Pain & sleep

ASSISTANCE FELLOWSHIP OF SLEEP MEDICINE

MASTER OF SCIENCE IN MEDICAL EDUCATION

FELLOWSHIP OF CLINICAL INFORMATICS

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- Sleep and pain are critical processes of life with great biologic and evolutionary value. In the normal state, pain perception and sleep regulation operate via a sensitive and well- orchestrated physiologic balance, which primarily serves to protect sleep function.

EPIDEMIOLOGY OF PAIN AND COMORBID SLEEP DISORDERS

- Chronic pain and impaired sleep are two major, yet unmet, public health challenges that are associated with enormous economic and societal cost because of their sheer prevalence and significant impact on morbidity.
- Community- based studies estimate that greater than 40% of people who suffer from chronic insomnia do so in the context of physical pain,whereas moderate to severe sleep disturbances and comorbid depression occur in up to 80% of patients with chronic pain.

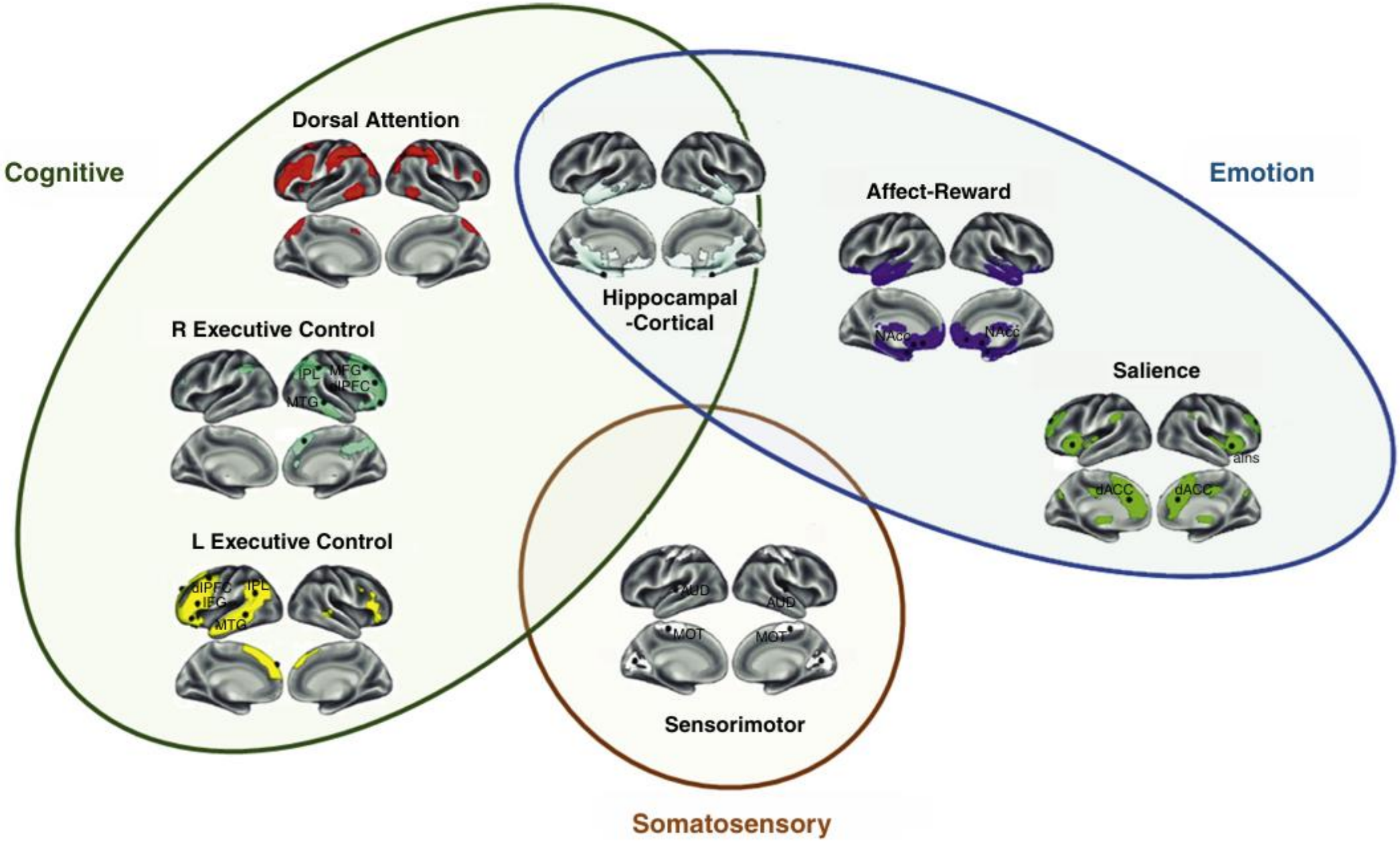
Insomnia as a Risk Factor for Chronic Pain

- disturbed sleep in pain- free subjects could significantly increase the risk (odds ratios [ORs] and relative risk ratios ranging from 1.3 to 3.8) for different chronic pain conditions, including musculoskeletal pain, chronic wide spread pain, headaches, postpartum bodily pain, and temporomandibular joint disorder.

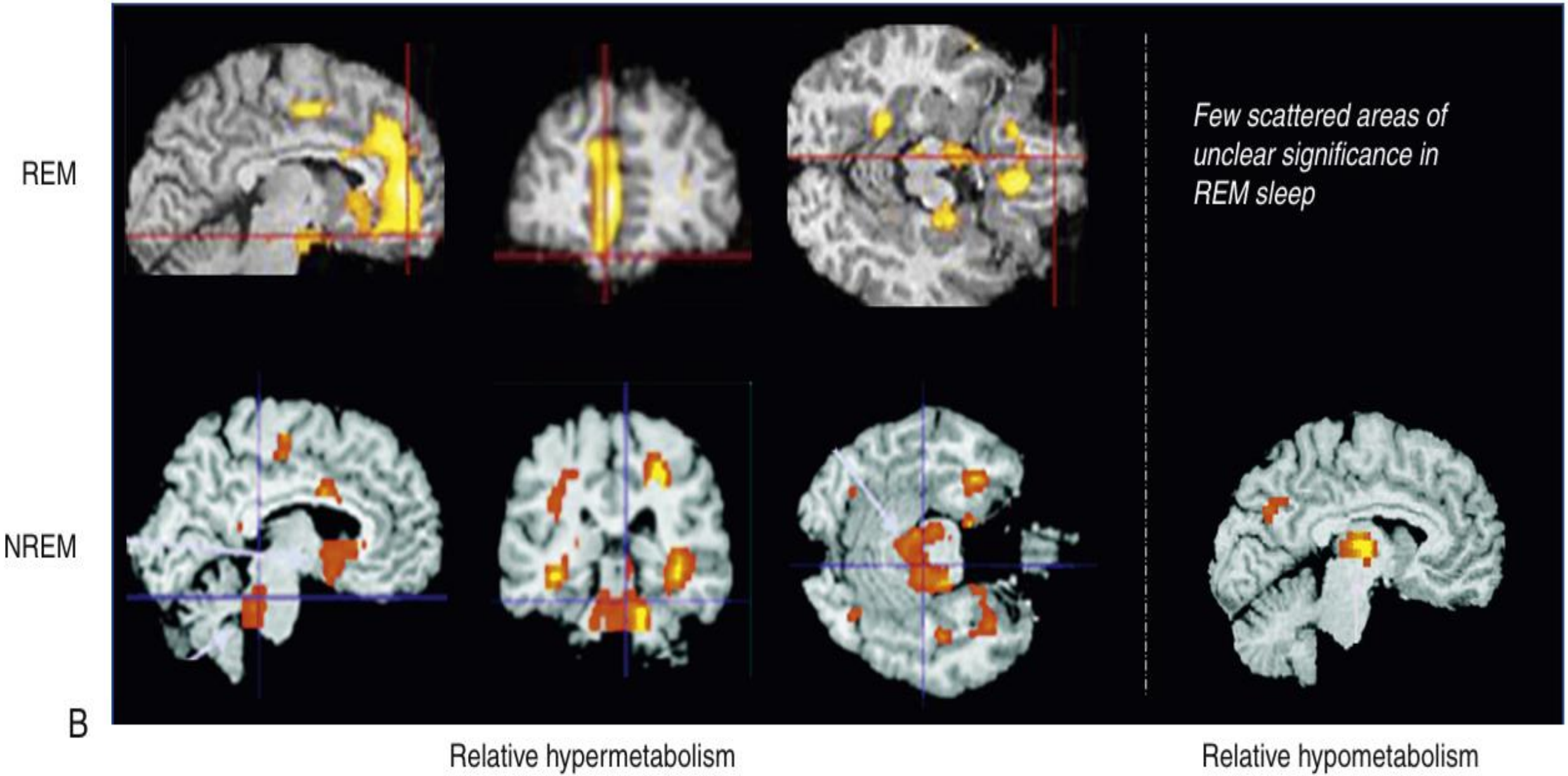
Pain as a Risk Factor for Insomnia

- various types of chronic pain complaints among older adults were associated with an increased risk of insomnia of up to four times for the next 3 years. Of interest, the combination of physical limitations and reduced social participation explained greater than 65% of the effect of pain on insomnia onset.

Mood Disorder as a Comorbid Link between Pain and Sleep

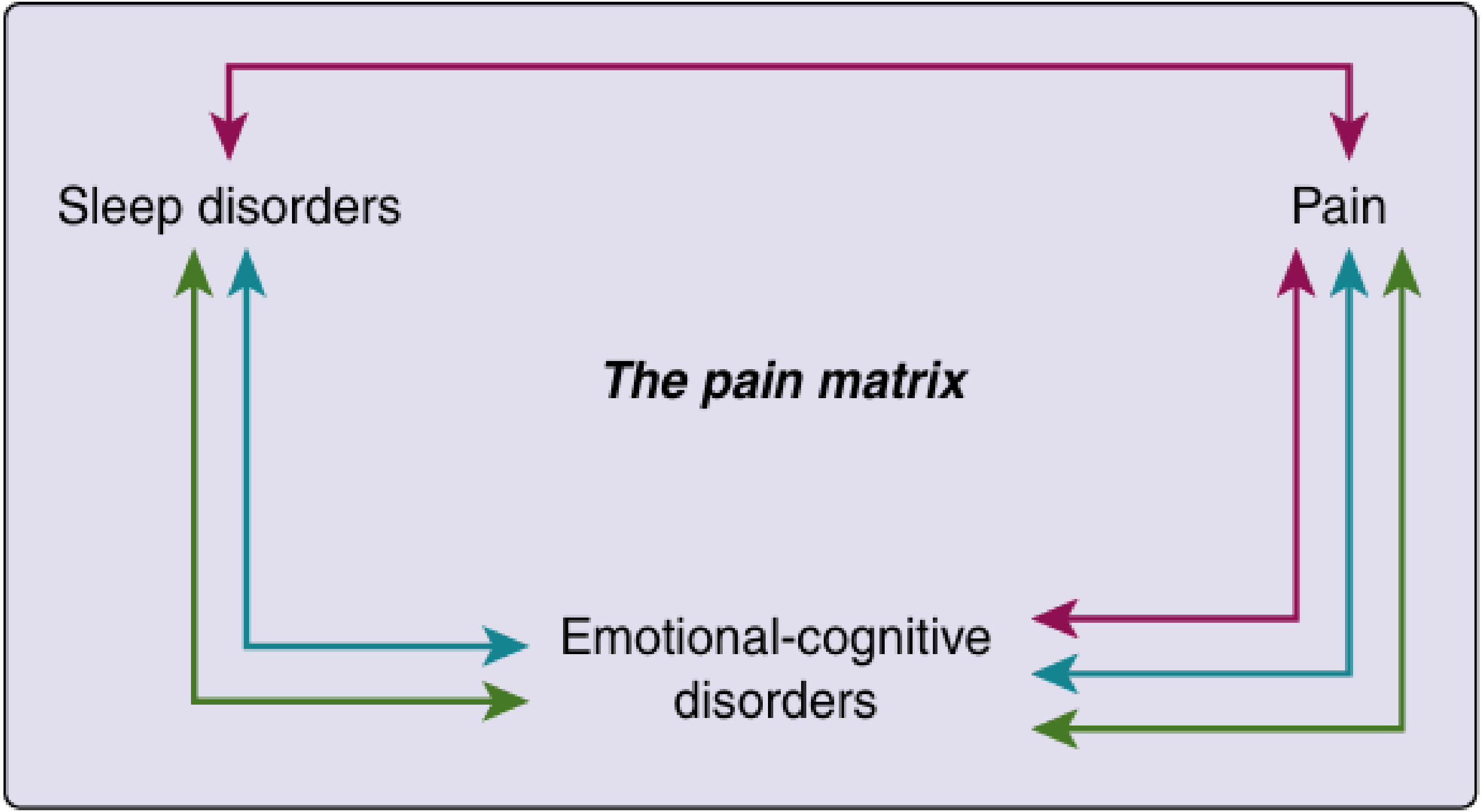

Cognitive
Emotion
Somatosensory
Dorsal Attention
Hippocampal
-Cortical
Affect-Reward
NAcc
NAcc
R Executive Control
IPL
MFG
dlPFC
MTG
Salience
ains
dACC
dACC
L Executive Control
dlPFC
IPL
IFG
MTG
ADD
ADD
MOT
MOT
Sensorimotor

- Select networks of the brain derived through independent component analysis contributing to the pain matrix: These networks are involved in processes combining somatosensory, cognitive, and emotional modalities, including pain information processing, and clustered according to their contribution in the three core components of the pain matrix (i.e., somesthesis, cognition, and emotion). The predominant forward flow of information from somesthesia to cognitive and emotion modular networks is further enriched by feedback flow within and between clusters, thus optimizing pain information consolidation.


REM
NREM
B
Few scattered areas of unclear significance in REM sleep
Relative hypermetabolism
Relative hypometabolism

Relative metabolic brain activity during sleep states compared to wakefulness

- Emotion networks are more active in rapid eye movement (REM) sleep, explaining the preferential emotional and procedural information consolidation during REM. Cognitive networks receive information from hippocampal structures during non–rapid eye movement (NREM) sleep, as represented by sharp- wave ripple hippocampal activity, translated into cortical spindle activity via thalamic relay; yet overall cortical activity remains relatively decreased in NREM sleep, in contrast to its relatively increased hippocampal activity. Finally, lower- level primary somatosensory and primary association cortical sensory networks remain relatively hypoactive across sleep stages, in line with the observed increased threshold required for sensory stimuli to induce a behavioral response during sleep.


Sleep disorders
Pain
The pain matrix
Emotional-cognitive disorders

- Mediating effects of the pain matrix networks between sleep, pain, and emotional- cognitive disorders: Modulation of somatosensory processes have a direct effect on the comorbidity of sleep and pain disorders, in both acute and chronic settings. In addition, indirect modulation of emotional and cognitive processes from either sleep or pain disorders further increase their comorbidity.

- studies indicate that both episodic and emotional memory consolidation are also achieved across longer circadian cycles through modulation of the respective brain networks and with some studies suggesting that emotional memory consolidation is more sensitive to circadian disruptions compared to episodic memory consolidation.

- dynamic information processing through feedback pathways explains the descending inhibitory control of pain processing, which is best achieved in deep sleep, allowing even peripheral pathways to modulate their responsiveness to pain stimuli over time and across sleep- wake states.

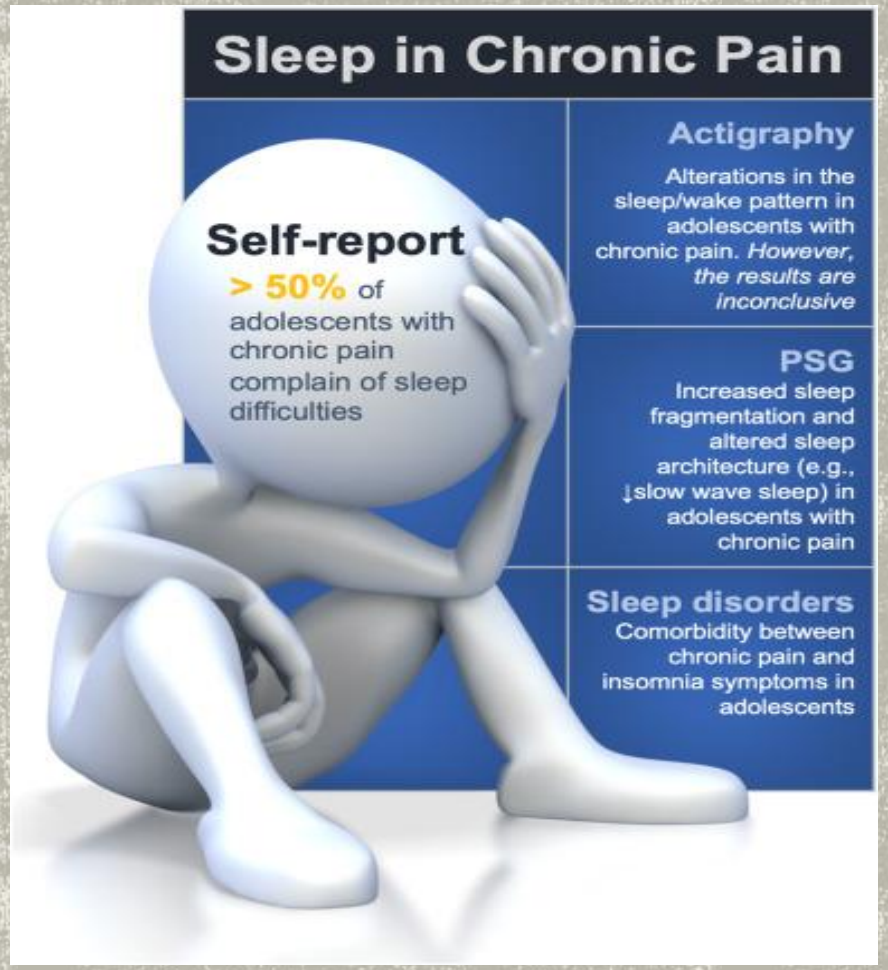
Sleep Disruption Leading to Conditioned Pain Modulation

- Studies in human volunteers have demonstrated that sleep disruption alters pain processing by activating major inflammatory pathways and promoting the expression of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin- 1β (IL- 1β), and interleukin- 6 (IL- 6), in the peripheral blood and/or by impairing central mechanisms of pain- inhibitory control (namely, conditioned pain modulation [CPM]),thus leading to hyperalgesia with musculoskeletal sensitization and spontaneous pain symptoms.

- This evidence seems to contradict findings from studies on neurodegenerative disorders and chronic hyperalgesia, where emotional and cognitive network hyperreactivity and thalamic hyperreactivity to stimuli is observed, yet highlight how poor sleep modifies brain function in addition to structural changes, when compared to neurodegeneration, as well as the long- term differential modulating effect of chronic conditions on the pain matrix networks, when compared to hyperalgesia syndromes.

CLINICAL IMPLICATIONS OF THE BIDIRECTIONAL RELATIONSHIP OF SLEEP AND PAIN

- The observed effects are attributed to impairment of central pain- inhibitory or amplification of descending pain-facilitatory pathways. Moreover, treatment with continuous positive airway pressure in subjects suffering from sleep- disordered breathing (SDB) can reverse the observed hyperalgesia, although it is not clear whether this effect was due to restoration of sleep continuity or resolution of nocturnal hypoxemia.



- a recent survey of patients referred to an academic sleep center showed that, although SDB comorbid with insomnia was related to more pain compared to either SDB or insomnia alone, no polysomnography (PSG) measures of SDB severity (e.g., number or arousals, or amount of hypoxia) mediated this effect

- The observed cognitive and emotional changes in patients suffering from pain or insomnia could also act as mediators or potential confounders on the relationship between sleep and pain. For example, the ability of attention to modulate pain perception is an important mechanism to cope with pain, and insomnia with short sleep duration has been shown to impair the control of executive attention function. Of interest, attentional bias toward pain and pain-related information reduced distraction from the painful stimuli, undermined sleep, and strengthened the association between pain severity and disability in patients with chronic pain.

- Presleep cognitive arousal in patients with chronic pain was found to be a more reliable predictor of subsequent sleep quality than was presleep pain. Combined, these intriguing findings point to the hyperarousal hypothesis for insomnia as a potential underlying mechanism linking insomnia to mood disorders and pain.

- certain patients either have a biologically driven cortical state of hyperarousal or fail to achieve adequate slow wave activity in the dorsal frontal lobes during sleep, whereas others become so after a maladaptive response to stimuli,thus conceptually linking chronic insomnia and its relation to pain via the 3P model (i.e., predisposing, precipitating, and perpetuating factors in the development of chronic syndromes)

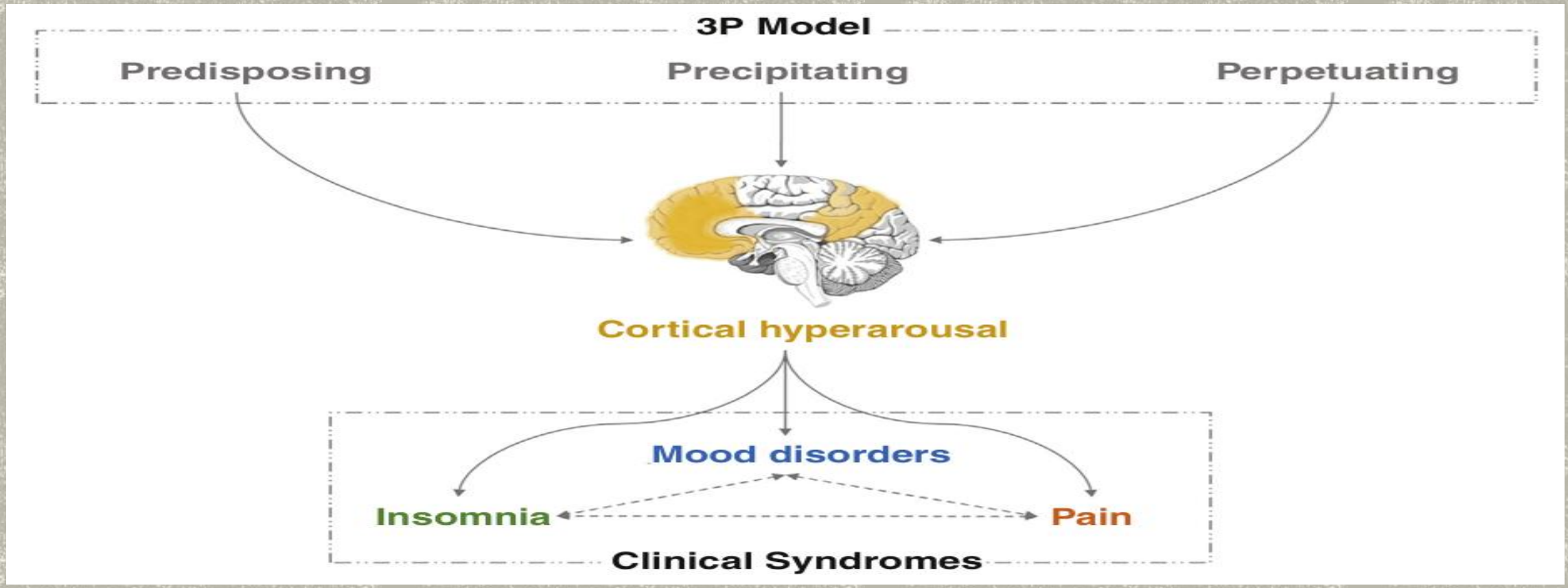


Figure 156.2 The 3P model (predisposing, precipitating, and perpetuating factors) in the development of cortical hyperarousal toward the chronicity of insomnia, pain, and mood disorders. According to the 3P model, predisposing factors, such as genes and brain development, provide a substrate for precipitating factors, such as bodily injury or social stressors, to introduce a hyperaroused cortical state, which can become chronic through perpetuating factors, such as maladaptive behaviors. This cortical hyperarousal can contribute directly to the chronicity of pain and sleep disorders, as well as indirectly through the mediating effects of comorbid mood disorders.

ASSESSMENT OF SLEEP IN THE CONTEXT OF CHRONIC PAIN

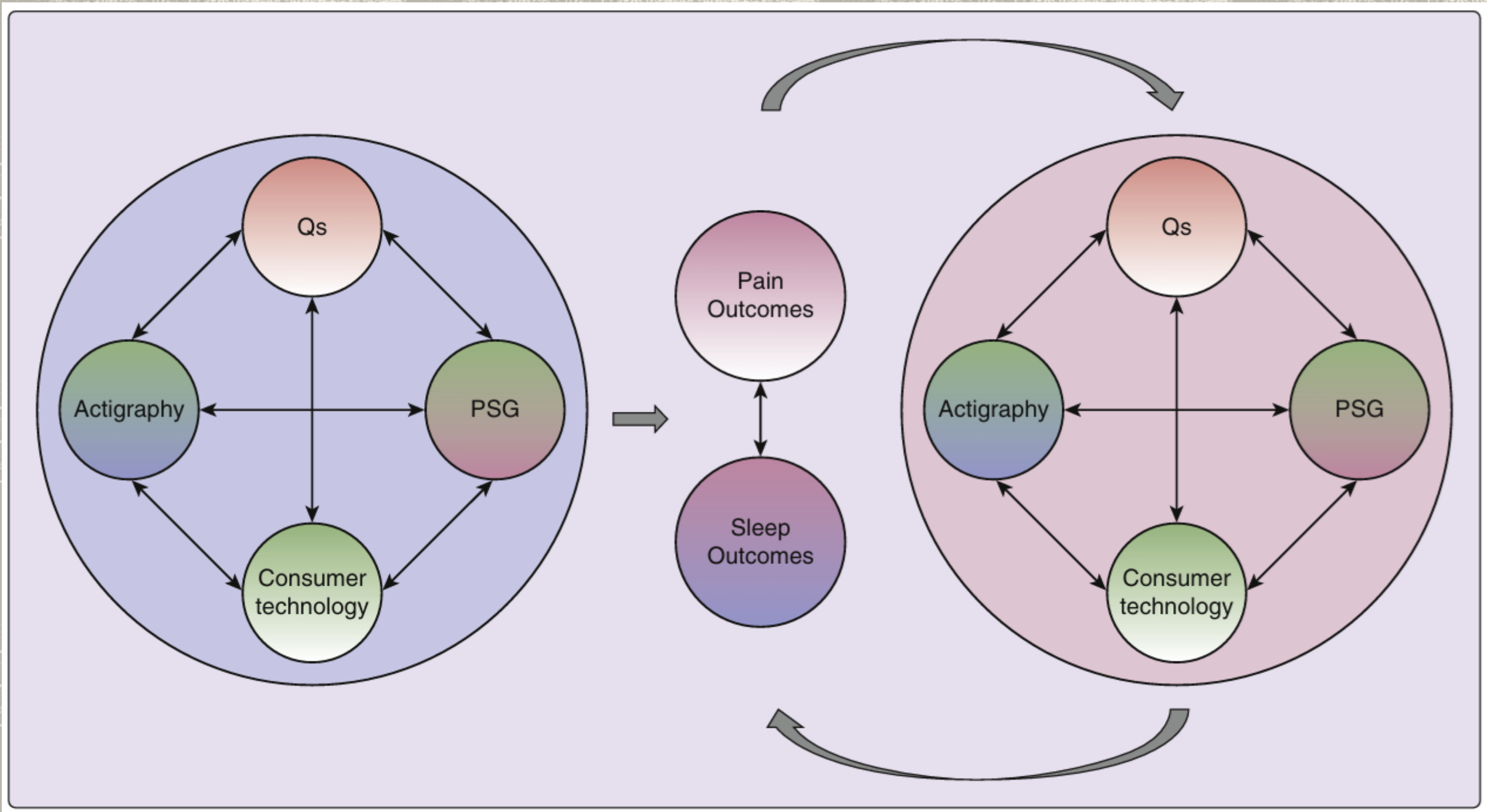
- Overnight attended PSG (i.e., the evaluation of quantitative and qualitative parameters of sleep with the use of electroencephalographic, respiratory, and electrocardiographic monitoring modalities) is considered a gold standard for the objective assessment of sleep.
- Actigraphy monitoring, another objective method for indirectly estimating sleep duration, although having less specificity than PSG , has been validated in large longitudinal cohorts of patients with chronic pain

- The significance of combining objective and subjective measures of sleep is highlighted in chronic insomnia, which is characterized by negative sleep discrepancy; that is, patients experience greater sleep disturbance than is measured objectively.

- In patients with chronic widespread pain who are treated with opioids, the discrepancy between actigraphy and self-reported assessments of sleep is both magnified and of high night- to- night variability with both negative and positive estimates.

- Pain intensity and treatment with opioids tend to increase the discrepancies between diary- and actigraphy-based assessments, with age being an important modifier of these effects. Patients with less severe pain show the greatest sleep disruption at higher doses of opioids, whereas in those with more intense pain, opioids may even prove beneficial by increasing the number of SWS.

- An outcomes- based research approach might be necessary to determine the type of sleep assessment that could add clinical value to the management of patients with chronic pain (e.g., objective vs. subjective tests, extended and more complex questionnaires vs. shorter and simpler ones, combination of objective and subjective methods)


Qs
Actigraphy
PSG
Consumer technology
Pain Outcomes
Sleep Outcomes
Qs
Actigraphy
PSG
Consumer technology

- Outcomes- based algorithm in the assessment of comorbid sleep and pain disorders. Outcomes-based algorithms can help in identifying better assessment protocols in the diagnosis and treatment response of comorbid sleep and pain disorders. Starting from a comprehensive assessment, objective and subjective measures can be selected and weighted according to sleep and pain outcomes and, after a few iterations of the process, define an optimal comprehensive protocol.

MANAGEMENT OF PATIENTS WITH CHRONIC PAIN AND COMORBID SLEEP DISORDERS

Pharmacologic Interventions Targeting Pain

Pharmacologic Interventions Targeting Pain

- This issue directly relates to the yet unanswered question about the clinical meaning of the various sleep phenotypes evaluated by different assessment methods.

Pharmacologic Interventions Targeting Insomnia

- Sodium oxybate
- eszopiclone

Condition	Study	Population	Blinding	Control	Follow-up	Intervention	Intervention Focus	Pain Metrics	Sleep Metrics	Outcome		Sleep-Pain Agreement
										Pain	Sleep	
Chronic widespread pain	Arnold et al., 2010[130]	CWP ($N = 507$)	Double	Placebo	12 wk	Duloxetine (SNRI)	Pain	BPI, SF-36 bodily pain	BPI and 11-point Likert scale (0–10)	Yes	Yes	Yes
	Moldofsky et al., 2010[134]	CWP ($N = 151$)	Double	Placebo	8 wk	Sodium oxybate (γ-hydroxybutyric acid)	Sleep	VAS, FIQ pain, SF-36 bodily pain	PSG, ESS, JSS, FOSQ	Yes	Yes	Yes
	Roth et al., 2012; Roth, 2012 #1634	CWP ($N = 206$)	Double	Placebo	4 wk	Pregabalin (anticonvulsant)	Pain and sleep	NRS (0–10)	PSG, self-reported sleep assessment	Yes	Yes	Yes
	Arnold et al., 2015[131]	CWP with comorbid depression ($N = 155$)	Double	Placebo (crossover)	6 wk	Pregabalin (anticonvulsant)	Pain	NRS (0–10, daily)	SSQ, subjective WASO, TST, LSO, and NAASO	Yes	Yes	Yes
Low back pain	Steiner et al., 2011[126]	CLBP ($N =$ 539)	Double	Placebo	84 days	Buprenorphine (partial agonist of the μ-opioid receptor)	Pain	NRS (0–10)	MOSS (0–100)	Yes	Yes	Yes
	Williams et al., 2014[123]	Acute low back pain ($N = 1596$)	Double	Placebo	3 mo	Paracetamol (mild analgesic)	Pain	Days until recovery from pain, NRS (0–10)	PSQI (item No. 6)	No	No	Yes
	Goforth et al., 2014[137]	CLBP ($N = 52$)	Double	Placebo	1 mo	Eszopiclone (nonbenzodiazepine hypnotic)	Sleep	VAS (0–100)	TST (sleep diary)	Yes	Yes	Yes
	Yarlas et al., 2016[127]	CLBP ($N =$ 660)	Double	Placebo	12 wk	Transdermal Buprenorphine	Pain	NRS (0–10)	MOSS, SPI	Yes	Yes	Yes
	Christoph et al.,	CLBP ($N =$ 360)	Double	Placebo and active	26 wk	Cebranopadol and tapentadol	Pain	NRS (0–10, daily)	CPSI (5 items)	Yes	Yes	Yes

	Raskin et al., 2016[172]	PDPN ($N = 147$)	Double	Placebo (crossover)	6 wk	Pregabalin on NSAID background	Pain	NRS (0–10), BPI	SI (0–10)	Yes	Yes	Yes
	Andresen et al., 2016[173]	Spinal cord injury neuropathic pain ($N = 58$)	Double	Placebo	12 wk	Palmitoylethanolamide (PEA, endocannabinoid potentiator)	Pain	NRS (0–10, daily)	ISI, sleep disturbance (NRS 0–10)	No	No	Yes
	Merante et al., 2017[146]	PDPN ($N = 452$)	Double	Active: pregabalin	5 wk	Mirogabalin (anticonvulsant)	Pain and sleep	VAS (0–10), BPI, SF-MPQ	DSIS (0–10)	Yes	Yes	Yes
	Liu et al., 2017[174]	Postherpetic neuralgia ($N = 220$)	Double	Placebo	8 wk	Pregabalin (anticonvulsant)	Pain and sleep	NRS (0–10), SF-MPQ	DSIS (0–10)	Yes	Yes	Yes
	Kato et al, 2019[175]	Postherpetic neuralgia ($N = 765$)	Double	Placebo	14 wk	Mirogabalin (anticonvulsant)	Pain and sleep	ADPS, VAS (0–10, SF-MPQ)	DSIS (0–10)	Yes	Yes	Yes
	De Greef et al., 2019[128]	Nav 1.7 mutations-related small fiber neuropathy ($N = 23$)	Double	Placebo (crossover)	13 wk	Lacosamide (sodium channel blocker)	Pain	NRS (0–10, daily)	DSIS (0–10)	Yes	Yes	Yes
Other types of chronic pain	Schwertner et al., 2013[139]	Endometriosis ($N = 36$)	Double	Placebo	8 wk	Melatonin	Pain and sleep	VAS (0–10, daily)	Sleep quality (VAS, 0–10, daily)	Yes	Yes	Yes
	Vidor et al., 2013[138]	Myofacial TMD pain ($N = 32$)	Double	Placebo	4 wk	Melatonin	Pain and sleep	VAS (0–10, daily)	Sleep quality (VAS, 0–10, daily)	Yes	Yes	Yes
	Strand et al., 2016[125]	Rheumatoid arthritis ($N = 556$)	Double	Placebo	12 mo	Tofacitinib (Janus kinase [JAK] inhibitor) or adalimumab (tumor necrosis factor inhibitor)	Pain	Patient assessment of arthritis pain (VAS, 0–10)	MOSS	Yes	Yes	Yes
	Maarrawi et al., 2018[129]	Chronic neck pain	Double	Placebo	2 mo	Amitriptyline (tricyclic antidepressant)	Pain	VAS (0–10)	BIS	Yes	Yes	Yes

Condition	Study	Population	Blinding	Control	Follow-up	Intervention	Intervention Focus	Pain Metrics	Sleep Metrics	Improved Outcome		Sleep-Pain Agreement
										Pain	Sleep	
Arthritis	Vitiello et al., 2013[158]	Elderly (>60 yr) patients with osteoarthritis ($N = 367$)	Double	Education-only	9 mo	CBT for pain and insomnia	Pain and sleep	Chronic pain scale (6 items; 0–10)	ISI, SE (actigraphy)	No	Yes	No
	Smith et al., 2015[154]	Knee osteoarthritis ($N = 73$)	Double	Active: behavioral desensitization	6 mo	CBT for insomnia	Sleep	VAS (0–100 mm)	WASO, TST, SOL, SE (Diary, PSG, actigraphy), ISI	Yes	Yes	Yes
	Ward et al., 2017[161]	Rheumatoid arthritis ($N = 25$)	Single	Active: "usual care"	13 wk	Yoga Intervention	Pain and sleep	VAS (0–100 mm)	ISI	Yes	Yes	Yes
Chronic widespread pain	Kashikar-Zuck et al., 2012[176]	Juvenile CWS, ($N = 112$)	Single	CWP education	6 mo	CBT	Pain	VAS (0–10 cm)	VAS (0–10 cm)	No	No	Yes
	Van Gordon et al., 2017[163]	CWS ($N = 85$)	Double	Active: cognitive behavior theory	6 mo	Meditation awareness training (MAT)	Pain and sleep	SF-MPQ	PSQI	Yes	Yes	Yes
	Wang et al., 2018[162]	CWS ($N = 85$)	Single	Active: aerobic exercise	52 wk	Tai chi (Yang style)	Pain and sleep	FIQR (0–100)	PSQI	Yes	No	No
	McCrae et al., 2019[153]	CWS comorbid with insomnia ($N = 74$)	Single	"Usual care"	6 mo	CBT for insomnia	Sleep	VAS (0–10 cm)	Sleep diary (WASO, TST, SOL, SE)	No	Yes	No
						CBT for pain	Pain			No	Yes	No
Other types of chronic pain	Slangen et al., 2014[177]	PDPN ($N = 33$)	No	No intervention: "best medical treatment"	6 mo	Spinal cord stimulation plus "best medical treatment"	Pain	Pain Severity Index	MOSS	Yes	No	No
	Palermo et al., 2016[178]	Adolescents with chronic pain and their parents ($N = 269$)	Single	Active: Internet-delivered education	6 mo	Internet-delivered CBT	Pain and sleep	NRS (0–10)	ASWS	No	Yes	No
	Smitherman et al., 2016[155]	Chronic migraine and comorbid insomnia ($N = 31$)	Single	Sham: "lifestyle modification"	6 wk	CBT for chronic migraine	Sleep	Headache diary	PSQI	Yes	Yes	Yes

Nonpharmacologic Interventions for Pain and Comorbid Insomnia

- Cognitive behavioral therapy (CBT) has been a successful psychological intervention for primary insomnia. The recognition of pain as an emotionally charged experience has prompted the development and application of such psychological interventions in the management of patients with chronic pain. However, two large meta- analyses of RCTs, comparing cognitive behavioral therapy for pain (CBT-P) with active or passive control treatments, have shown that CBT- P had only a small, short- lived effect on pain outcomes.

- As shown in Tables 156.2 and 156.3, for a variety of chronic pain conditions, an agreement between treatment- induced changes in pain and sleep outcomes is common, independent of how effective is the therapy under evaluation. This observation confirms previous findings from a systematic review of Cochrane meta-analyses, showing that changes in sleep and pain outcomes of various interventions tend to be in the same direction. Although these findings indicate a strong link between sleep and pain, and even general well- being, it is evident that, when used alone and independent of targeted function (i.e., sleep or pain), no current pharmacologic or CBT modality is both sufficiently safe and effective to improve pain in the long term.