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ORIGINAL ARTICLE

The Role of Sleep and Attention in the Etiology and Maintenance of Fibromyalgia

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Abstract Fibromyalgia (FM) is a prevalent, debilitating condition characterized by widespread, intense pain experienced as emanating from in the muscles, tendons, and ligaments. Other symptoms include disabling fatigue, poor sleep quality, gastrointestinal complaints, cognitive difficulties and often depression. Lack of apparent muscle pathology or other obvious physiological causes of FM pain make the etiology of FM unclear. This manuscript reviews extant FM literature and integrates research on sleep and the burgeoning literature from the domain of cognitive neuroscience to formulate the Sleep and Pain Diatheses (SAPD) model of FM. This model proposes that a wide range of biopsychosocial stressors can set the stage for FM by activating diatheses for sleep disruption and pain sensitivity. Sleep disruption in those most sensitive to pain initiates a cascade of symptoms that are codified as FM. Once this process is initiated, the symptoms of FM are perpetuated and aggravated by increased vigilance to a broad range of threat-related biopsychosocial stimuli. Thus, it is proposed that sleep is integral to the etiology of FM and also energizes a cognitive feedback loop that maintains or amplifies symptom severity over time.

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Introduction

Fibromyalgia (FM) is characterized by widespread, intense pain combined with the symptoms of extreme fatigue, poor sleep quality, gastrointestinal complaints, cognitive deficits, and often depression (e.g., Bennett et al. 2007; Wolfe et al. 2000; Wolfe and Skevington 2000). Determining the etiology of FM is made even more challenging by the presence of this diverse spectrum of symptoms and no clear physiological cause for the reported pain (e.g., Bennett 2005). FM has traditionally been conceptualized as a pain disorder because of the high salience of pain symptoms. It may, however, be more fruitful to model sleep disruption as an upstream etiological factor, activating a cognitive feedback loop that serves to maintain a broad range of FM symptoms. The purpose of this paper is to synthesize existing research on FM and use it to formulate a comprehensive biopsychosocial theoretical model that can be used to inform research and treatment of FM.

The prevalence of FM is approximately 2% in the general population, and the disorder is seven times more common among women than men (Wolfe et al. 1995). The average FM patient does not improve markedly with medical care, yet will visit health care professionals 10 times per year on average, generating thousands in annual medical costs (Wolfe et al. 1997a, b). Clearly, there is a need for greater understanding of this disorder to inform more effective treatment of this condition.

Understanding FM has been hampered by both clinical and theoretical problems. Chief among these problems is that the symptom profile of FM is likely to be the endpoint of multiple causes; it is thus difficult to develop a single theoretical model

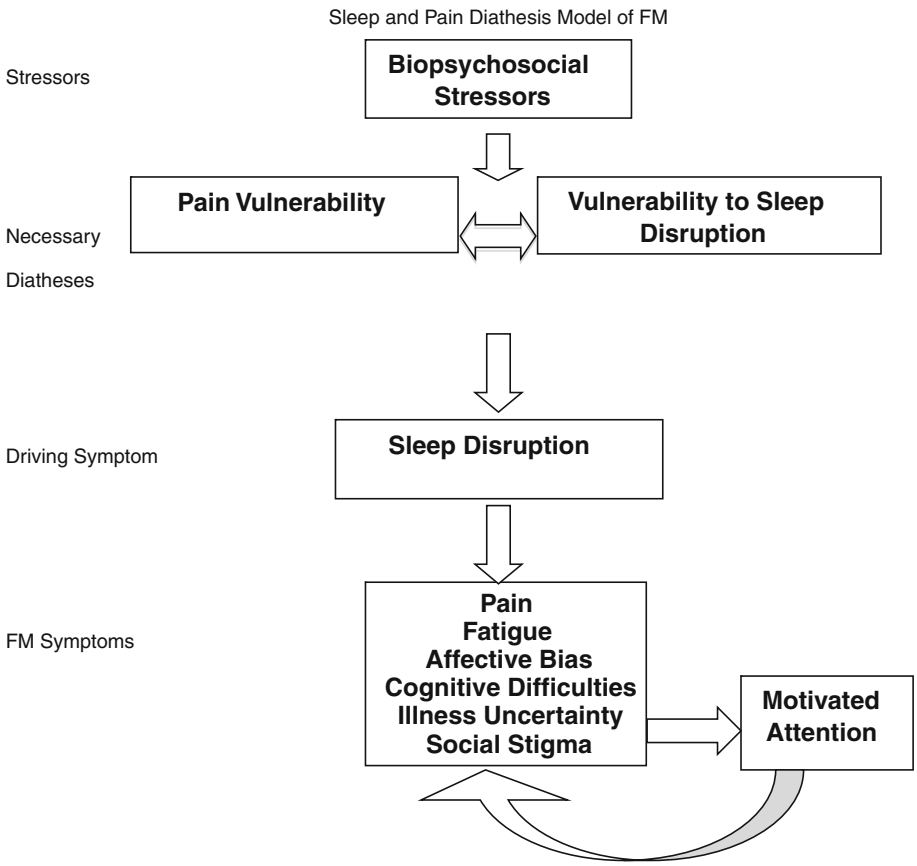

Fig. 1 Sleep and pain diathesis model of FM

that "fits" all patients. Thus, it may be fruitful to identify large subgroups of FM patients that are defined by a common etiology. The *Sleep and Pain Diatheses (SAPD) model* of FM uses a diathesis-stress formulation to define a sleep subtype of FM (see Fig. 1). This model proposes that a wide range of biopsychosocial stressors can set the stage for FM by activating diatheses for sleep disruption. Sleep disruption in those most sensitive to pain then initiates a cascade of symptoms, including most notably increased bodily pain, fatigue, cognitive "sluggishness," and gastrointestinal discomfort. Once this process is initiated, the symptoms of FM are perpetuated and aggravated by increased vigilance to a broad range of threat-related stimuli. We propose that sleep is integral to the etiology of this type of FM and also energizes an escalating cognitive feedback loop that maintains or amplifies symptom severity over time. Note that the SAPD model does not claim to provide an etiological model for ALL patients with FM. We do however argue that onset of chronic sleep disruption is *sufficient* in those with low pain tolerance to account for the symptom profile that is described as FM.

Triggering Events: Stressors

The stress-diathesis formulation of the model specifies that underlying vulnerabilities may be triggered by the occurrence of a stressor. This supposition is consistent with the experience of many FM patients. Recently, an internet survey of more than 2,500 people with FM indicated that at least 73% identified an antecedent event such as illness or stress (Bennett et al. 2007). In addition to illness and psychosocial stress, early menopause and hysterectomy are commonly reported by FM patients (ter Borg et al. 1999) and may be construed as a biological stressor. It should be noted that there is controversy about whether trauma plays a role in onset of FM. Although PTSD is common comorbid condition (Sherman et al. 2000), at least one study showed no increase in FM diagnoses following 9/11, an event with high likelihood of producing PTSD (Raphael et al. 2004). Thus, it is possible that recalled events provide meaning for FM, but do not trigger the onset of FM symptoms. What is important here is that most FM patients recall onset following events or problems (e.g., illness, injury, stress, trauma, menopause, hysterectomy) that have been found to precipitate sleep disruption in healthy adults (e.g., Dahan et al. 2006; Kim and Lee 2001; van Liempt et al. 2006).

Diatheses

Pain Sensitivity

The SAPD model suggests that high pain sensitivity is one of two diatheses necessary for the development of FM.

Several studies have shown clustering of FM within families (e.g., Arnold et al. 2004), suggesting a genetic component to FM. Differences between FM patients and pain free controls have been found in genes coding for neurotransmitter systems associated with pain processing such as the serotonin, dopamine, and the catecholamine systems, as well as a substance P receptor subtype (see for a reviews: Buskila 2007; Fillingim et al. 2008). Of particular interest is recent research showing that FM patients have a greater likelihood to posses a polymorphism in the Catecholamine-0-Methyltransferase (COMT) gene that is associated with reduced activity of an enzyme that degrades catacholamines (Diatchenko et al. 2005; Gursoy et al. 2003; Zubieta et al. 2003). Both the COMT and μ-opiod receptor genes correlate with individual differences in pain threshold and tolerance and increased risk for chronic pain (Diatchenko et al. 2005; Fillingim et al. 2005; Zubieta et al. 2003). Another good candidate for investigation would be a gene coding for GTP cyclohydrolase (GCH-1). Polymorphisms in this gene have been linked to persistent pain following spinal surgery and pain severity ratings in healthy adults during experimentally induced pain (Tegeeder et al. 2006). It is likely that that more pain related polymorphisms will be identified in the near future. Emerging techniques using gene "Chips" may be a key to indentifying likely genetic candidates. However, theoretical models of pain perception and modulation (e.g., Melzack and Wall 1965) should be used to guide this research. The complexity of pain processing ensures that phenotypic pain sensitivity is determined by a number of genes, and possibly epigenetic material, rather than a single polymorphism (see for a comprehensive discussion of pain diatheses: (Yunus 2007).

Sleep Disruption

The defining feature of the SAPD model is the proposition that sleep disruption combined with a high sensitivity to pain and/or low pain tolerance are key diatheses for FM. Before presenting the evidence for this claim, it may be helpful to review some basic information about sleep. Polysomnographic (PSG) data show that sleep is divided into Rapid Eye Movement Sleep (REM) and non-REM (NREM), with NREM further subdivided into stages 1–4 based on characteristic EEG signals. Relaxed wakefulness is characterized by high frequency low amplitude alpha waves. Stage 1 is the lightest stage of sleep and is defined by asynchronous high frequency theta (4–8 Hz) waves. Stage 2 sleep is deeper than stage 1, contains similar theta activity, sleep spindles, and K-complexes that are thought to dampen response to external stimuli and thus maintain sleep. The deepest sleep occurs during stages 3 and 4, characterized by high amplitude low frequency Delta waves (2–4 Hzs) commonly referred to as Slow Wave Sleep (SWS). Stage 1-Rapid Eye Movement (REM) sleep is characterized by high-frequency low amplitude EEG, and minimal muscle tone. When individuals have sleep disorders, SWS, and REM are commonly replaced by either wakefulness (alpha EEG) or stages 1 and 2 sleep (see for greater detail: Hirshkowitz et al. 1997).

The defining feature of the sleep subtype of FM defined by the SAPD model is objective evidence of disrupted sleep. In a large study that randomly selected community residents with pain, those with FM reported high levels of non-restorative sleep (92%), insomnia (84%), and extremely high levels of daytime sleepiness (e.g., White et al. 1999). Up to 94% of those diagnosed with FM also experience clinically significant fatigue and many meet criteria for chronic fatigue syndrome (Shaver et al. 1997; Wolfe et al. 1996). Interestingly, in a recent survey of more than 2,500 people with FM, fatigue and non-restorative sleep were rated as more severe than pain (Bennett et al. 2007). These data show that the vast majority of FM patients report disrupted sleep and fatigue and may best be characterized by the sleep subtype.

Moldofsky and colleagues were among the first to identify an EEG abnormality in FM patients that correlated with non-restorative sleep (Moldofsky and Scarisbrick 1976; Moldofsky et al. 1975). Subsequent research showed that disrupting sleep with an auditory tone produced FM-like symptoms in healthy young men (Moldofsky and Scarisbrick 1976). Arousal disturbances were indicated by the presence of alpha EEG waveforms in NREM (Delta wave) sleep and were thought to interfere with the restorative function of SWS. Since these initial studies, other research groups have documented high alpha activity throughout the sleep cycle of FM patients and correlated this phenomenon with overnight increases in fatigue, pain, and sluggishness (e.g., Drewes et al. 1995a, b; Roizenblatt et al. 2001) and perceptions of "shallow" sleep (Perlis et al. 1997a). It should be noted, however, that alpha-Delta sleep is not unique to FM nor is it present in all patients with FM (e.g., Cote and Moldofsky 1997; Drewes et al. 1998; Moldofsky 1989). Thus, the alpha-Delta hypothesis has largely been abandoned as the unique cause of FM. However, other PSG studies have documented that FM patients have up to three times as many wakeful arousals as healthy controls (Jennum et al. 1993; Kooh et al. 2003; Rizzi et al. 2003; Sergi et al. 1999), more Stage 1 sleep (Rizzi et al. 2003; Roizenblatt et al. 2001; Shaver et al. 1997), less slow-wave sleep (Rizzi et al. 2003), a higher sleep fragmentation index (Shaver et al. 1997), and fewer sleep spindles (Landis et al. 2003). Thus, Moldofsky may have been right to identify disrupted sleep as an upstream factor in FM, but the alpha-delta model may have focused too specifically on a single cause of disrupted sleep.

The SAPD model specifies that vulnerability to sleep problems is a key diathesis for FM. However, the nature of the diathesis and the sleep disturbance itself is likely to be heterogeneous. For some, an underlying vulnerability to insomnia (Spielman et al. 1987) could be activated by the experience of a traumatic event, an injury, illness, or symptoms related to menopause (e.g., hot flashes, night sweats). For others, weight gain related to, or independent of, menopause could enhance the risk of Sleep Disordered Breathing (SDB) that results from orofacial features that interfere with nighttime respiration (see summary: Hirshkowitz et al. 1997). Thus, the specific type of sleep disruption is not germane, rather the important issue is that sleep is inadequate, or fragmented, and not restorative.

Consistent with our model, FM patients show a high prevalence of sleep disorders. The prevalence of Obstructive Sleep Apnea (OSA) is relatively high among FM patients (estimates range from 11 to 83%; May et al. 1993; Shah et al. 2006). The latter number represents the prevalence rate of OSA in a small sample of FM patients unselected for symptoms of sleep disorders. A recent small study found evidence of a less severe form of respiratory related sleep disorder, Upper Airway Resistant Syndrome (UARS) in 96% (27 of 28) of FM patients referred for a sleep clinic evaluation (Gold et al. 2003). Still others with FM may have arousals secondary to sleep disorders such as Restless Leg Syndrome (RLS; Yunus and Aldag 1996), Periodic Limb Movements (PLM; Tayag-Kier et al. 2000). Disorders such as OSA, UARS, RLS, and PLM, disturb sleep continuity and may be an undiagnosed cause of nonrestorative sleep.

It is important to note that the SAPD model specifies that sleep problems alone are not sufficient for the development of FM. The prevalence of FM in sleep clinic populations is relatively low (1–2%), indicating that most people with sleep problems do not develop FM. The SAPD model predicts that FM will result from sleep disruption only in those individuals who also have a genetic vulnerability to high pain sensitivity and/or low pain tolerance.

Summary and Conclusions

Despite the high prevalence of sleep problems, most models of FM do not address sleep problems as part of the etiology or maintenance of FM symptoms. Although, there has yet to be a large-scale epidemiological study of sleep problems in FM patients, existing studies clearly indicate the presence of the SAPD model's driving symptom in a large number of people with FM. Almost all patients with FM report sleep problems and we would argue that PSG abnormalities and sleep disorders are the most consistently found objective clinical symptom of FM.

Sleep Diathesis and FM symptoms

The majority of FM patients report sleep disruption, the defining feature of the sleep-subtype of FM defined by the SAPD model. Consistent with the SAPD model, research presented below documents that sleep disruption alone can produce the hallmark symptoms of FM, notably somatic symptoms like pain, fatigue, as well as cognitive and affective disruptions such as dysphoric mood, and problems with attention and memory.

Pain, Fatigue, and Dysphoric Mood

Longitudinal (Nicassio et al. 2002) and daily process data show that sleep is related to a broad range of physical, cognitive, and emotional symptoms. For instance, a study using ecological momentary assessment methodology documented that sleep duration and sleep quality were related to the affective reaction to pain and stress in individuals diagnosed with FM and rheumatoid arthritis (Affleck et al. 1996). Specific to FM are daily dairy data showing that disrupted or inadequate sleep predicted increased pain and enhanced attention to pain (Affleck et al. 1996), reduced progress on social and fitness related goals (Affleck et al. 1998), as well as higher levels of negative affect and fatigue and lower levels of positive affect (Hamilton et al. 2008). Shorter sleep durations also prevented recovery from social stressors (Hamilton et al. 2008). Moreover, short sleep durations and poor sleep quality also predict stress and pain reactivity (Hamilton et al. 2007). We interpret these data to mean that for individuals with FM, sleep is a scarce biobehavioral resource that limits the ability to actively pursue meaningful and rewarding goals, affects attentional processes, and predicts increased pain and distress associated with pain and stressful events.

It should be noted that the sequelae of sleep disruption are not at all unique to FM patients. Self reported sleep disruption and/or insomnia have been linked to increased pain, changes in affect, and higher fatigue in patients with rheumatoid arthritis (Nicassio and Wallston 1992), bed-partners of men who have OSA (Smith et al. 2009) and healthy adults (Buysee et al. 2007; Totterdell et al. 1994; Zohar et al. 2005). Moreover, experimental partial and total sleep deprivation, as well as selective deprivation of REM and SWS sleep have been shown to substantially reduce pain thresholds and tolerance in healthy adults (e.g., Kunderman et al. 2004; Onen et al. 2001; Roehrs et al. 2006). Chronic sleep deprivation is likely to be more troubling than acute sleep problems. Multiple nights of experimental partial sleep deprivation produce a progressively worsened mood, reduced ability to concentrate, and increased reports of psychosomatic symptoms, including

pain (Dinges et al. 1997). These data are important because they indicate that with the exception of high pain reports, FM patients do not differ qualitatively from other populations in their response to sleep disruption. Inadequate or non-refreshing sleep impairs affective, somatic, and cognitive well-being. Arguments that sleep plays no role in the pathogenesis of FM would need to provide a plausible explanation for why or how FM patients with disrupted sleep are somehow immune to this well-established relationship between sleep and outcomes such as increased pain, vigilance, fatigue, and dysphroic mood.

There is strong evidence linking sleep to increased pain, fatigue, and dysphoric mood. However, the biological mechanism explaining this link is more speculative. Experimental sleep disruption has been shown to disrupt the normal circadian rhythms of a number of hormones such as cortisol and ACTH (see for a review, Vgontzas and Chrousos 2002), growth hormone (Jarrett et al. 1990) and pro-inflammatory cytokines (Vgontzas et al. 2002, 2004). Efforts to link FM to abnormal levels of pro-inflammatory cytokines, blunted (or excessive) cortisol, or reduced levels of growth hormone have produced inconsistent results, perhaps because many researchers did not examine individual differences in sleep disruption and/or measured hormones or cytokines at a single time point rather than evaluating differences in circadian rhythms (e.g., Wallace et al. 2001). Interestingly, one study that excluded patients with sleep disorders and carefully regulated FM patient's sleep cycles showed normal circadian hormonal rhythms (see as an exception: Gur et al. 2004). As noted above, hormone and cytokine cycles respond to acute disruptions in sleep. Thus, it should be no surprise that regularizing sleep schedules should also be correlated with normal circadian rhythms.

The research presented thus far suggests that many patients with FM may belong to the FM sleep subtype described by the SAPD model. Also consistent with the SAPD model, sleep disruption also correspond to changes in pain perception, fatigue, attentional difficulties (e.g., vigilance and trouble with attention), and emotional lability in FM patients and healthy adults.

General Cognitive Disruptions

Because the SAPD model predicts that sleep disruption is the driving symptom of for patients with the sleep subtype of FM, we are theoretically motivated to examine cognitive functions that are most disrupted by poor sleep. The majority of FM patients have cognitive complaints that are colloquially known as "fibrofog." Up to 83% of FM rheumatology patients report cognitive difficulties (Katz et al. 2004). Despite the salience of cognitive problems to FM patients, most models of FM do not address cognitive complaints as part of the etiology or maintenance of FM symptoms. One reason for omitting cognitive problems from theoretical models of FM is that neuropsychological assessment has typically failed to detect deficits in short-term memory (i.e., memory for new information) or an altered learning curve (e.g., Grace et al. 1999; Landro et al. 1997; Suhr 2003). FM patients appear able to encode novel information, recall it after short delays, and learn at a normal rate. Although some of the discrepancy between perceived performance and actual performance is likely to be due to inaccurate patient appraisals, standard assessment batteries may have failed to measure the appropriate memory process.

Sleep and Memory Consolidation

Neuropsychological research on FM patients has focused exclusively on the acquisition of new memories and to our knowledge has never evaluated overnight memory consolidation. This is a glaring omission in light of the robust and compelling evidence that sleep, particularly NREM sleep, promotes consolidation of both procedural memories (memory for a new skill) and also declarative memories (i.e., memory for specific events or stimuli; for review see Stickgold et al. 2001).

Both experimental and quasi-experimental study designs have shown that after a period of extended sleep, newly learned material is more resistant to interference and can be better recalled or recognized (e.g., Ellenbogen et al. 2006; Gais et al. 2006). These studies indicate that memory consolidation is dependent upon NREM sleep, and cannot be better accounted for by the effects of fatigue or circadian variation in alertness. Supporting this hypothesis, manipulation of NREM by transcranial direct current stimulation (tDCS) increased SWS and sleep spindles and was associated with greater verbal recall, higher positive affect, and decreased negative affect (Marshall et al. 2004). It is theorized that during NREM, memories temporarily stored in the hippocampus are reactivated then transferred to the neocortex where they become integrated into long-term memory. Additional experimental research shows that memory consolidation is suppressed by exogenous cortisol (Plihal and Born 1999) and high endogenous levels of cortisol are related to poor memory consolidation in healthy sleepers and those with insomnia (Backhaus et al. 2006). These data suggest that typical FM sleep problems, night-time arousal and/or the lack of adequate NREM could inhibit memory consolidation and provide a plausible mechanism for memory problems that could easily be missed by a standard neuropsychological assessment battery.

Although memory consolidation has not been evaluated in FM patient, poor memory consolidation has been observed in insomnia patients (Backhaus et al. 2006). It would be fruitful to compare FM patients to insomnia patients and healthy sleepers on overnight memory consolidation. Possible confounds with medications should be carefully considered because memory consolidation could be inhibited by insomnia medications or anti-depressants.

Sleep and Attention

Thus far we have proposed and provided evidence that sleep disruption predicts symptoms of pain, fatigue, and problems with memory. However, the intersection of sleep research with cognitive neuroscience suggests that we should examine attention as a second key cognitive process. Attention can change in a number of ways, including simultaneous decreases in overall attention combined with increases in selective attention or attentional bias. Extant research suggests that sleep deprivation affects both aspects of attention.

The most well established effect of sleep deprivation is difficulty with sustained attention (e.g., Taylor and McFatter 2003; Williams et al. 1959). Full sleep deprivation and partial sleep deprivation are associated with lapses in attention, response errors and greater variability in performance (e.g., Doran et al. 2001). Most relevant to FM patients, cumulative effects of partial sleep deprivation appeared to produce lapses in attention and reaction times that increased across 7 days of testing (Dinges et al. 1997). These data are consistent with and may help to explain why FM patients appear to differ from healthy controls on tasks that require sustained attention and/or those tasks that put heavy demands on working memory (e.g., Cote and Moldofsky 1997; Grace et al. 1999; Park et al. 2001; Sletvold et al. 1995). It should be noted that self-reported sleep difficulties have not shown the expected relationship to attention and working memory (Dick et al. 2002; Grace et al. 1999). However, more sleep time spent in Stage 1 sleep predicted poor performance on a task that measured FM patients ability to quickly focus and shift attention (Cote and Moldofsky 1997). These data suggest that it would be important to employ PSG or actigraphy to accurately assess the relationship between sleep and FM symptoms including cognitive functioning.

Motivated Attention: A Mechanism for Maintaining FM Symptoms

Like other sleep-deprived people, sleep-subtype FM patients may have difficulty sustaining attention to repetitive or mundane tasks (e.g., Cote and Moldofsky 1997; Grace et al. 1999; Park et al. 2001; Sletvold et al. 1995). However, decreased overall attention may be less problematic than selective vigilance to certain kinds of stimuli. Borrowing from the cognitive neuroscience literature, the SAPD model proposes that symptoms of FM fail to decay because of an otherwise adaptive response to threat, motivated attention (for a description of model of Motivated Attention see (Bradley et al. 2001). In simple terms, motivated attention reflects an attentional bias toward stimuli with immediate survival value (usually negative in valence) and away from other stimuli with no immediate survival implications (positive or neutral in valence). Motivated attention could be construed as the cognitive "engine" driving continued pathology in FM patients.

According to the theory of motivated attention, perceived vulnerability biases the earliest stage of attention (controlled by sub-cortical, limbic system structures). This type of bias should not be construed as voluntary, inherently pathological, or abnormal. Biased attention plays an important evolutionary role because it allows for vigilance, or enhanced detection and perceptual processing of negative or threatening stimuli that might cause harm (Bradley et al. 2001). Pain and fatigue constitute a perceived threat to the physical integrity of the organism, which in turn biases attentional resources toward other stimuli that have immediate survival value while positive and neutral stimuli (with distal positive consequences) are relatively ignored. Using the motivated attention framework, we would expect a general attentional bias toward *all* negative information (environmental and somatic), and away from non-threatening positive and neutral stimuli.

Motivated Attention and Pain

The motivated attention model would argue that very early attentional sensory processing systems (both cortical and subcortical) are specifically tuned to detect high arousing stimuli that might reflect external threat, possibly even before the specific valance of the stimulus is detected. Researchers have provided EEG evidence for this early influence of stimulus significance on sensory processes by examining Somatosensory Evoked Potentials (SEPs; Junghofer et al. 2001; Keil et al. 2003).Early sensory components that occur before 100 ms in the EEG ERP waveform, specifically P50 and N80, are thought to originate from primary sensory cortex regions that are responsive when detecting sensory input (Montoya et al. 2005). Importantly, there appear to be threat related differences in these early sensory components. A perfect example of this kind of early sensory modulation is provided by Montoya and colleagues who have showed that early P50 and N80 SEPs are influenced by negative mood state. For patients with FM, the particular pattern of ERP SEP responses

measured by Montoya and colleagues may mean that the earliest cortical regions that control the sensing of tactile stimuli are simply more responsive to sensory input. This would mean that even at the very earliest stages pain detection, FM patients would show evidence of feeling pain stimuli more keenly.

Examples of a mechanistic explanation for these kind of neurological changes are emerging with research showing that emotional processes related to defensive (threat perception) and appetitive (reward perception) circuits, modulate nociceptive processing via descending spinal and supraspinal circuits (de Wied and Verbaten 2001; Meagher et al. 2001; Rhudy et al. 2005). Specifically, the Nociceptive Flexion Reflex (NFR), an involuntary response to a painful electrical stimulation, is facilitated by negative mood and inhibited by pleasant stimuli (Rhudy et al. 2005). The NFR paradigm is particularly compelling because response is reflexive and not, therefore, contaminated by individual differences in motivation or self-presentation.

The concept of motivated attention is also consistent with fMRI data. Two high quality studies have now shown that FM patients do not differ qualitatively from healthy adults in their response to painful stimuli. Instead, FM patients show a similar pattern of response (i.e., increased activity in areas associated with sensory discrimination and association, motor response, and affective processing), when matched on perceived pain intensity rather than stimulus intensity (e.g., Cook et al. 2004; Gracely et al. 2002). Unlike healthy controls, FM patients responded to non-painful levels of blunt thumb nail bed pressure (Gracely et al. 2002) and heat stimuli (Cook et al. 2004) with activation in anterior cingulate cortex, various frontal lobe and motor regions. Vigilance to negative stimuli in general may explain how low-level aches and pains normally associated with chronic sleep deprivation could activate pain processing centers and that are not normally activated by such low intensity tactile stimuli.

Theories of motivated attention emphasize that perceived threat biases early attention. The SAPD model contends that sleep-deprivation constitutes yet another perceived threat to integrity and thus biases attention. Consistent with this proposition, experimentally disrupted (but not restricted) sleep was shown to block pain-inhibitory signals by minimizing (by 86%) the pain buffering effects of Diffuse Noxious Inhibitory Control (DNIC; Smith et al. 2007), or the ability of one pain stimulus to diminish the perceived magnitude of another pain stimulus. Reduced efficacy of the DNIC has been observed in FM patients (Kosek and Hansson 1997) and is thought to reflect a change in the central processing of pain. Thus, experimental sleep disruption produces the same type of disturbance in pain modulation that has been observed in FM patients.

It is well known that attention to pain and increased negative emotions escalate the sensory salience of pain (Melzack and Wall 1965). Thus, theories of motivated attention are consistent with what we know about pain in general. Motivated attention adds to our knowledge of chronic pain by proposing a cognitive mechanism for pain perpetuation, documenting that hypervigilance occurs extremely early in the attentional process which would be consistent with early stages of fear-related processing.

Motivated Attention and Perceived Cognitive Functioning

The motivated attention component of the SAPD model of FM has the potential to explain deficits in cognitive functioning. As shown in Fig. 1, the SAPD model suggests that motivated attention to somatic symptoms may interfere with other more task-focused activities. In qualitative terms, concern about threatening symptoms such as pain and fatigue may preclude attention to other tasks. Supporting this supposition are data showing that pain and fatigue were correlated with FM patients' performance on neurpopsychological tests (Cote and Moldofsky 1997; Dick et al. 2002). Thus, attending to physical symptoms may limit attention to the tasks at hand.

In addition to explaining objectively documented fatigue and pain related attentional deficits, motivated attention also offers an explanation for why FM patients often overestimate the extent of their cognitive deficits. Compounding the problem of symptom-related vigilance, motivated attention may promote attention to mistakes or the perceived difficulty of a test. One study found that FM patient's estimate of his or her own cognitive problems was almost four times greater than the actual observed differences between FM and healthy controls (Grace et al. 1999). Thus, the pervasive negative bias of motivated attention may result in actual decreased performance capability, because of reduced attentional processing capacity and also a diminished perception of cognitive efficacy because attention is drawn to mistakes and away from correct trials.

Motivated Attention and Illness Uncertainty

FM may engage motivated attention to a greater degree than many other illnesses with defined etiologies and illness trajectories. FM patients experience their illness as being highly mysterious (Reich et al. 2006) and the perception of FM as an ambiguous illness is associated with a greater reliance on ineffective coping strategies such as catastrophic thinking and lower coping efficacy (Johnson et al. 2006). It is not surprising that FM patients would perceive their illness as ambiguous, given that little definitive information is available about FM. Unfortunately, the

ambiguity of FM may further stimulate motivated attention in the form of a "symptom search" process that is both likely to detect unpleasant bodily sensations and also ascribe FM related meaning to those symptoms. Thus, motivated attention may explain the wide range of symptoms typically reported by FM patients (Bennett et al. 2007) and would limit attentional capacity for other more positive, internal or external stimuli.

Motivated Attention and Sleep

Although the SAPD model suggests that sleep disruption and fatigue are upstream of motivated attention, it may certainly be the case that motivated attention (or vigilance) is triggered by the initial stressor (assault, illness, injury). However, we would strongly argue that subsequent sleep disruption perpetuates the motivated attentional processes. Consistent with this formulation, are data linking insomnia to hypervigilance during sleep and wake periods (Perlis et al. 1997b). Several recent studies suggest that people with insomnia are more likely to interpret ambiguous stimuli as having a threatening rather than neutral meaning (Ree et al. 2006), particularly when the person with insomnia is feeling sleepy (Ree and Harvey 2006). Motivated attention may also explain hyperarousal found in many insomnia patients (Bonnett and Arand 1995). Consistent with theories of motivated attention, feeling fatigued or sleepy may promote a state of hyper-vigilance to negative stimuli and thus may ironically further impair sleep.

Future research should seek to clarify the degree to which attentional impairment in patients with FM is global and pervasive, rather than a reflection of a depressive information-processing bias in which attentional function is fully intact with respect to negatively toned information, especially pain, but selectively attenuated with respect to non-negative stimuli.

Motivated Attention and Overlap with Extant Theories

Theories of motivated attention offer a parsimonious theoretical explanation for the wide range of symptoms, including the cognitive difficulties, often reported by FM patients. Moreover, the motivated attention facet of the SAPD model offers a unifying framework for many of the most well-validated and influential models of FM. For instance, enhanced processing of negative information underlies the Central Sensitization (CS; to pain) model of FM (e.g., Staud 2005; Yunus 2002) and models proposing a central role of the stress response (e.g., Okifuji and Turk 2002) and anxiety sensitivity (Turk 2002). Conversely, attentional bias away from positive stimuli may also account for observations that FM patients differ from other pain patients because of deficits in the positive affect system (Davis et al. 2001; Zautra et al. 2005). Although there are differences in terms of level of analysis, each of these models posits that the pathology of FM is driven by attentional biases. These theories have much in common, however extant research has not disentangled pain reactivity from an overall negativity bias, nor is it clear whether FM patients are more reactive to negative information, less reactive to positive stimuli, or both.

Motivated attention as construed by the SAPD model is also consistent with stress-diatheses models of pain in FM (Turk 2002) and insomnia (Spielman et al. 1987). Although Turk and Spielman's models differ on the surface, both models posit that a stressor (an injury or life event, respectively) can trigger an underlying trait or sensitivity to dysfunction (pain disorder or insomnia) that perpetuates symptoms. Moreover, both models specify attentional bias as the driving force responsible for onset of a chronic process, anxiety sensitivity in the case of FM, and conditioned arousal in the case of insomnia. Attentional bias plays the key role in the attention-intention-effort pathway theory of insomnia (fear of sleeplessness creating increased arousal and perpetuating dysfunctional compensatory behaviors; Espie et al. 2006). Likewise, a key process for maintenance of FM symptoms and insomnia is that attention to threatening stimuli leads to cognitive and behavioral responses that perpetuate symptoms (e.g., catastrophization and fear of pain leading to pain avoidance and disability). It is no accident that the SAPD model overlaps these two important models, if (as we suspect) anxiety sensitivity and hyperarousal leading to insomnia are both tapping a similar psychobiological process, than it would seem likely that developing hyperarousal in one domain would also activate hyperarousal and vigilance in other domains.

Important Disclaimers

Although the SAPD model posits that sleep disturbance is critical to the onset and maintenance of FM, this is unlikely to be true for all patients. Although we believe that the SAPD model accurately identifies the causal trajectory of a sleep-subtype of FM, there are undoubtedly other causal trajectories. For instance, FM like symptoms have been reported by people who have suffered from a rare but serious muscle-wasting reaction to statin medications (Thompson et al. 2003). In addition, FM comorbid with arthritis and other pain disorders (Wolfe and Cathey 1983) may result from sleep disruption due to unmanaged pain. Interestingly, at least one study has shown that experimentally induced muscle and joint pain produce sleep EEG changes (i.e., decreased SWS and increased alpha sleep) similar to those observed in FM patients (Drewes et al. 1997).

In fact, the SAPD model would predict that sleep disruption would worsen symptoms of other medical condition by adding on a layer of generalized pain and fatigue and increasing motivated attention. Thus, it may be more profitable to view FM in terms of a "pie." Rather than attempting to identify factors common to all FM patients, we are likely to make more progress by attempting to identify common subgroups of patients (large pieces of the pie) with common causal trajectories.

We must also acknowledge that some people with FM may overestimate sleep problems. Sleep state misperception (the presence of sleep complaint unaccompanied by objective sleep dysfunction) may be at least as prevalent in patients with FM as it is in patients with insomnia (Edinger and Krystal 2003). Thus, collection of objective sleep data (i.e., poloysomnograph, actigraph) would be critical for evaluation of the SAPD model and identifying members of the sleep subtype.

Implications for Treatment

Models of FM as a pain disorder have either explicitly or implicitly informed the vast majority of interventions for FM patients. Common interventions for FM patients include analgesic medications, antidepressants, pain-management training, and exercise (Rossy et al. 1999; Sim and Adams 2002). Relatively few studies have targeted sleep symptoms in FM patients. However, if poor sleep quality is related to increased pain, fatigue, dysphoric mood, and problems with attention and memory, a treatment designed to improve sleep quality should improve these outcomes as well. Consistent with this prediction, FM patients with comorbid SDB were treated with Continuous Positive Airway Pressure (CPAP) and showed a 46% reduction in fatigue, a 39% reduction in sleep problems, and most importantly, a 38% reduction in reported pain (Gold et al. 2004). Treatments for insomnia have also been found to be beneficial for FM patients. Cognitive Behavioral Therapy for Insomnia (CBT-I) altered self-reported insomnia outcomes and both CBT-I and a simple sleep hygiene intervention resulted in improved mood, improved mental health, and reductions in pain (Edinger et al. 2005).

Motivated attention offers a second target of intervention. Interventions designed to increase control over attention, such as mindfulness meditation have proved useful in other pain populations (Kabat-Zinn et al. 1985, 1986) and the effects of these interventions may be to reduce motivated attention. Furthermore, newer therapies such as acceptance and commitment therapy may also have value by decreasing anxiety about uncomfortable somatic symptoms (McCracken et al. 2005).

Model Summary and Conclusions

FM is a prevalent disorder, especially among middle-aged women. Those who suffer from FM are faced with the difficulties of managing symptoms without a medical explanation for their problems and largely without effective medical intervention. Most patients with FM believe that a stressor triggered the onset of FM symptoms (Bennett et al. 2007). The SAPD model suggests that in the sleep-subtype, stressors also triggered onset of sleep disruption which had downstream effects on pain, fatigue, mood and cognitive functioning (i.e., attentional deficits, poor memory consolidation). However, few people with insomnia or other sleep problems go on to develop FM. It is likely that a second pain-vulnerability diathesis must be present to heighten the severity of these symptoms. Finally, the maintenance of FM can plausibly be explained via a pervasive attentional bias that exacerbates pain, fatigue, and further impairs attention to non-somatic stimuli. Thus, for the sleep-subtype, sleep disruption is integral to the etiology of FM, and also energizes a positive feedback loop that maintains or amplifies symptom severity over time.

Although pain is undoubtedly an important symptom of FM, focusing exclusively on pain has lead research away from examining other FM symptoms such as sleep disruption. From a theoretical perspective, it is advantageous to begin with sleep. There is a wealth of basic science and translational research on sleep, which could be used to further inform research on FM. For instance, the sex differences in insomnia and menopause-related increases in SDB may in part explain the sex differences in FM prevalence (Kripke et al. 2002; Owens and Matthews 1998). In addition, differentiation of sleep-subtype FM patients from non sleep-subtypes may help to sort out some of the inconsistent biological data. For instance, sleep-subtype FM patients may have show a more consistent pattern of HPA irregularities than non sleep-subtype FM patients. More importantly, the SAPD model can be used to make specific predictions. Most obviously, improving sleep would be expected to produce change in a wide range of FM symptoms. At a specific level, increasing NREM sleep should improve overnight memory consolidation.

Finally, from the patient's perspective, there are two important reasons for addressing the role of sleep in FM. First, safe and effective treatments exist for most sleep disorders. Second, understanding the role of sleep disruption in the etiology and maintenance of FM may provide a much-needed explanation for the symptoms of FM and thus reduce motivated attention to symptoms and subsequent symptom exacerbation. Thus, it is our position that identifying sleep-subtype FM patients, and treating sleep problems offers a highly productive avenue for reducing pain and increasing quality of life.

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