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Fear of pain in children and adolescents with neuropathic pain and CRPS

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Abstract

A significant proportion of children and adolescents with chronic pain endorse elevated pain-related fear. Pain-related fear is associated with high levels of disability, depressive symptoms, and school impairment. Due to faulty nerve signaling, individuals with neuropathic pain and CRPS may be more prone to develop pain-related fear as they avoid use of and neglect the affected body area(s), resulting in exacerbated symptoms, muscle atrophy, maintenance of pain signaling, and ongoing pain-related disability. Not surprisingly, effective treatments for elevated pain-related fears involve exposure to previously avoided activities to down-regulate incorrect pain signaling. In the context of intensive interdisciplinary pain treatment of youth with neuropathic pain, decreasing pain-related fear is associated with improved physical and psychological functioning, while high initial pain-related fear is a risk factor for less treatment responsiveness. An innovative approach to targeting pain-related fear as well as evidence of a neural response to treatment involving decoupling of the amygdala with key fear circuits in youth with CRPS suggest breakthroughs in our ability to ameliorate these issues.

Keywords

chronic pain; youth; pain-related anxiety; brain imaging; amygdala

Chronic pain in childhood is a significant public health concern with median prevalence rates of 11 to 38% [25], with 3 to 5% of children suffering from significant pain-related disability [12; 22], costing society $19.5 billion annually in the US alone [18]. Although no published prevalence rates for neuropathic pain in childhood exist, approximately one quarter of patients who present to our tertiary care pain clinic are diagnosed with neuropathic pain (complex regional pain syndrome [CRPS] and non-CRPS), ranging from 23% (total sample=697;[47]) to 26% (total sample=321;[57]). Based on these estimates, it is expected that approximately 3–9% of children suffer from chronic neuropathic pain. Beyond

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the personal suffering and persistent physical and economic consequences for families, chronic pain in childhood can predispose the development of adult chronic pain[69]. Identifying targets for intervention is a challenge as the chronic pain experience involves physiological, psychological, and social factors contributing to pain-related outcomes [14]. The current review will focus on one particularly salient influence on pain outcomes, fear[13; 51; 74; 75].

The evolution of pain-related fear

Humans are programmed to experience fear, and in most cases, fear is adaptive. Pain (an unconditioned noxious stimulus; US) triggers our fear response and alerts our flight-or-fight system to act (an unconditioned response; UR). This is where pain and fear can go awry. After experiencing a painful stimulus or injury, a previously neutral experience, such as movement or even anticipation of movement (a conditioned stimulus; CS) can elicit fear (a conditioned response; CR), even in the absence of pain. Although adaptive in the short-term to promote healing, individuals who continue to perceive movement as threatening after the painful stimuli are no longer present or the initial injury has healed (conditioned fear) can experience a number of psychological and physical sequelae, including hypervigilance, muscular reactivity, escape/avoidance, and guarding behaviors that maintain or exacerbate pain and promote pain-related disability [65]. Unfortunately, pain-related fear learning can develop after only a few repetitions, generalizes quickly, and can be maintained through pain anticipation, converting to an operant process of reinforcement [67].

Pain-related fear and associated behavioral avoidance has been identified as a key factor influencing the development and persistence of pain-related disability across patients with low back[21; 60; 61], neuropathic[8; 52], upper extremity[10], abdominal[39], fibromyalgia[7; 29], and headache pain[5; 41; 54], irrespective of pain intensity. The Fear Avoidance (FA) Model of Chronic Pain [67] is a theoretical framework put forth to explain the impact of pain-related fear. According to the model, individuals who develop fear of pain, injury, and/or physical activity engage in guarding or avoidance behaviors that maintain or exacerbate pain[31]. Continued avoidance and physical inactivity leads to disuse, disability, and depression[24; 65]. Conversely, individuals who confront their pain experience and progressively resume physical activities, thereby testing and correcting pain expectations, subsequently experience a recovery in their pain symptoms[33]. Although some debate exists regarding the cyclical nature of the model [73], evidence for its core tenets is robust [77].

Pain-related fear in youth

Studies that have examined pain-related fear in children have supported its link to adverse outcomes. In a small pilot study of youth with chronic pain, pain-related fear accounted for 40% of the variance in pain-related disability [35] with a second small study finding that pain-related fear predicted child physical activity limitations beyond the influence of pain level and depressive symptoms [76]. When examined within a larger tertiary care pain clinic sample, higher levels of pain-related fear were associated with more healthcare utilization and functional disability [56]. In the context of acute post-surgical pain, pain-related fear

was associated with pain unpleasantness and functional disability two weeks after major surgery [45].

Most studies have focused on the influence of pain-related fear on disability-related outcomes [77], rather than the temporal influence of fear on subsequent pain levels. The current evidence suggests that the concurrent relation between pain-related fear and pain intensity in children and adolescents is modest (Table 1). Although more research is needed, it appears that the magnitude of the association is larger among post-surgical patients (in an acute pain context) and among patients after completing intensive pain rehabilitative treatment.

Applying the Fear Avoidance (FA) Model of Chronic Pain to the pediatric context has yielded promising results (Simons & Kaczynski, 2012; Figure 1a–b). Key elements of the model for the individual patient (pain, pain catastrophizing, fear of pain, avoidance of activities, disability/depression) have been thoroughly examined to evaluate separate models for children and adolescents. The predictive model for functional disability was robust and consistent with the theorized adult model (catastrophizing -> fear -> avoidance -> disability; Figure 1a), whereas for the outcome of depression, pain-related distress (pain catastrophizing, fear of pain) had a direct influence on depressive symptoms (Figure 1b). Developmental differences emerged with fear of pain more influential on avoidance behavior among adolescents, suggesting that targeting anxiety-related pain cognitions (“I walk around in constant fear of hurting”) may potentially yield greater gains in returning to previously avoided activities than in younger pain patients.

Beyond individual factors, researchers have called for modifications to the FA model for pediatric application to incorporate contextual influences (Asumundson et al., 2012; [16]). Fear can be acquired, reinforced, or resistant to extinction through social transmission[43] with parent emotional responses serving as key guides to a child’s learning about safety and danger and influencing subsequent behavior[30; 38]. New neurobiological evidence in a preclinical model supports parental transmission of fear behaviorally[11]. Growing evidence in the psychosocial literature supports parent pain catastrophizing and protective behavior in prioritizing pain control[4], higher functional disability[34; 70], and school dysfunction[32] in children with pain. This is coupled with recent evidence supporting the influential role of parents on the formation of negative pain memories[40].

As a result, the interpersonal fear avoidance model (IFAM) of pain was recently developed [16] and tested (Simons et al., 2015; Figure 2a-b). The IFAM expands upon the FA Model to include parent cognitive-affective and behavioral factors that have either been proven to impact child outcomes or are theorized to do so. Within the IFAM (Figure 2a), when parents interpret a child’s pain expression through the lens of their own catastrophic appraisals and pain-related fears, they are more likely to engage in maladaptive avoidant or protective parenting behaviors. These parent behaviors influence whether the child avoids or limits activities, potentially leading to greater functional disability. In addition, parents may suffer emotionally and experience interference of their own life goals as a result of their child’s pain, getting caught up in a cycle of avoidance and activity restriction. To examine parent pain-related fear and avoidance, we developed and validated the Parent Fear of Pain

Questionnaire (PFOPQ)[58] in a sample of 321 parents of chronic pain patients and tested the Interpersonal Fear Avoidance Model in a separate sample of 163 patients[58]. Parent protective and avoidance behavior contributed directly and indirectly to child avoidance. Additionally, parent fear and catastrophizing contributed indirectly to child avoidance through parent behavior and child fear and catastrophizing, in turn, influencing child functional disability levels (Figure 2b).

Treatment of pain-related fear

Reversing the impact of fear learning is complex and difficult. Extinction, or learning of an inhibitory response, of acquired fear is resistant to automatic generalization, requiring massed rehearsal in a variety of contexts during stressful and non-stressful circumstances to prevent renewal [44; 48]. Graded in-vivo exposure (GEXP), a cognitive-behavioral therapy developed by Vlaeyen and colleagues [66] targets fear of pain and disability through exposing patients to activities previously avoided due to fear of pain or re-injury [9; 10]. A pain psychologist and physical therapist jointly deliver GEXP in an outpatient setting. This intervention has been identified as more effective than wait-list controls in improving disability and reducing pain-related fear [1].

To date, no studies have explicitly targeted pain-related fear through GEXP in children. One study with adolescents who participated in an exposure and acceptance-based treatment program reported decreases in pain-related fear [71], and when examining mediators of change, the investigators identified pain impairment beliefs (psychological flexibility/pain acceptance) and pain reactivity (worry and emotional reactivity to pain) as significant mediators of improvements in pain interference and depressive symptoms [72]. Although not a primary target of the exposure and acceptance-based program, the investigators also observed a significant decrease in pain intensity that was maintained across follow-up periods and was not observed in the multidisciplinary treatment group [71]. Within the context of an intensive day hospital pain rehabilitation program that involves psychological, physical, and occupational therapy, a decrease in pain-related fear was associated with improvements in functional disability and depressive symptoms at the end of treatment and at two month follow-up among patients with neuropathic pain [52]. In this investigation pain intensity was observed to significantly decrease across time, and interestingly as detailed in Table 1, the concurrent association between fear of pain and pain intensity actually increased in magnitude from 0.15 at admission to 0.43 at 1-month follow-up. The increasing resonance between pain intensity and fear of pain deserves further inquiry. Of note, high levels of pain-related fear at admission predicted less reduction in functional disability and depression at discharge, suggesting that high levels of pain-related fear may be a risk factor in relation to treatment outcomes. These findings underscore the need to specifically target pain-related fear in children to potentially avert sustained pain-related disability.

We recently initiated the first pilot implementation of GEXP for youth with chronic pain. In this intervention, the primary goal for the patient is returning to valued activities of daily life and restoring daily functioning, including returning to school. Sessions are conducted with a cognitive-behavioral (CB) therapist, physical therapist (PT), the child, and a parent (as developmentally appropriate). The treatment manual for children and adolescents with

chronic pain was adapted from the adult published treatment manual[68]. Briefly, the initial phase of treatment focuses on psychoeducation of the Interpersonal Fear Avoidance Model, values-based goal setting, and fear hierarchy development through the use of the English version (Simons et al., unpublished) of Photographs of Daily Activities (PHODA)-Youth, a diagnostic tool to determine the perceived harmfulness of different activities[64]. In the second phase of treatment, graded exposure begins. The CB therapist and PT jointly lead some of the exposure sessions. During other sessions, the PT leads the exposures while the CB therapist meets individually with the parent. The final phase of treatment focuses on relapse prevention and future goal setting. Results of this initial trial are forthcoming with GEXP expanding treatment options for children struggling with persistent pain, fear, and disability.

Brain circuitry of pain-related fear

Beyond the phenotypic presentation of pain-related fear and its treatment, brain imaging can provide insight into the underlying neural pathways of fear of pain and fear conditioning in humans, work previously limited to animal models (Figure 3). Evoked brain response to fear conditioning is observed in the amygdala[3; 28], insula[17; 63], and anterior cingulate[26], with the magnitude of the amygdala response predictive of conditioned response strength[28; 46]. Brain structure correlates of conditioned fear have associated greater posterior insula thickness with a larger conditioned response, while greater amygdala volume has been associated with less fear acquisition[19].

Brain regions critical to the acquisition of extinction learning (the target of GEXP) include the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus. Recent pre-clinical evidence suggests that successful extinction silences basal amygdala excitatory neurons previously active during fear conditioning[62] and decreases excitatory tranismssion of mPFC projections to the basolateral nucleus of the amygdala[6]. The vmPFC is necessary for the retention and recall of extinction, wherein damage to this area results in preservative behavior[59]. fMRI studies of extinction learning in humans report a decrease in amygdala activation[15; 27; 28; 46] while BOLD signals in the vmPFC increase during extinction learning and extinction retrieval[46]. This association is extended to measures of brain structure with increased thickness in the vmPFC associated with extinction retention[19]. Lastly, fMRI studies that examine context-dependent recall of extinction point to the function of the hippocampus[23; 37] and vmPFC[49]. Overall, extinction learning in humans seems to depend on the integrated functioning of a neural circuit that includes the amygdala, the vmPFC, and the hippocampus.

Beyond evaluation of fear learning/extinction pathways, few studies have examined neural correlates of pain-related fear, particularly among patients with chronic pain. In a study conducted with healthy adults, the authors found a link between higher fear of pain levels and greater activation in the medial PFC, orbitofrontal cortex, and cingulate in response to noxious stimuli [42]. In a more recent study of healthy adults, higher back pain-related fear avoidance beliefs were associated with greater amygdala activity and greater synchronicity in activity between the amygdala and pregenual anterior cingulate cortex [36]. In the only study in adults with chronic pain examining the influence of pain-related fear on evoked

brain activity, participants viewed aversive movements, and no differences were noted among high and low fear back pain patients and healthy controls in brain responses to stimuli [2]; although, this may be explained by the method used to elicit fear [50].

Our group has recently reported the first data for youth with chronic pain that suggests that fear circuits are altered [55]. In this study, patients with Complex Regional Pain Syndrome (CRPS) who presented for intensive interdisciplinary pain rehabilitation were scanned prior to the start of treatment and at discharge from the program. Within the sample, 70% of patients reported elevated or clinically elevated pain-related fear at treatment admission. When examining resting state functional connectivity of the amygdala to the rest of the brain, higher pain-related fear scores were associated with stronger functional connectivity between the left amygdala and insula, hippocampus, prefrontal cortex, anterior cingulate, middle temporal gyrus, brain stem and cerebellum, after controlling for pain level (Figure 4a). After intensive psychophysical treatment, persistently higher fear scores were associated with stronger functional connectivity between the left amygdala and hippocampus, prefrontal cortex, anterior cingulate, and middle temporal gyrus (Figure 4b). Together, these results link key fear brain circuits with the pain-related fear phenotype; although, further research is needed to evaluate the degree to which these alterations are due to heightened fear learning and ineffective extinction.

Beyond alterations in fear circuitry, we found that brain response to intensive pain rehabilitative treatment can be tied to reductions in pain-related fear[55]. Paired analysis of amygdala connectivity changes within patients was examined (Figure 5). Decreased functional coupling between the left amygdala and prefrontal cortex, supplementary motor area, anterior cingulate cortex, and insula after treatment was associated with decreases in pain-related fear. Changes in pain did not correlate with changes in amygdala connectivity. These results suggest that improvements in function and fear are closely linked to decoupling of the amygdala with key fear circuits in youth with CRPS. It is yet unknown if these changes reflect greater neural plasticity in children compared to adults, and future research that includes both pediatric and adult patients is necessary to answer this lingering question.

Conclusions

There is strong support for the detrimental impact of fear of pain and associated avoidance and disability on children suffering with chronic pain. Additionally, emerging evidence highlights the additive impact of parent variables, including fear and avoidance, on the child chronic pain experience. Fortunately, initial findings suggest that exposure-based treatments and intensive interdisciplinary pain programs result in improvements in pain-related fear. Additionally, innovative imaging studies that examine fear-related brain circuitry coincide with the phenotypic presentation of pain-related fear in the clinic. Moreover, we have captured changes in fear circuits that correlate with improvements in pain-related fear, suggesting brain plasticity with recovery. Further work is necessary to determine if these changes are unique to the pediatric CRPS patient. As we look forward, it will be essential to integrate our accumulating knowledge of basic learning mechanisms to our understanding

and treatment of pain-related fear in youth. Tenets and perhaps even whole theories will need to be refined or redefined to keep pace with the rapidly evolving field.

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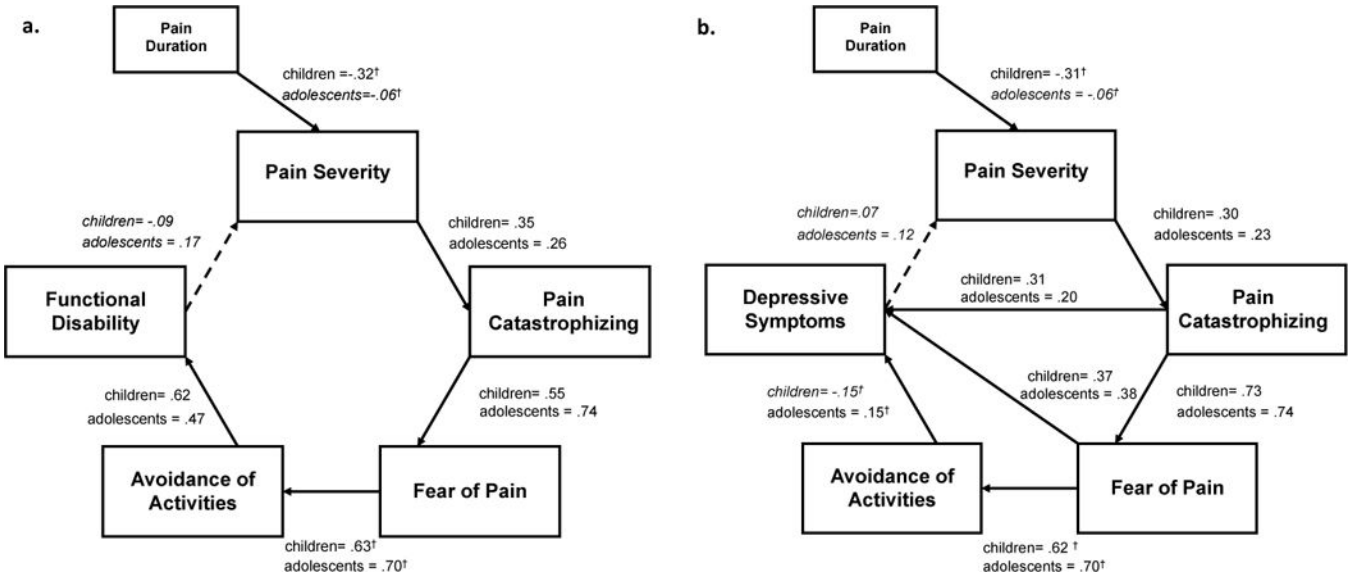

Figure 1. Model with Functional Disability and Depression as Concurrent Outcome

For functional disability (**a**) the FAM was robustly upheld. For depressive symptoms (**b**), additional direct pathways for pain catastrophizing and fear of pain were necessary for acceptable model fit. Solid lines are significant at $p < .05$. Error variances were not included in the figure for simplicity and interpretability. Italicized regression coefficients are non-significant pathways. †denotes values that significantly differ from one another within a specific pathway.

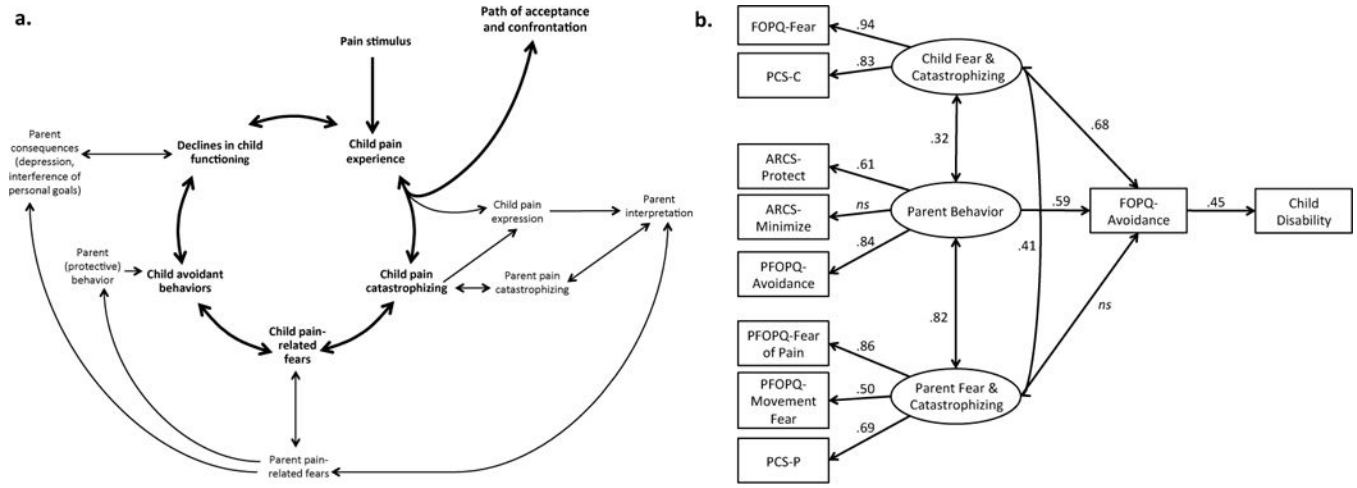

Figure 2. Interpersonal Fear Avoidance Model of Pain (IFAM)

a. In the IFAM model, a child or adolescent develops pain, often in response to an event; although, it can also begin spontaneously. In the context of the child's pain experience, (s)he either responds with progressive confrontation and acceptance of pain in his/her life for now or continues to perceive the presence of pain as threatening. This expression of threat and fear is observed and interpreted by the parent and reciprocally interacts with a parent's own catastrophic thinking about his/her child's pain. This, in turn, leads to hypervigilance and persistent fear in the child and parent. In the context of heightened fear, the child avoids activities that (s)he perceives as potentially harmful to his/her with parent protective behavior providing further encouragement for avoidance behavior. Ultimately, this leads to declines in child functioning and limitations in the life of the parent/caregiver. **b.** Child fear and catastrophizing and parent behavior had a direct and indirect influence on child avoidance behavior, while parent fear and catastrophizing indirectly influenced child avoidance. Overall, the model accounted for 20% of the variance in functional disability, $X^2(30) = 46.95$, CFI = .97, RSMEA = .06 (CI=.02–.09). Child avoidance is measured with the Avoidance of Activities subscale of the Fear of Pain Questionnaire, Child report (FOPQ). Child disability is measured with the Functional Disability Inventory (FDI). Parent Avoidance is measured with the Parent Avoidance subscale of the Parent Fear of Pain Questionnaire (PFOPQ). PCS-C: Pain Catastrophizing Scale, Child report; ARCS: Adult Responses to Child's Symptoms; PCS-P: Pain Catastrophizing Scale, Parent report.

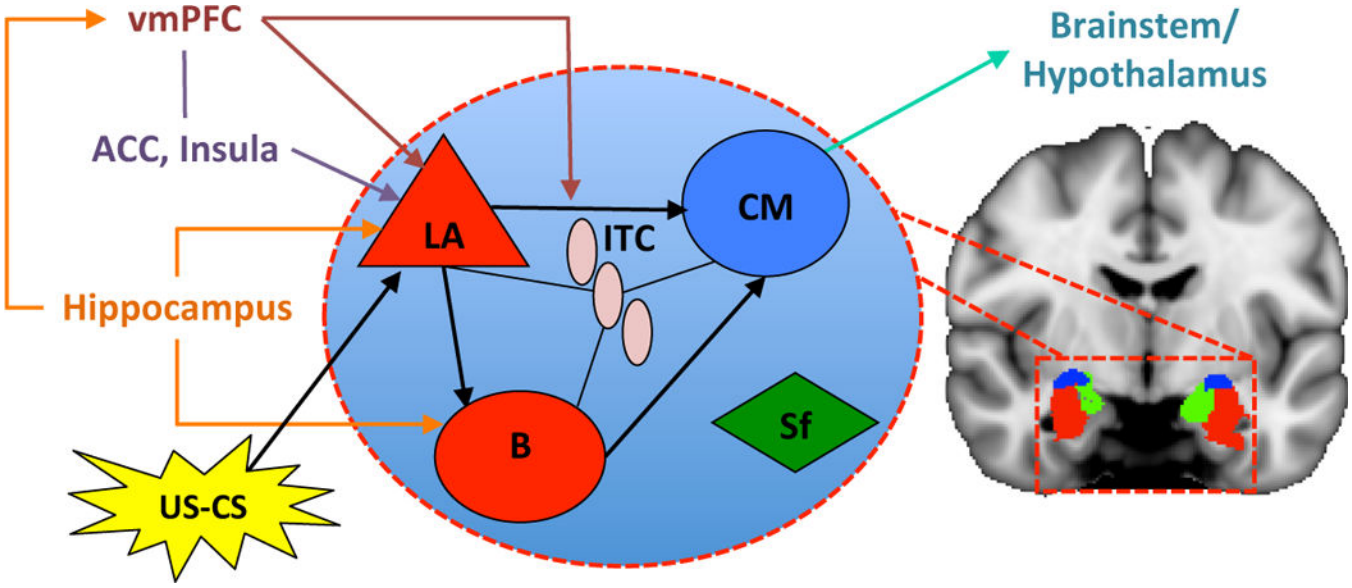

Figure 3. Neural Pathways of Fear Learning

In fear conditioning, an emotionally neutral conditioned stimulus (CS; e.g., movement) is presented with an aversive unconditioned stimulus (US; pain). The CS and US converge at the lateral nucleus (LA). The LA then connects with the centromedial nucleus (CM), controlling the expression of the conditioned fear responses (CR) in the brain stem and hypothalamus. Projections from the hippocampus to the basal nucleus (B) of the amygdala process contextual information during conditioning, while the insula and anterior cingulate (ACC) influence threat encoding. *During extinction learning*, inhibitory connections between the ventromedial prefrontal cortex (vmPFC) and intercalcated (ITC) cell masses are established. During extinction recall, these connections inhibit fear expression through projections to the CM. Inhibitory connections between the vmPFC and LA may also regulate fear expression through the CM. Contextual modulation of extinction expression is mediated by projections from the hippocampus to the vmPFC and/or LA. Adapted from[20; 53].

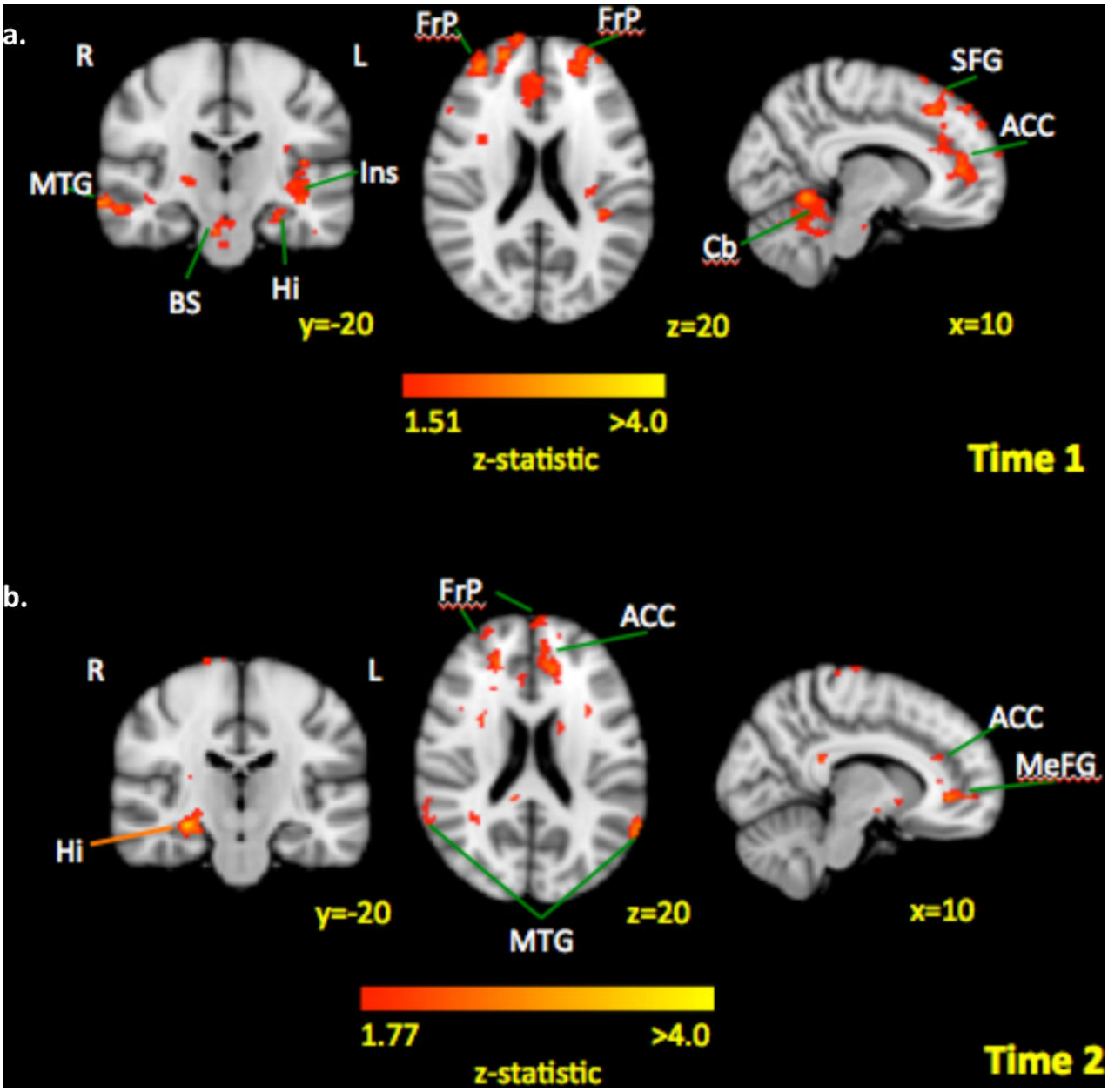

Figure 4. Connectivity strength by levels of pain-related fear in patients (Left Amygdala)

Across time, areas associated with fear circuitry were consistently associated with higher pain-related fear scores. Key: MTG: middle temporal gyrus; BS: brain stem; Hi: hippocampus; Ins: insula; FrP: frontal pole; ACC: anterior cingulate cortex; SFG: superior frontal gyrus; Cb: cerebellum; MeFG: medial frontal gyrus.

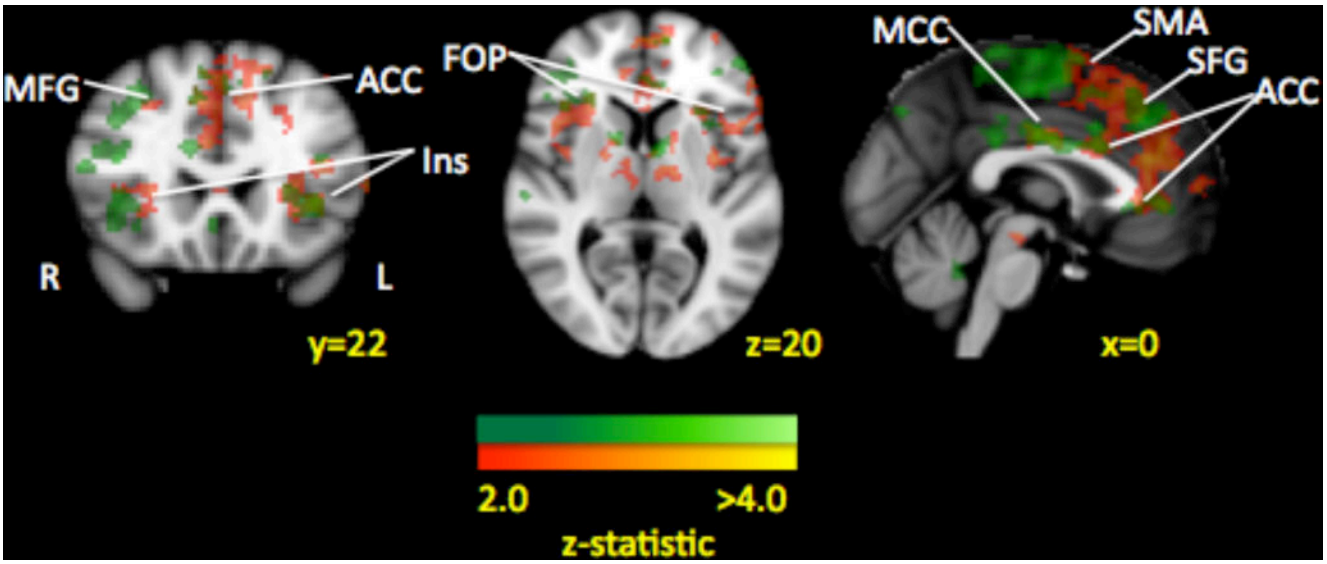

Figure 5. Treatment Response from Time 1 to Time 2: Decrease in functional connectivity and pain-related fear

Paired analysis of amygdala connectivity changes within patients is depicted in green while connectivity changes that correlated with changes in pain-related fear are displayed in red. Many of the amygdala connectivity decreases were correlated with decreases in pain-related fear after treatment, suggesting that changes in intrinsic brain functional connectivity can be linked to symptom improvement. Key: MFG: middle frontal gyrus; Ins: insula; SMA: supplementary motor area; ACC: anterior cingulate cortex; MCC: middle cingulate cortex; FOP: frontal opercular cortex.

Table 1

Association between pain and pain-related fear in children

Authors		Sample Size	Zero-order correlation: pain & pain-related fear	Pain-related fear	Pain rating
Martin et al., 2007	Chronic pain	n=21	−0.04	CPASS	Current
Wilson et al., 2011	Chronic pain	n=42	0.22	FABQ	Usual
Simons et al., 2011	Chronic pain	n=299	0.24	FOPQ	Average
Huguet et al., 2011	School children	n=225	0.30[1]	PPFS	Highest (FPS-R)
	Chronic pain	n=159	0.15	PPFS	Highest (FPS-R)
Page et al., 2011	Post-surgical	n=83	0.43[a]	CPASS	Current
		n=69	0.36[b]	CPASS	Current
Simons et al., 2012	Intensive pain rehabilitation	n=134	0.15[aa]	FOPQ	Average
		n=122	0.30[bb]	FOPQ	Average
		n=110	0.43[cc]	FOPQ	Average
Carpino et al., 2014	Headache	N=195	0.22	FOPQ	Average

Note. CPASS=Child Pain Anxiety Symptom Scale; FABQ=Fear Avoidance Beliefs Questionnaire; FOPQ=Fear of Pain Questionnaire; FPS-R=Faces Pain Rating Scale-Revised; PPFS=Pediatric Pain Fear Scale.

[1] Correlation was corrected for gender.

[a] 48–72 hours post-surgery,

[b] 2-weeks post-surgery,

[aa] admission,

[bb] discharge,

[cc] 1-month follow-up.