

Did ‘The Princess on the Pea’ suffer from fibromyalgia syndrome?

The influence on sleep and the effects of acupuncture

Thomas Lundeberg, Iréne Lund

Thomas Lundeberg
senior consultant
Rehabilitation Medicine
University Clinic
Danderyds Hospital AB
Stockholm, Sweden

Iréne Lund
post-doctoral researcher
registered physiotherapist
Department of
Physiology and
Pharmacology
Karolinska Institutet
Stockholm, Sweden

Correspondence:
Thomas Lundeberg

thomas.lundeberg@ds.se

Abstract

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterised by central sensitisation resulting in hypersensitivity of the skin and deeper tissues as well as fatigue. Possibly the princess in Hans Christian Andersen’s ‘The Princess and the Pea’ suffered from FMS since chronic sleep disturbances are typical in FMS. These sleep disturbances have been attributed to a dysfunction in the systems regulating sleep and wakefulness resulting in loss of deep sleep. In addition, many patients with FMS experience cognitive dysfunction, characterised by impaired concentration and short term memory consolidation, a complaint also commonly reported in other sleep disorders.

In recent reviews evaluating the efficacy of acupuncture in FMS it has been concluded that acupuncture has no specific effect. A prerequisite for this conclusion is that all the major symptoms in the syndrome have been assessed. However, previous studies have generally focused on the pain alleviating effect of acupuncture in FMS. We have observed that not only pain but also sleep and cognitive dysfunction may be ameliorated in response to acupuncture, suggesting that these variables should be taken into account when evaluating the effects of acupuncture in FMS. Furthermore, the results demonstrated great individual variability apart from the systematic effects related to the group, indicating that individually performed treatment strategies are required. Our suggestion is supported by experimental and clinical studies showing that acupuncture may affect insomnia and alertness, and that there may be neurophysiologic bases for these specific effects.

Keywords

Acupuncture, fibromyalgia, sleep, review.

Introduction

‘The Princess and the Pea’ or ‘How to tell a True Princess’ is a Danish fairy tale by Hans Christian Andersen, first published in 1835. In the plot, a handsome prince in a rich kingdom searched for a princess, to take her place beside him. So the prince travelled around the world and met with all the princesses. Alas, none of the princesses he met suited him. He was sad and lonely once again having returned from yet another one of these trips. The very next evening, during a terrifying storm, there was a knock at the palace gate. The old king asked the guards to open it. Outside in the roaring storm was a girl claiming to be a princess. Although no one believed her, she was invited in to stay for the night. The queen then planned to check the young girl’s claim and without

saying a word she went to the bedroom, uncovered the bedclothes, and put just one small yellow pea in the bottom of the bed. Then she took twenty mattresses and piled them on the pea and above that twenty eiderdown feather beds. Up on top of all these the princess was to spend the night. All through the night, the young girl tossed and turned, in pain every time she lay on her side. Her shoulders and hips were so sore and she could not think why, as it was such a comfortable bed. The next morning when the girl woke up, the queen asked how she slept. ‘Oh, very badly!’ she said. ‘I barely closed my eyes all night. Heaven only knows what was in the bed, but I was lying on something hard, and now I am black and blue all over my body. It’s awful! I am sorry to complain’ The prince smiled to himself for then he knew he had found a real

princess, as nobody but a princess could be so delicate that she could have felt one pea all the way through all mattresses and feather beds. The Prince decided to marry this princess in great haste.

Possibly this fairy tale is one of the best descriptions of the characteristics of a woman with fibromyalgia syndrome (FMS). FMS is a chronic syndrome characterised by central and peripheral sensitisation resulting in hypersensitivity in the skin and deeper tissues as well as fatigue and sleep disturbances.¹⁻³ In addition, many patients with FMS experience cognitive dysfunction, including impaired concentration and short term memory consolidation.^{4,5} It has been suggested that all these symptoms are triggered by or associated with sleep disturbances.^{6,7}

The basic function of sleep is still relatively unknown because of its complexity.⁸⁻¹⁰ It has been suggested that sleep is a dynamic time of healing and growth and that deprivation may result in a number of disorders.^{11,12} Sleep deprivation also results in increased sensitivity to noxious stimulation in animals and humans.¹³⁻¹⁸ As reported by the princess in the tale, pain may interrupt sleep and it has been shown that that poor sleep influences pain perception,¹⁹⁻²¹ but also that sustained nociception may produce a marked sleep disturbance and alterations in prolactin and growth hormones.²²⁻²⁵ Interestingly, many of the brainstem structures which control sleep are also involved in the modulation of pain processing.²⁶ Furthermore, sleep seems to have a key function in memory processing and consolidation.²⁷ Early nocturnal sleep enhances hippocampus dependent declarative memory, and dreams enhance amygdala dependent emotional memory.²⁸ During our dream stages there is also consolidation of spatial and procedural memory.²⁸ In total, pain, sleep and memory processing share many regulatory neurophysiological systems.

We have observed that the responses to acupuncture treatment in patients with FMS are amelioration of pain, sleep and cognitive dysfunction, though the results demonstrated a great individual variability, ie the individual's rated change in response to acupuncture was varied.²⁹ These observations are supported by experimental and clinical studies showing that acupuncture may affect insomnia and alertness, and that there may be a neurophysiological basis for specific effects. Unfortunately, most reviews on the efficacy of acupuncture in fibromyalgia have

focused on pain alleviation as the primary outcome variable, thereby neglecting the effect of acupuncture treatment on sleep and cognition.

Sleep

Sleep is the state of natural rest involving complex physiological and behavioural processes, usually accompanied by a reduction in voluntary body movement, temporary blindness, decreased reaction to external stimuli, loss of consciousness, an increased rate of anabolism, and a decreased rate of catabolism.³⁰⁻³² Sleep may be divided into two main types based on the results of assessment of the encephalogram (EEG): sleep with rapid eye movement (REM) and without REM, non-REM (NREM).^{33,34}

NREM sleep accounts for 75–80% of total sleep time in which the body is active, the brain inactive with relatively little dreaming. It consists of four stages:

1. Stage N1, somnolence, or 'drowsy sleep', appears at sleep onset with near disappearance of the alpha waves seen in awake states, and appearance for the first time of theta waves (frequency 4-7 Hz).
2. Stage N2, 45–55% of total sleep time, the conscious awareness of the external environment disappears and muscle tone lowers. It is characterised by, 'sleep spindles' (12–16 Hz) and 'K-complexes' of the EEG.
3. Stage N3, 3–8% of total sleep time when bedwetting, sleepwalking, and sleep talking can occur. Slow wave sleep (SWS) where delta waves or delta rhythms (0.5–4 Hz) appear.
4. Stage N4, is a deeper version of N3, in which the deep sleep characteristic, such as delta waves, are more pronounced. During Stages N3 and N4 growth hormone levels increase, and immune function is restored.

REM sleep occupies between 20% and 25% of total sleep time where the brain is active and the body inactive, and this is when most dreaming occurs. It is associated with muscle atonia, intermittently interrupted by muscle twitching, and saccades of quick conjugate eye movements (REMs). The EEG has low amplitude waves and mixed high frequency, similar in appearance to the awake EEG. REM sleep is linked with suspended thermoregulation and

autonomic dysregulation such as irregular respiration and irregular heart beats.^{35,36}

Both REM sleep and NREM sleep stages N3 and N4 are homeostatically driven; that is, if deprived of one of these, it rebounds once the person is allowed to sleep and the individual will sleep with an increased duration and intensity to compensate for lost sleep. This suggests that both are essential in the sleep process and its many functions. REM sleep may also be driven by a circadian oscillator, as studies have shown that REM is temporally coupled with the circadian rhythm of temperature.³⁷⁻³⁹

Clinical studies have demonstrated that acupuncture may influence the ability to sleep and to ameliorate insomnia.⁴⁰ In an experimental study by Yi and collaborators,⁴¹ it was reported that electroacupuncture (EA) stimulation of *Anmian* (extra points) resulted in increased REMs and SWS. Pharmacological blockade of muscarinic cholinergic receptors by systemic administration of scopolamine dose dependently attenuated EA induced changes in REMs and SWS and bilateral lesions of the nucleus tractus solitarius (NTS) blocked the EA induced sleep enhancement. These results suggest that the NTS may be involved in the regulation of EA induced sleep alterations. It has also been reported that acupuncture to sacral segments influences the EEG,⁴² and has a suppressive effect on the state of vigilance.⁴³⁻⁴⁵

Regulation of sleep and wakefulness

The cycle of sleep and wakefulness is regulated by activity in brain stem circuits, the thalamus, by external stimuli, and by various hormones produced in the hypothalamus. More specifically, essential brain regions for sleep include: the suprachiasmatic nucleus, the lateral hypothalamus, ventrolateral preoptic nucleus, and the pineal gland.

- The suprachiasmatic nucleus (SCN) participates in homeostasis and circadian regulation. The homeostatic mechanism sets the sleep quota,⁴⁶⁻⁴⁸ and the circadian mechanism sets the time frame for sleep during each day.⁴⁹ The SCN also promotes arousal during the day. Loss of input from the SCN causes a loss of sleep consolidation.^{50,51}
- The lateral hypothalamus is the source of arousal promoting peptides hypocretins I and II. Lateral hypothalamic neurons start firing before the transition from sleep to wakefulness.^{52,53}

- The ventrolateral preoptic nucleus is a sleep generating centre. Two major nuclei have been identified: one located in the ventrolateral preoptic nucleus (VLPO) associated with non-REM sleep and the other located dorsal and medial to the VLPO (the extended VLPO) that is closely linked to REM sleep.^{54,55} Ventrolateral preoptic nucleus neurons are activated by sleep inducing factors such as adenosine and prostaglandin D2. The nuclei are also temperature (warm) sensitive. These neurons in the VLPO contain inhibitory transmitters like gamma-amino butyric acid (GABA) and galanin, and project to arousal neurons in the hypothalamus and brain stem. The GABA release into the arousal areas increases during REM sleep and the VLPO regulates the amount of delta wave activity. Because the activation of the VLPO is required for normal regulation of sleep, it is an essential element of the sleep wake central circuitry.
- The pineal gland, located on the posterior aspect of the third ventricle, secretes melatonin into the surrounding cerebral sinuses in response to photic information received primarily by the eyes. Upon exposure to light, retinal ganglion cells release melatonin into the SCN.⁵⁶ It has been suggested that the concept of a biological night for humans involves melatonin, cortisol, body temperature, and sleep propensity fluctuations.⁵⁷

The brain stem also plays a key role in sleep regulation. Regions of neurons in the rostral reticular formation (RAS) send projections to the forebrain through two main pathways critical for regulation of sleep wake cycles.^{58,59}

1. One pathway ascends dorsally through the lateral hypothalamus to the basal forebrain and projects to multiple thalamic nuclei, which in turn have widespread projections to cortical areas. Neurons in the rostral pons and caudal midbrain are the primary source of the ascending projections and fire rapidly during wakefulness, but slow down during slow wave sleep and resume rapid firing again during REM (active) sleep. Acetylcholine release in the thalamus increases during wakefulness and REM sleep, and is primarily excitatory.
2. Another pathway originates in the noradrenergic nucleus, the locus coeruleus, and in the

serotonergic dorsal and median raphe nuclei. It ascends ventrally through the lateral hypothalamus and terminates on magnocellular neurons in the substantia innominata, medial septum, and the diagonal band. These regions contain cortically projecting neurons whose cells fire actively during wakefulness and become inactive during REM sleep.

It has recently been demonstrated that different modes of acupressure may induce alertness or relaxation, suggesting that acupuncture may influence the regulation of sleep and wakefulness.^{60,61} Interestingly, participants' beliefs as to which treatment they had received did not significantly alter the observed treatment effect implying that there may be a physiological substrate behind the effects reported.

We have reported that acupuncture and also massage-like stimulation induce the release of oxytocin,⁶²⁻⁶⁴ and that oxytocin may have an anti-nociceptive effect.⁶⁵⁻⁶⁸ These results are supported by Yang and collaborators,⁶⁹ who reported that EA stimulation of *Zusanli* (ST36) elevated oxytocin concentration in the hypothalamic suprachiasmatic nucleus, hypothalamic ventromedial nucleus, thalamic ventral nucleus, and periaqueductal gray – areas that contribute to pain modulation and also to the regular cycling between sleep and wakefulness. A role of oxytocin in sleep and wakefulness is furthermore supported by its influence on the sleep modulating hormone orexin.⁷⁰

Stimulation by acupuncture has been shown to influence the activity in the suprachiasmatic nucleus, the lateral hypothalamus, the ventrolateral preoptic nucleus, the pineal gland, the rostral reticular formation, the dorsal thalamic nuclei, the substantia innominata and the medial septum, supporting that it may influence the anatomical substrate regulating sleep and wakefulness.⁷¹⁻⁸¹

Sleep and pain

In a review by one of the pioneers in the field, Harvey Molodofsky, in 2001,⁸² it is concluded that noxious stimuli and painful disorders hinder sleep, and that disturbances in sleep also add to the occurrence of pain. Noxious stimuli of muscles during SWS (slow wave sleep) result in decreases in delta and sigma but an increase in alpha and beta EEG frequencies during sleep.⁸³ Noise that results in the disruption of

SWS induce unrefreshing sleep, diffuse musculoskeletal pain, tenderness, and fatigue in normal healthy subjects and in patients with musculoskeletal pain.⁸⁴⁻⁸⁸ These symptoms are accompanied by alpha EEG sleep patterns. The alpha EEG patterns comprise phasic and tonic alpha EEG sleep as well as periodic K alpha EEG sleep or frequent periodic cyclical alternating pattern.^{89,90} Also, disturbances in sleep and psychological distress negatively influence the likelihood of return to work in patients with low back pain.^{91,92}

Chronic paroxysmal hemicrania and possibly cluster headaches are connected to dysfunctional REM sleep.⁹³ On the other hand, morning headache is not explicit in any primary sleep disorder but is linked with snoring and sleep apnea.⁹⁴⁻⁹⁶ Yet, the treatment of the sleep disorder alleviates both morning headache and migraine.⁹⁷ Furthermore, alpha EEG sleep, as well as sleep related breathing disorders and periodic limb movement disorders, happen in some patients with FMS, rheumatoid arthritis and osteoarthritis.⁸⁷ Also, patients with irritable bowel disorder commonly complain of disturbed sleep and studies have shown that they have increased REM sleep.⁹⁸⁻¹⁰³ However, in somatoform disorder, depression and sleep with absence of alpha on EEG are common features.¹⁰⁴

Many of the brainstem structures which control the function of sleep³³ are also involved in the modulation of pain processing.⁸² It has been reported that changes in neuronal discharge rates in the noradrenergic locus coeruleus or the serotonergic raphe nuclei are associated with changes in the sleep stage as well as descending pain modulation.^{33,105} Also, acupuncture stimulation has been shown to modulate activity in locus coeruleus and the raphe nuclei.¹⁰⁶⁻¹⁰⁸

In summary, there is a reciprocal relationship between sleep quality and pain.^{83-85,109} The recognition of sleep disturbances should influence the management of painful disorders. Possibly, acupuncture stimulation may contribute to ameliorate the condition.

Sleep disturbance in FMS

In 1975, Moldofsky and collaborators described an alpha EEG, 7.5–11Hz, NREM sleep anomaly in patients with FMS.¹¹⁰ They proposed that the alpha EEG sleep was related to unrefreshing sleep, diffuse

		Rated sleep disturbance <i>before</i> acupuncture, 0-10											
		0	1	2	3	4	5	6	7	8	9	10	Total freq
Rated sleep disturbance <i>after</i> acupuncture, 0-10	10												0
	9								1		1		2
	8												0
	7								2	1	1		4
	6						2	1	1	2	2		8
	5						2	1	2				5
	4					5	3	3	4	1			16
	3				1	3	4	3	3	3			17
	2		1	4	3	4	5		2	2			21
	1	1	4	3	3	3	3		1				18
	0	4	2		2	2	1		1				12
Total freq		5	7	7	9	17	20	8	17	9	4	0	103

Figure 1 Paired data are shown for frequency of rated change in sleep disturbance in patients with FMS (n=103), in response to acupuncture treatment period using an 11 category numeric rating scale (0=no disturbance, 10=worst possible sleep disturbance). The frequency of rating for each category of the scale is shown in this figure. The grey shaded diagonal from the lower left to the top right in the figure indicates unchanged level of rated sleep disturbance.

myalgia, numerous localised areas of tenderness in specific anatomic areas and mood symptoms. This suggestion was supported by the reports from healthy controls being exposed to noise disruption of stage 4 NREM (delta, SWS) or deep sleep.^{111;112} Later a number of investigators confirmed the alpha EEG sleep disorder in patients with fibromyalgia.¹¹³⁻¹²¹ Furthermore, the sleep disturbances are intimately related to the somatic symptoms in fibromyalgia.^{112;123} So, the poorer the sleep, the greater the number of tender points found in patients with FMS. However, the number of tender points and painful regions, and the frequency of poor sleep and fatigue, do not appear to be related to psychological status.¹²⁴

The possibility of a familial or genetic influence in the pathogenesis of the disorder is implicated by finding of the alpha EEG sleep pattern in the children and their mothers.¹²⁵ Although alpha EEG sleep may

be found in non-complaining people the sleep pattern may be a sensitive indicator for the subjective complaints of unrefreshing sleep and daytime symptoms.¹²⁶

Acupuncture, sleep disturbance and FMS

In recent reviews regarding the efficacy of acupuncture in FMS, it has been concluded that acupuncture has no specific effect.¹²⁷⁻¹²⁹ However, most of the reviews on the efficacy of acupuncture in fibromyalgia have focused on pain alleviation. We have observed that both sleep disturbances may be ameliorated suggesting that this variable also should be taken into account when evaluating the effects of acupuncture in FMS.

In a complementary medicine unit, 103 patients diagnosed as suffering from FMS and with sleep disturbances were treated with acupuncture. The

patients rated the sleep disturbance using an 11 category numeric rating scale (0-10) with the zero level indicating no sleep disturbances and 10 worst possible sleep disturbance. The data of the ratings were collected in a standardised way for the purpose of a clinical qualitative evaluation of the treatment. When evaluating the results it was found that the median level of the patients' rated sleep disturbance was 5 (range, 0 to 9) before acupuncture and 2 (range, 0 to 9) after acupuncture treatment. Five of the patients (5%) rated increased sleep disturbance after a treatment period of acupuncture, 24 (23%) rated unchanged and 74 (72%) rated decreased sleep disturbance after the acupuncture treatment period ($P < 0.001$), Figure 1. The results were analysed for information of effects in common for the group, named relative position (RP) and ranging from -1 to 1. We also analysed the individual variation, named relative rank variance (RV) ranging from 0 to 1, ie the individual contribution to the results not explained by the effect of the group. The results demonstrated significant effects on the group level, RP -0.46 (95% CI -0.56 to -0.37), but also for the individual, RV 0.16 (95% CI 0.09 to 0.24). These results show that in this group there is an effect on rated sleep disturbances after acupuncture compared to before. Before drawing conclusions on causality a study using a control group or a waiting list control is needed.

Our clinical experience shows that the sleep disturbances among patients with FMS may be improved by acupuncture. However, it is important to emphasise that patients diagnosed as suffering from FMS are probably not a homogenous group, which could influence the variability in the results. This suggestion is supported by the great individual variation in response in the 103 patients, eg the change in number of rated categories was 7 (from 9 to 2) for some individuals but just 1 category (from 7 to 6) in others.

A close interaction between sleep, pain and the effects of acupuncture is supported by a previous study showing that patients with FMS and severe sleep disturbance perceived acupuncture treatment to be less effective compared with patients who had FMS and light sleep disturbance.¹³⁰ Possibly, the function of the hypothalamo-pituitary-adrenal (HPA) axis plays a key role in FMS related to these effects.¹³¹ Studies evaluating patients with FMS have shown

disturbances in the HPA axis, including evidence of elevated cortisol levels lacking diurnal fluctuation,^{132;133} and impaired cortisol secretion in response to stress and corticotropin releasing hormone stimulation testing.^{132;134;135} Interestingly, acupuncture has been shown to modulate the activity in the HPA axis.¹³⁶⁻¹⁴²

Acupuncture and insomnia

A role of acupuncture in insomnia is also supported by a recent review by Cheuk.¹⁴³ The studies included compared acupuncture with placebo or sham or no treatment, or acupuncture plus a treatment compared with the same (excluding acupuncture) treatment of insomnia.¹⁴⁴⁻¹⁵⁰ These seven studies included 590 participants with insomnia. Meta-analysis was limited because of considerable heterogeneity between comparison groups and between outcome measures. The analysis showed however, that acupuncture and acupressure may help to improve sleep quality scores when compared to placebo or no treatment. However, the efficacy of acupuncture of many sleep variables was inconsistent between studies. The authors concluded that larger high quality clinical trials employing appropriate randomisation concealment and blinding combined with longer follow up are needed to further evaluate the efficacy and safety of acupuncture for the treatment of insomnia.

Sleep and memory processing

New studies indicate that sleep has a key function in memory processing and consolidation.¹⁵¹⁻¹⁵⁴ Memory consolidation reflects processes that convert labile memory representations into more permanent ones available for continued reactivation and recall over extended periods. Consolidation is the process by which recently acquired memories, stored in the hippocampus, are taken over by the neocortex with time. It has, for example, been shown that sleep triggers overnight learning on a motor sequence memory task, whereas equivalent waking periods produce no such improvement.¹¹⁸ This improvement in motor memory is reflected in increased activation of the right primary motor cortex, medial prefrontal lobe, hippocampus, and left cerebellum. These changes support faster motor output and more precise mapping of key press movements. On the other hand, there is a decrease in activity in the parietal cortex, the left insular cortex, the temporal pole, and the frontal

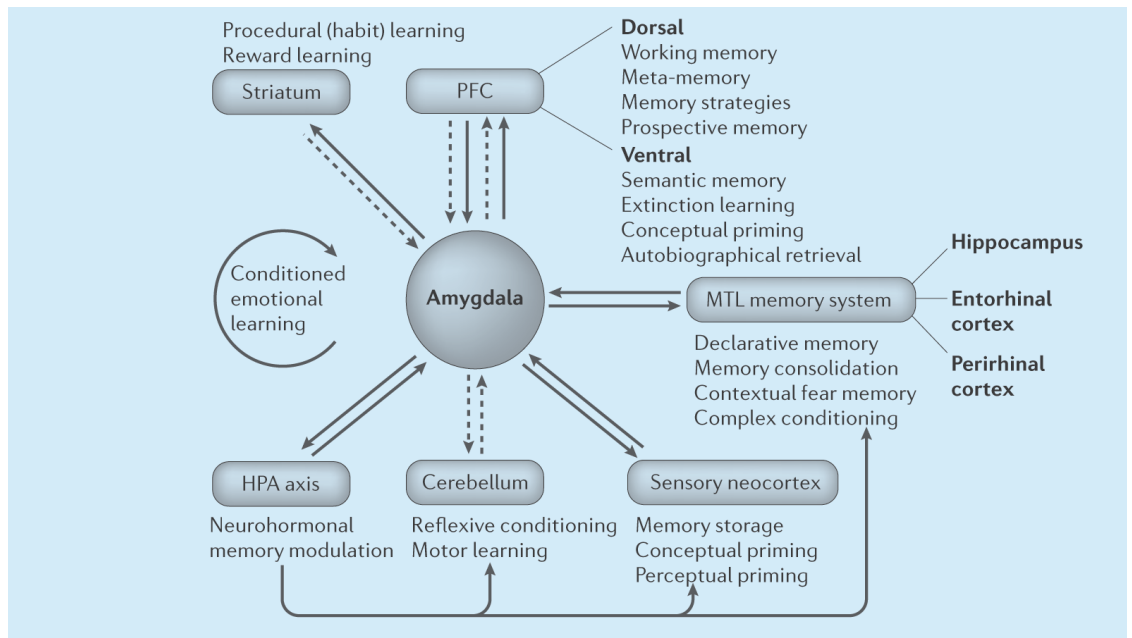


Figure 2 Potential mechanisms by which the amygdala mediates the influence of emotional arousal on memory: PFC – prefrontal cortex; MTL – medial temporal lobe. Reproduced with permission of the publishers from page 55 of Labar KS, Cabeza R. *Cognitive neuroscience of emotional memory*. *Nat Rev Neurosci* 2006;7(1):54-64.

region, reflecting a reduced need for conscious spatial monitoring and a decreased emotional task burden. These findings have important implications for acquiring real life skills and in clinical rehabilitation after brain trauma and stroke.¹⁵²

It has been suggested that cerebral input is first saved in a temporary memory store, and then encoded and transferred into long term memory during sleep (see Figure 2).^{155,156} This is supported by studies showing that sleep influences the mechanism underlying remembering and forgetting.¹⁵⁷

Memory processing, FMS and acupuncture

Our clinical experience shows that patients with FMS, sleep and memory disturbances may be improved by acupuncture. In the above reported group, acupuncture resulted in pain alleviation, improved sleep, short term memory consolidation, speed of performance and the ability to multi task performance (unpublished observations).

Recently, Han and collaborators demonstrated that acupuncture exerted a protective effect on cognitive impairment caused by cerebral multi-infarction in rats.¹⁵⁸ Furthermore, in patients with vascular dementia acupuncture treatment resulted in improved cognitive functions including memory,

orientation and calculation and also in self managing ability in daily living.¹⁵⁹ However, due to the limited numbers of randomised controlled trials in the field, Peng and coworkers concluded that randomised double blind placebo controlled trials are urgently needed to resolve the question of whether acupuncture has a role in the treatment of cognitive impairment following vascular dementia.¹⁶⁰

Integrating the evidence

Chronic sleep disturbances are characteristic of FMS syndrome and it has been suggested that these sleep disturbances are the result of a condition in which deep sleep is frequently interrupted by bursts of brain activity similar to wakefulness (ie alpha waves).¹⁶¹ The sleep disturbance theory postulates that FMS, as well as chronic fatigue syndrome and post polio syndrome, are related to impaired sleep quality. According to the sleep disturbance theory, an event such as a trauma or illness causes sleep disturbance and initiates the dysfunction in descending pain modulating systems. This dysfunction results in an increased release of substance P in the spinal cord which induces central sensitisation of the neurons in the spinal cord and thereby the observed spread of the pain. Also, this may explain the development of

'tender points' that are characteristic of FMS. The sleep disturbance theory holds that deep sleep is critical in order to reset modulation of the pain inhibiting system. This would support a close interaction between pain and sleep disturbance in FMS. A common denominator between pain and sleep is the synthesis and functioning of serotonin. Interestingly, lower levels of serotonin have been found in the cerebrospinal fluid of fibromyalgia sufferers as compared to low back pain patients or healthy controls.¹⁶² Also, an increased frequency of the short allele in the serotonin transporters (5-HTT) gene has been found in patients with fibromyalgia as compared to healthy controls.^{163;164}

Our results show that there is a marked effect on rated sleep disturbances in patients with FMS after acupuncture as compared to before. Strikingly, acupuncture has been shown to increase the synthesis and release of serotonin.¹⁶⁵⁻¹⁷⁵

Implications for research

In recent reviews of the efficacy of acupuncture in fibromyalgia it has been implied that acupuncture has no specific effect. This conclusion is based on the assumption that superficial needling or needling away from the 'specific site' is inert. This assumption is not correct for several reasons.¹⁷⁶⁻¹⁸⁰

1. FMS is characterised by central sensitisation and disinhibition, ie superficial needling induces similar physiological effects to muscle stimulation. This is likely to be true also in a number of other pain conditions such as migraine, low back pain etc.¹⁷⁸
2. In some studies, control needling has been carried out away from the 'specific site' and outside the affected myotome (most painful area). However, even if the needles are inserted outside the affected myotome, repeated needling results in increased receptive fields thereby possibly affecting the descending pain inhibitory systems of the affected myotome, in a similar way as needling within the affected area.¹⁷⁸
3. Superficial needling may result in deactivation of limbic structures, which is not somatotopically dependent, ie superficial needling has an effect on limbic structures wherever the needles are inserted (though the effect may have different potency depending on the site).^{176;180}

It is likely that acupuncture can induce alterations in connectivity in the brain, thus influencing cognitive, affective and sensory functions.¹⁷⁶⁻¹⁸⁰ In previous studies we have concluded that acupuncture may affect the sensory as well as the affective components of pain and that these may be separated.¹⁸¹⁻¹⁸⁵ We have also reported that the response to acupuncture depends on the aetiology of the pain,¹⁸⁶ and that patients' responses are highly variable,^{177;187} suggesting that the patients should be allowed to use the modality they prefer to maximise expectancy.^{188;189}

Conclusions

Probably, the princess was suffering from FMS and this was revealed by the 'sleep test'. We have previously reported that there is a close association between poor sleep quality, pain intensity, anxiety and depression.¹⁹⁰ Our experience is that some patients with FMS show significant improvement in pain, sleep and cognitive functions following acupuncture. Before one concludes that acupuncture has no effect in a complex syndrome like FMS, all the major symptoms have to be taken into account.

It is important to remember that the responses to acupuncture are individual and that evidence based medicine is only a tool to use for guidance when choosing a treatment, or as Sherlock Holmes stated in *The Sign of Four*: 'While the individual man is an insoluble puzzle, in the aggregate he becomes a mathematical certainty. You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant.'

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