis could only indirectly speak to CMI-related functional connectivity abnormalities between brain regions, which to directly evaluate would require measures of coherent activation between brain regions using functional MRI.

To our knowledge, there is only one published functional MRI study on CMI patients that includes measures of cognitive function, pain, and symptomatology. Houston and colleagues (2021) examined case-control differences in cerebro-cerebellar functional connectivity using resting-state fMRI (see Fig. 11.3). As with their previous studies, Houston et al. (2021) also examined the relationship between these case-control differences and measures of chronic pain and cognitive performance. The authors identified both CMI-related functional hyper connectivity and hypoconnectivity between cerebellar seed regions and cerebral destinations that were associated with both chronic pain and attention deficits exhibited by CMI patients (see Figs. 11.8 and 11.9).

Chronic pain could account for the relative hypoconnectivity exhibited by CMI patients between left cerebellar lobule III and the left inferior frontal gyrus/right Crus II as well as between the cerebellar vermis I/II and the left superior frontal gyrus. However, functional hypoconnectivity in CMI patients between the posterior cerebellar pathway and right supramarginal gyrus, as well as cerebellar vermis VII and right lingual gyrus, was not associated with chronic pain. Patterns of CMI-related functional hyperconnectivity were also associated with pain. Relative hyperconnectivity between the posterior cingulate and left parahippocampal gyrus, as well as between Crus I and the left superior frontal gyrus, were attributed to CMI-related chronic pain. By comparison, CMI-related functional hyperconnectivity between the posterior cingulate and left globus pallidus, left cerebellar lobule VIII and left postcentral gyrus, and vermis IX and precuneus was found to be independent of chronic pain.

Patterns of relative hypo- and hyperconnectivity in CMI patients were interpreted as being the result of pain drawing upon attentional resources, likely resulting in downstream deficits in cognition. Pathways of relative hypoconnectivity were also identified that were independent of pain and attention, which were posited to be the result of functional alteration of the pathway due to prolonged pain sensation. Moreover, both cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways were implicated in the results interpretation. While not addressed in the study, there remains the possibility that CMI-related functional connectivity abnormalities could also reflect disruptions in the development of structures underlying the central modulation of pain during development and resulting in hyperalgesia and associated cognitive deficits (Ossipov et al. 2010; Moulton et al. 2010). However, there is some evidence to suggest against this notion. Initial evidence from our

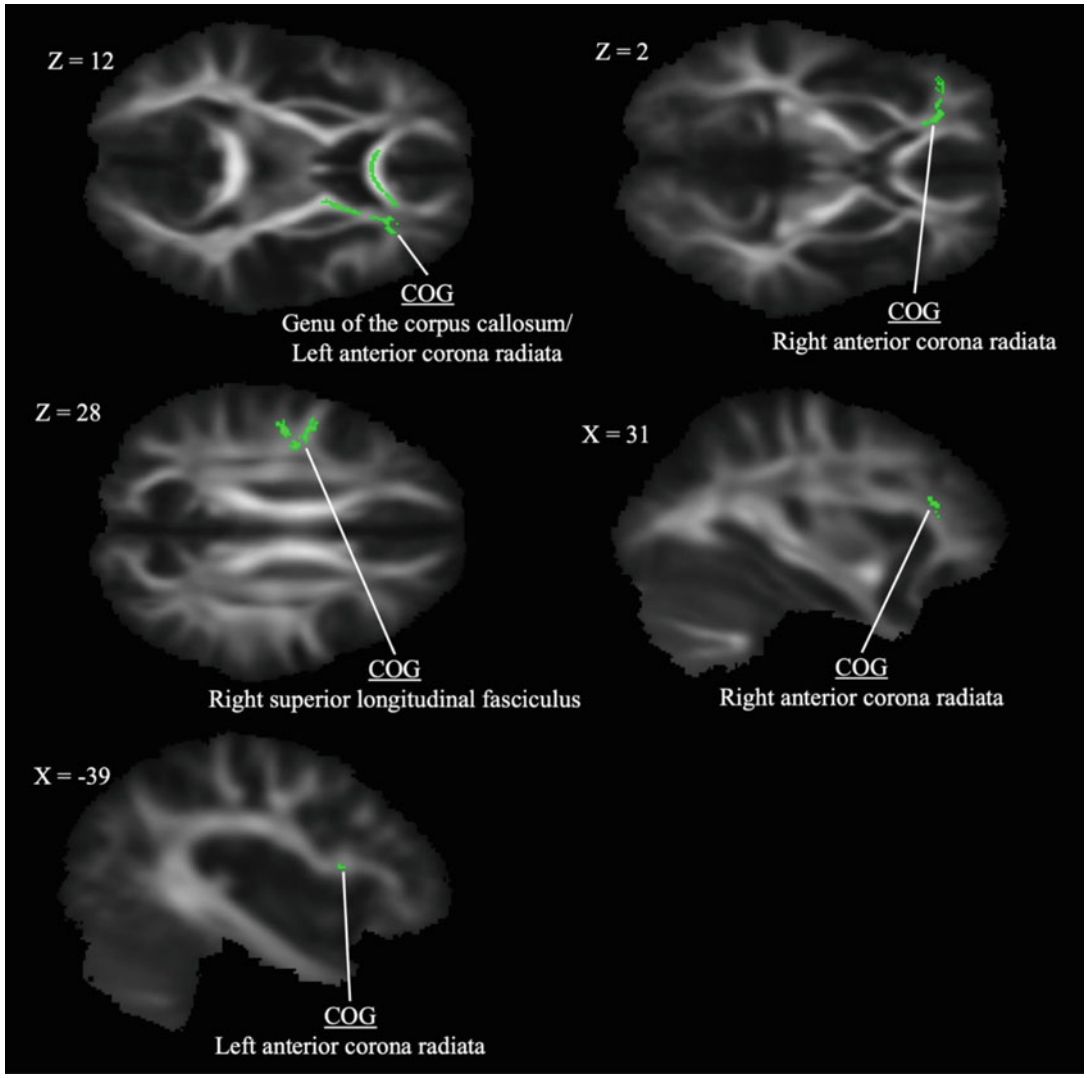


Fig. 11.7 Clusters of significant positive correlation between fractional anisotropy and self-reported pain in a sample of CMI patients and age-, sex-, and education-matched controls. Figure adapted from Houston et al. (2020)

ongoing research suggests that chronic pain is not as common a symptom in pediatric Chiari cases relative to adult-onset CMI. We also feel that the replicated finding of greater fractional anisotropy (i.e., rather than lower FA) in DTI studies better indicates reactive mechanisms akin to those observed in cerebellar lesion studies (Ruscheweyh et al. 2014).

Compared to the behavioral literature, the neuroscience literature on the dynamics between chronic pain and CMI-related cognitive dysfunction and emotion dysregulation is still in early stages. Initial findings implicate anterior CSF space compression, as well as a series of brain microstructure abnormalities and functional connectivity irregularities involving afferent and efferent pathways between the cerebellum and cerebrum, with CMI-related chronic pain. Early results also suggest that brain microstructure analyses may be the most promising sources for

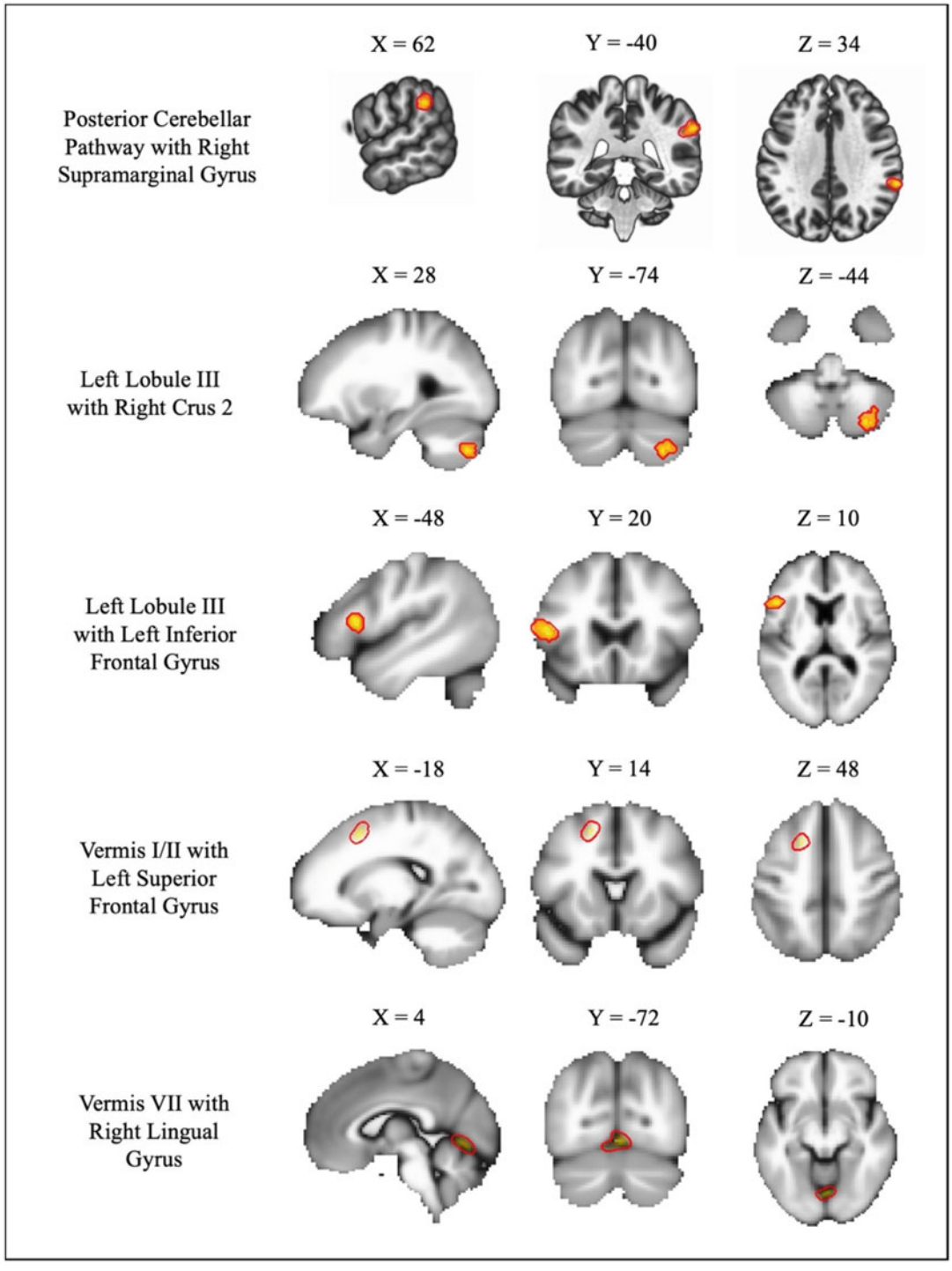


Fig. 11.8 Regions of CMI-related relative hypoconnectivity between cerebellar seeds and areas of connectivity. Figure adapted from Houston et al. (2021) and originally published under CC BY 4.0

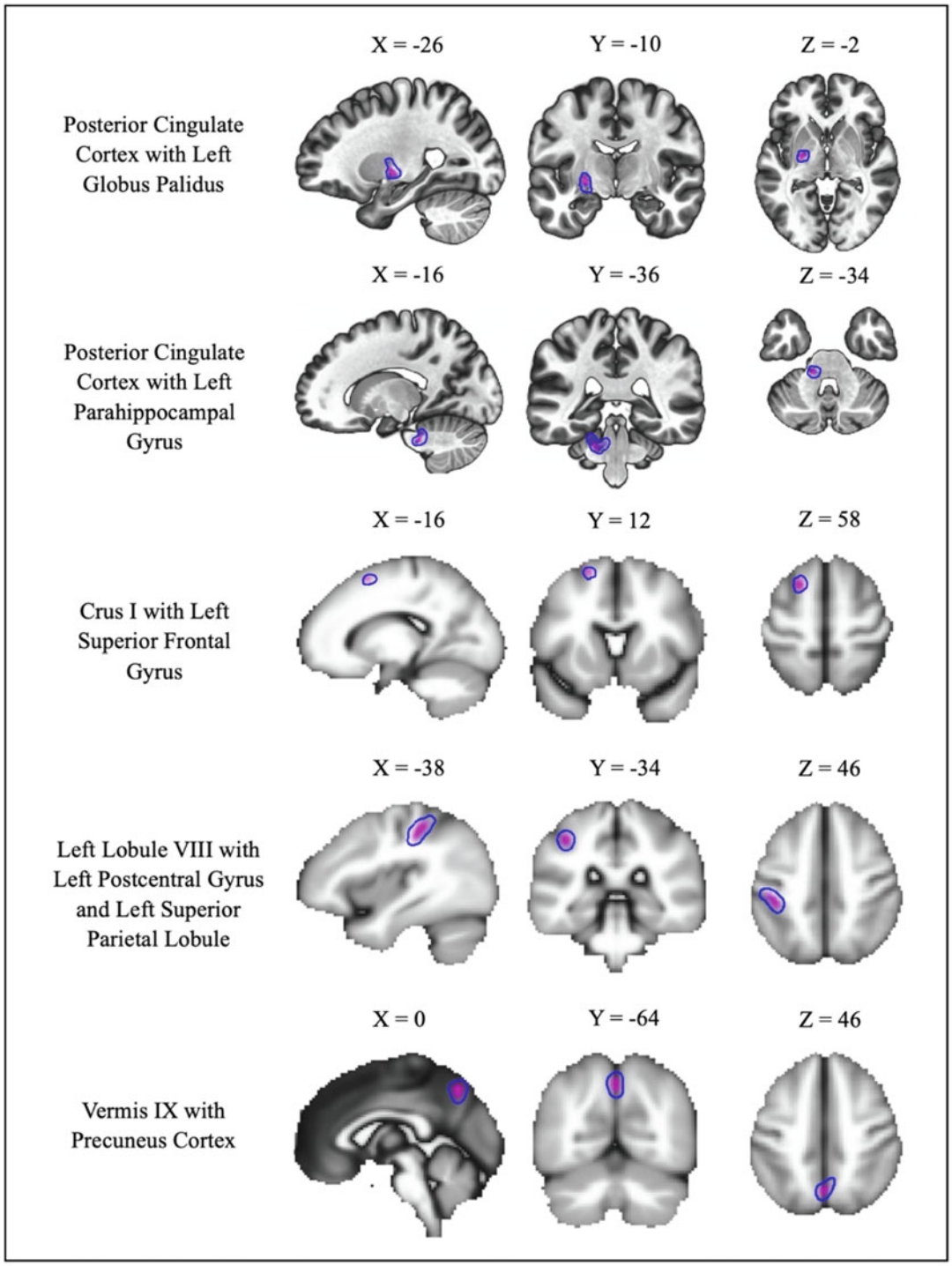


Fig. 11.9 Regions of CMI-related relative hyperconnectivity between cerebellar seeds and areas of connectivity. Figure adapted from Houston et al. (2021) and originally published under CC BY 4.0

elucidating the mechanisms behind CMI cognitive and emotion processing deficits as well as the relationship between these deficits and chronic pain. However, much of this early work is based upon few and generally small datasets of CMI patients, and replication studies are critically needed to better inform clinical care.

11.5 Clinical Considerations

Irrespective of the condition being considered, pain is a difficult construct to evaluate because of its subjective nature. That is, pain has been exceptionally difficult to objectively study because radiological evidence of structural abnormalities or damage is often not distinguishing of the patient pain experience. For example, it is not uncommon for two CMI patients presenting with similar posterior cranial fossa or cervical spine abnormalities to report meaningfully different pain severity. This has led to the use of self-report measures such as the numerical rating pain scale and the visual analog scale that link either words or graphical pictures describing pain intensity (Haefeli and Elfering 2006), as well as the revised short form of the McGill Pain Questionnaire (Dworkin et al. 2009) that includes a series of 22 describing words for pain symptoms rated on an 11-point scale. All three of these types of self-report pain scales have shown clinical utility, and the McGill Pain Questionnaire has been particularly valuable as it includes separate subscales for continuous, intermittent, neuropathic, and affective pain.

CMI patients' scores on these types of assessments along with qualitative pain reports during clinical interviews often provide a major consideration for treatment approach. Yet, it is important to remember that these static measures of pain only provide a small, fuzzy snapshot of the pain experience. As indicated by the biopsychosocial model of pain introduced earlier, many of a patient's person-environment interactions can be affected by their pain experience. When considering the longevity of the typical chronic headache and neck pain symptomatology in CMI, this likely includes thousands of patient's person-environment interactions. From deciding not to attend a child's sporting event because of the pain elicited by sitting on gymnasium stands to resigning from employment because of the physical demands they cannot meet, day-to-day decision-making processes are consistently affected across many contexts. These contexts include decision-making tied to physical and mental health, interpersonal relationship dynamics, and the capacity to work (see Fig. 11.1). It is important to remember the continuous nature of the person-environment interactions. As discussed, patients engage in reflective and ruminative processes tied to previous decisions related to their health and quality of life. Allen and colleagues (2018) provided an empirical example of these processes when they suggested that Chiari patients who have undergone decompression surgery are disappointed when they continue to experience chronic headaches and experience negative consequences to cognitive function as a result.[3] Given these considerable complexities, we encourage clinicians to take a holistic view of the pain exhibited by their CMI patients when suggesting treatment options.

There is also a potential positive aspect to the pervasiveness of chronic pain on CMI symptomatology when discussing the symptom maintenance and improvement. Given that a considerable degree of CMI-related cognitive dysfunction and emotion dysregulation can be attributed to the pain experienced by CMI patients, there leaves open the potential for interventions targeting the alleviation of pain, attenuation of pain, or pain acceptance to have a meaningful impact on the capacities of CMI patients. While the empirical work on this topic is largely lacking, there have been initial efforts to address whether pain alleviation could improve cognitive and emotion function in CMI. For example, Holmes et al. (2019) reported a case study on the use of group Acceptance and Commitment Therapy (ACT) in six middle-aged CMI

[3] The authors speculated that this was because neuropathic pain networks underlying the central sensitization of pain are not directly targeted by decompression surgery.

patients. This treatment approach, based on relational frame theory and emphasizing mindfulness, focuses on functional contextualism. For example, a patient experiencing chronic pain might be led to better understand how their personal pain experience might negatively impact their beliefs associated with being able to live a meaningful life. The patient may then be led to learn methods to orient themselves to here-and-now experiences and prioritize aspects of their lives that they find meaningful. CMI patients participating in the case study showed self-rated improvements in pain, coping, and daily functioning based on descriptive data. Much more work is needed in this area, particularly work that empirically evaluates the relationship between psychotherapy outcomes, chronic pain, and behavioral and the neurobiological irregularities discussed previously.

Focusing specifically on the pain assessment of CMI patients, self-reports of chronic pain in CMI, particularly headache pain, can also confound CMI diagnosis. CMI patients with whom we have interacted in our lab have commonly expressed their frustrations of being previously diagnosed with conditions such as chronic migraine, fibromyalgia, or other neurologic conditions. While it is noteworthy that in many of these cases, the patients also met the diagnosis standards for these comorbid conditions (i.e., CMI with fibromyalgia, Raynaud's syndrome, etc.), it was nevertheless frustrating to the patients that the Chiari "puzzle piece" was missing from their diagnosis. In particular, patients felt disheartened that their ultimate treatment intervention, typically Chiari decompression surgery, was delayed, often for years, as a result of the missed diagnosis. Chiari awareness campaigns seek to lessen the likelihood of these patient experiences. CMI diagnosis sensitivity will also likely benefit from increased academic research interest in the cerebellum and increased clinical research interest in cerebellar conditions, though to what degree it remains to be seen.

Going beyond the challenges and potential boons presented by patient self-reports, the budding neurobiological literature that emphasizes cerebellum and posterior cranial fossa tissue strain and cerebro-cerebellar connectivity also presents the potential for more objective, or at least more predictive, measures of chronic pain. In other words, where patient self-reports of pain are highly dependent on cognitive, affective, and personality variables, neurobiological markers of pain may better predict patient pain symptomatology and treatment trajectories. In particular, we feel that imaging studies of brain microstructure and functional connectivity may provide a foundation on which to build an understanding of neurobiological markers of CMI-related pain (Houston et al. 2020, 2021). If the research in these areas were to be better clarified, one could imagine the benefits of providing individualized treatment suggestions based on a patient's specific neurobiological profile.

One final clinical consideration for which there is largely a void of evidence is how the cognitive dysfunction and emotion dysregulation in CMI is associated with other cerebellar conditions, namely Cerebellar Cognitive Affective Syndrome (CCAS), also known as Schmahmann's Syndrome (Schmahmann and Sherman 1998; Manto and Mariën 2015; Hoche et al. 2018). For example, many of the disruptions in cognitive and emotion function identified in the CMI literature would be consistent with CCAS. Similarly, both cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways have been indicated in each condition. Future CMI studies would benefit from the inclusion of the relatively new CCAS scale (Hoche et al. 2018) and ideally include a comparison CCAS sample without CMI. Studies incorporating this design could not only better clarify the underlying etiology behind CMI-related deficits through the much more expansively studied CCAS framework but also provide additional understanding of the influence of pain on the neurobiological networks underlying the deficits in both conditions.

11.6 Conclusion

It is clear that CMI is characterized by the disruption of cognitive function and emotion regulation. Current evidence implicates deficits in attention

and executive function, along with deficits in forming emotional attributions as being central to CMI presentation. Moreover, CMI-related chronic pain has been demonstrated to divert resources away from effortful cognitive and affective processes, leading to disruptions in episodic memory, working memory, processing speed, and emotion recognition. Initial evidence attributes these deficits to disruptions in CSF flow dynamics in the anterior-posterior cranial fossa and abnormalities in the afferent and efferent pathways associated with cerebro-cerebellar communication. Advancements in pain assessment and treatment will be critical to improving patient outcomes and understanding the underlying etiology behind CMI-related disruption in cognitive and emotion function due to pain.

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