Commonalities in the central nervous system's involvement with complementary medical therapies: limbic morphinergic processes

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Summary

Background: Currently, complementary and alternative medicine (CAM) are experiencing growing popularity, especially in former industrialized countries. However, most of the underlying physiological and molecular mechanisms as well as participating biological structures are still speculative. Specific and non-specific effects may play a role in CAM. Moreover, trust, belief, and expectation may be of importance, pointing towards common central nervous system (CNS) pathways involved in CAM.

Material/Methods: Four CAM approaches (acupuncture, meditation, music therapy, and massage therapy) were examined with regard to the CNS activity pattern involved. CNS commonalities between different approaches were investigated.

Results: Frontal/prefrontal and limbic brain structures play a role in CAM. Particularly, left-anterior regions of the brain and reward or motivation circuitry constituents are involved, indicating positive affect and emotion-related memory processing – accompanied by endocrinologic and autonomic functions – as crucial components of CAM effects. Thus, trust and belief in a therapist or positive therapy expectations seem to be important. However, besides common non-specific or subjective effects, specific (objective) physiological components also exist.

Conclusions: Non-specific CNS commonalities are involved in various CAM therapies. Different therapeutic approaches physiologically overlap in the brain. However, molecular correspondents of the detected CNS analogies still have to be specified. In particular, fast acting autoregulatory signaling molecules presumably play a role. These may also be involved in the placebo response.

key words: limbic system • placebo • belief • acupuncture • relaxation response • music therapy • massage • morphine • nitric oxide

BACKGROUND

The popularity of complementary and alternative medicine (CAM) is rapidly growing, particularly in former 'industrialized' countries. In the U.S.A, the NCCAM (National Center for Complementary and Alternative Medicine, established in 1998 by the U.S. Congress as a 'division' of the National Institutes of Health/NIH) had a budget of $114.1 million in the fiscal year 2003 (source: NCCAM, National Institutes of Health 2004). This is almost twice as much funding as in the year 2000 and an impressive marker for the increasing importance of CAM therapies and research in modern medicine.

The NCCAM presently defines CAM as covering 'a broad range of healing philosophies (schools of thought), approaches, and therapies that mainstream Western (conventional) medicine does not commonly use, accept, study, understand, or make available' [1]. The research landscape, including NCCAM-funded research, is continually changing and is subject to vigorous methodological and interpretive debates. Part of the impetus for greater research dollars in this area has been increasing consumer reliance on CAM to dramatically expand [1].

Despite popularity, little is known about the physiological pathways and biological structures involved in many areas of CAM. Thus, one important focus of current research in this field is the physiological concept underlying CAM therapies. While NCCAM's top priority is supporting clinical trials of alternative therapeutics, increasingly it is supporting basic and preclinical research [2]. Virtually all aspects of CAM modalities are open for investigation. Current NCCAM projects are investigating Reiki, Tai Chi exercise, Qigong, meditation, spirituality, biofeedback, acupuncture, Ayurvedic herbals, hawthorn, phytoestrogens, Ginkgo biloba, ethylenediaminetetraacetic acid chelation therapy, and special diets [2].

CAM potentially includes a huge array of very different therapies and approaches. However, besides specific effects that CAM therapists claim for themselves and for each single approach, trust, belief, and other subjective or more general factors may play a role in CAM. Thus, non-specific effects may exist as well. With this work, we'll investigate such assumed non-specific commonalities between different CAM approaches and will therefore focus upon the central nervous system (CNS) and its involvement in CAM. Particularly, the role of belief, emotions, and limbic activation will be of interest.

The common idea that the limbic system is solely concerned with emotion is at best a half-truth, but there certainly is a connection, which is probably relevant to CAM [3]. Yet, the limbic system is a rather 'slippery' concept, and it is made up of the limbic lobe and certain additional structures [3]. The limbic lobe surrounds the corpus callosum and consists of the cingulate gyrus and the parahippocampal gyrus. The hippocampus, which is in the floor of the temporal horn of the lateral ventricle, is also included in the limbic lobe. Additional structures incorporated in the limbic system, i.e., the limbic con-

cept, are the dentate gyrus, amygdala, hypothalamus (especially the mammillary bodies), septal area (in the basal forebrain), and thalamus (anterior and some other nuclei). Functionally, the 'hippocampal formation' consists of the hippocampus, the dentate gyrus, and most of the parahippocampal gyrus [3].

With regard to CAM, the limbic system is strongly associated with memory (emotional memory), i.e., positive or negative emotions, and the CNS-located reward circuitry: Belief has an emotional component in that the brain motivation and reward circuitry – linked to the limbic system – will be reinforced with a positive emotional valence attached to the believed in person, idea, or thing [4]. This emotionalized memory, potentially accompanied by 'somatic markers' (bodily sensations that may escort an emotion), sets the 'feeling tone', i.e., it strongly influences what 'feels right' to a person [4]. Furthermore, emotion may reinforce a belief and trigger positive physiological reactions even 'against' rationality [5]. Thus, belief in regard to a doctor or a therapy (e.g., CAM) may stimulate naturally occurring 'healthy' processes [4]. These subjective processes may particularly involve limbic structures, i.e., 'remembered wellness' [4]. Hence, subjective modulation of incoming information in the brain – e.g., following prior stimulation of the sensory organs – may be an important factor in CAM as well, that is, CAM may influence emotion-related information processing.

Many of the clinical results observable in CAM, presumably, have a psychoneurological explanation, i.e., lowering blood pressure (Figure 1). Thus, besides possible specific effects, non-specific commonalities probably exist in CAM that are associated, for example, with the limbic system, reward circuitry, and other subjective CNS phenomena. These common phenomena will be the focus of our examination in the following. For our analysis, we have chosen four different therapeutic approaches that cover the broad horizon of CAM: Acupuncture, meditation (relaxation response techniques), music, and massage therapy (therapeutic touch).

ACUPUNCTURE

Acupuncture, an ancient therapeutic technique originating from China more than 3000 years ago, is widely used in the clinical treatment of various diseases like pain syndromes, affective and psychosomatic disorders ('emotional dysfunctions'), or visceral dysfunctions. Furthermore, acupuncture may regulate autonomic and endocrine functions [6,7]. Hence, acupuncture is attaining widespread recognition in CAM and, most recently, in modern scientific medicine. It is usually performed by insertion of needles at locations on the skin that are called 'acupuncture points'. These points often show lowered electric skin resistance when a particular condition is treated [6]. Further, after insertion of a needle at a 'sensitive' acupuncture point, *deqi* occurs – a subjective phenomenon that indicates the correct needle placement and consists of radiating sensations coming from the insertion point and following hypothetical 'meridians' (invisible energy tracks) [6–8].

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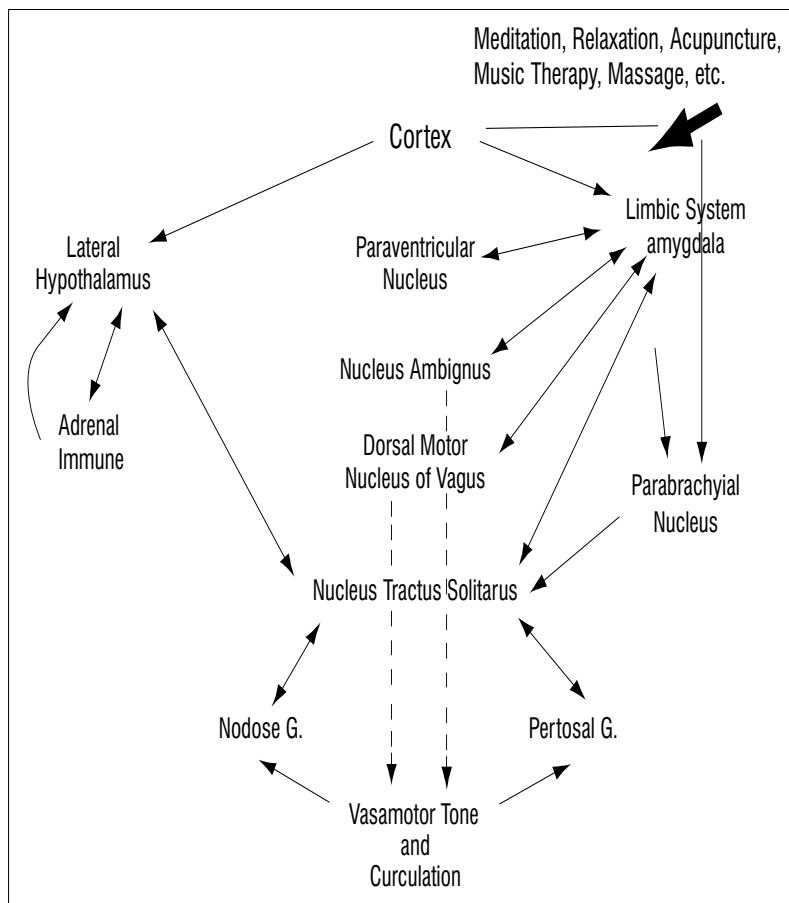
Figure 1. Representative connections among the limbic-hypothalamic pituitary adrenal axis, demonstrating that these centers are linked to vital functions, which appear to be modified by complementary medical therapies. This figure specifically depicts vascular tone regulation. This pathway suggests how belief, trust and emotion may exert a level of top-down control on vasomotor activity. The illustration is not meant to be all-inclusive.

Acupuncture has gained increasing popularity in health care and recognition in the scientific community lately. However, in the first line, it is emerging as an important modality of Western complementary medicine [7]. Its therapeutic mechanism is not fully understood, a factor that still limits its general use within in the medical framework. Traditionally, acupuncture is embedded in naturalistic theories that are compatible with Confucianism and Taoism [8]. Such ideas as *yin-yang*, *qi*, and 'wind' represent East Asian concepts that emphasize the reliability of ordinary, human sensory awareness [8]. However, many physicians who practice acupuncture reject such pre-scientific notions. Numerous randomized, controlled trials have already evaluated the clinical efficacy of acupuncture, and basic science research now starts to provide evidence that may offer plausible mechanisms for the presumed physiological effects of acupuncture [8].

Research indicates that many of the beneficial effects of acupuncture may be mediated at the subcortical level in the brain, i.e., CNS-located pathways [7]. Depending on the technique used, acupuncture may increase or decrease cerebral blood flow directly [9,10]. Thereby, it is clinically accepted that the curative potential of hand-managed acupuncturing is different from that of electric devices, i.e., electroacupuncture [11,12]. Furthermore, hand-managed acupuncturing coincides more with the acupuncture theories in Chinese medical practice [8,9,11]. This may be due to the fact that manual acupuncture is producing more discriminable or stronger (→'deeper') tactile sensations. Normally, *deqi* is elicited by hand-managed acupuncture only. Hence, manual acupuncture obviously has a stronger impact upon the limbic system (see below) [7,12]. This suggests that different brain mechanisms may be recruited during manual and electroacupuncture [12]. However, the experience of non-painful acupuncture sensations like *deqi* seems to be important for observable results: Acupuncture without production of sensations or, in contrast, painful acupuncture both show physiological effects (if any) that are different from regular acupuncture [3,7,11].

Much of the current theorizing about acupuncture concentrates on the spinal cord with particular reference to pain [13]. However, modern radiological techniques offering functional neuroimaging (fMRI, PET, SPECT) have uncovered a more complex CNS involvement in acupuncture: Some found increases in activity in vegetative centers – in the hypothalamus, caudate nucleus, brain stem – or in the temporal lobe, cerebellum, and primary or secondary somatosensory cortices/postcentral gyrus (e.g., following acupuncture point 'Stomach 36' stimulation) [7,11]. In contrast, other studies/analyses found prominent signal decreases in 'deep' – primarily limbic – structures (especially when accompanied by *deqi* feelings), e.g., amygdala, hippocampus, parahippocampus, hypothalamus, septal nucleus, caudate, putamen, nucleus accumbens, cingulate gyrus, anterior insu-

la (temporal lobe) and temporal pole, or fronto-orbital cortex [7,12]. Interestingly, subjects that experienced painful needling demonstrated signal increases in these regions instead. In addition, whole brain imaging revealed prominent signal decreases with *deqi* sensation in further brain regions that are closely linked to the limbic system, such as the frontal pole, prefrontal cortex, and cerebellar vermis [7]. However, some studies found increases particularly in the deep brain structures [10,14]. Thus, activity patterns potentially show inconsistent results – possibly depending on the concrete acupuncture point(s) stimulated.

Acupuncture reaches deep CNS structures like the limbic system and modulates brain activity patterns [7–12,14]. These changes of brain activity may be an important factor for the clinical effects of acupuncture: Acupuncture possesses a coordinating influence on a network of cortical and subcortical limbic and paralimbic structures, regions that are intimately involved in the regulation of emotions and autonomic, endocrine, or vegetative functions. Modulation of this neuronal network could initiate a sequence of effects by which acupuncture regulates multisystem functions [7]. The effects on the limbic system could well contribute to its efficacy for the treatment of diverse affective and psychosomatic disorders [3,7,8].

As in other CAM therapies, belief and expectation are crucial components of acupuncture treatment. When patients actively participate in their treatment, i.e., positively anticipate clinical effects, the chosen therapy presumably is more effective. This seems to be true for acupuncture strategies as well [3,15]. Hence, patients vary considerably in their responsiveness to acupuncture: Some fail to respond at all, while others (strong reactors) experience marked effects [3]. Strong reactors would be people whose CNS, including the limbic system, is particularly sensitive to sensory stimulation. In the case of the limbic system, there are nociceptive receptors in the cingulate cortex that have large receptive fields that may encompass the whole body [16]. Strong reactors, for example, could be people with many such receptors or a generally enhanced CNS responsiveness [3]. In contrast, patients who are unwilling to have acupuncture or are afraid of it seldom respond well to the treatment [3]. Thus, acupuncture partly seems to be a subjective therapy where patients have to trust/believe in the outcome. Congruent with that is the observation that many – but not all – patients react with feelings of calm and relaxation, unexplained and sudden laughter or tears, euphoria etc, i.e., subjective emotional response. These phenomena, as well as reported spiritual or 'out-of-the-body' experiences, may be produced by activation of parts of the limbic system [3].

Certain of the hippocampal cells are thought to be involved in the formation of new memories. In fact, the limbic system in general is closely connected with memory formation [17]. Clearly, the connection of memory, emotion, and endocrine functions is a useful biological principle. For example, when a stressful event occurs (i.e., threat), the activation of physiological stress response pathways (via endocrine mechanisms) will potentially protect the stressed organism from harm. The stressor will be memorized, presumably, together with an emotion, e.g., fear [17]. Given the connection between hippocampus and memory formation, one might expect that acupuncture would have some effects on this. In fact, isolated reports exist that attribute better memory performance to acupuncture treatment [3]. Finally, looking at the amygdala as a special part of the limbic system – a region that is also closely related to emotion (especially fear) – we find another interesting association: The amygdala has many post-synaptic receptors for which gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, and diazepam and other anxiolytics mimic the action of GABA at this site. Researchers on acupuncture physiology have hypothesized that part of the calming effects of acupuncture may be due to the release of GABA in the amygdala and other limbic areas [3]. This is a field which would definitely repay additional research and observation.

MEDITATION/RELAXATION RESPONSE TECHNIQUES

The relaxation response (RR) is defined by a set of integrated physiological changes that are elicited when a person patiently engages in a repetitive mental or physical activity and passively ignores distracting thoughts [18,19]. This behavior – seen in meditation, certain forms of prayer, Tai Chi/Qigong, Yoga, autogenic training etc. – is associated with instantly occurring physiological changes that include decreased oxygen consumption or carbon dioxide elimination (i.e., reduced metabolism), lowered heart rate, arterial blood pressure, and respiratory rate, accompanied by an overall decrease in brain activity (with increases in some particular regions as described below). In addition, slight increases in skeletal muscle flow and skin temperature are emerging [19]. These changes are different from those reported during sleep or quiet sitting [20].

Active elicitation of the RR (when constantly practiced for an adequate period of time) may produce long-term physiological changes not only when the RR is being brought forth [18,19]. This appears to be a reasonable observation, especially when RR-based medical approaches are used in combination with other life-style adjustments, i.e., nutritional, exercise, and stress management interventions [18]. Clearly, the introduction of the RR and related mind/body medical techniques into therapeutic mainstream or standard medicine is becoming increasingly popular [21,22]. Moreover, research has documented that regular elicitation of the RR results in alleviation of many stress-related medical disorders [18], i.e., it antagonizes the stress response and its potentially harmful effects: Herbert Benson, who first described the RR, identified it as the physiological counterpart of the stress or *fight-or-flight* response [18–20].

With regard to the CNS, the RR activates areas in the brain responsible for emotion, attention, motivation, and memory (e.g., anterior cingulate, hippocampal formation, amygdala) and may also serve the control of the autonomic nervous system [19,23,24]. This specific pattern of acti-

vation may exert protective effects on the brain, although still a speculative prospect [18]. However, such a protective mechanism could be related, for example, to a generally decreased production of metabolism-derived harmful by-products, i.e., oxidative stress. Also, the RR seems to be effectively capable of improving concentration and cognitive function, e.g., memory [18,25]. This may be due to hippocampal/limbic activation (see above), including reward or motivation circuitry involvement [4]. We now also know that stress may reduce neurogenesis in the adult hippocampus, possibly facilitating memory impairment [17]. Thus, the RR – and the reduction of stress with it – may be clinically relevant in dementia syndromes [17,18]. In addition, RR techniques have also been described to be helpful in the treatment of anxiety and depression [18,26]. Here, anxiolytic effects of the RR may occur by promotion of an inhibitory (GABAergic) tone in specific areas of the brain [26].

Meditation has been shown to increase left-sided anterior activation of the brain, a pattern that is associated with positive affect [27]. Again, positive emotion-related brain activity is a substantial part of the CNS reward circuitry, and the frontal regions of the brain not only are involved in RR pathways, but also exhibit a specialisation for certain forms of positive and negative emotion [28]. Interestingly, reliable increases in left-sided activation are observable with meditation training in response to both the positive and negative affect induction [27]. Davidson et al. suggested recently that left-sided anterior activation is associated with more adaptive responding to negative and/or stressful events [27,29]. Specifically, individuals with greater left-sided anterior activation have been found to show faster recovery after a negative provocation [29].

Deep CNS structures are crucial components of the neural RR pathways. These components primarily consist of limbic structures, but not solely. Hence, increases in regional cerebral blood flow (i.e., brain activity) following or coming along with meditation have been detected, for example, in the dorsolateral prefrontal cortex, inferior or orbital frontal cortices/anterior regions, inferior parietal lobes, pre- and postcentral gyri, temporal lobes, cingulate gyrus, hippocampus and parahippocampus, amygdala, globus pallidus/striatum, thalamus, and the cerebellar vermis [23,24,27,30,31]. However, inconsistent results have been reported with regard to the parietal cortices: Some studies demonstrated an inverse correlation between the dorsolateral prefrontal and the ipsilateral superior parietal lobe blood flow change: This correlation may reflect an altered sense of space experienced during meditation [24,30]. Clearly, meditation is a complex phenomenon that involves several coordinated cognitive processes and autonomic nervous system alterations. RR techniques modulate CNS activity patterns with particular focus on structures associated with attention, emotion, and memory.

Knowing details on the brain activity patterns or CNS involvement in the RR, e.g., through neuroimaging techniques, doesn't necessarily help us with the interpretation of these results. However, we do know now that limbic system activation is an integral part of the brain physiology involved in the RR. Hence, the very same structures that revealed increased activity in the RR, as described, are well-known components of the brain reward and motivation circuitry: Prefrontal and orbitofrontal cortex, cingulate gyrus, amygdala, hippocampus, and nucleus accumbens [4]. Thus, RR and reward circuitry seem to be physiologically interconnected. Memories of the pleasure of wellness, i.e., 'remembered wellness', are accessible to this circuitry through hippocampal mechanisms. Further, belief affects mesocortical-mesolimbic appraisal of an experience, leaving one, for example, well and relaxed. Yet, trust or belief in a therapy/therapist may facilitate positive affect, sense of well-being, and motivation, thereby involving limbic/reward circuitry activation, possibly leading to relaxation (i.e., elicitation of the RR) or initiating a beneficial placebo response [4].

MUSIC THERAPY

Music has become an important part of different medical settings over the last decades [32,33]. In CAM, music therapy can be interpreted as an integral component of professionally assisted self-healing strategies. Encompassing much more than simple listening to music, music therapy may involve song writing, discussion of lyrics, performing, or other activities related to music. In the so-called 'receptive music therapy', patients listen to a piece of music that elicits memories and associations, which can thereupon be lived-through in a new, protected, or simply pleasant way [33]. In the 'active music therapy', patients improvise on instruments of their choice and thus create a new way of communicating their inner feelings, emotions, and unspoken 'words'. Yet, a common misconception about music therapy is that its recipients need to have some level of musical ability and expertise. In fact, no musical talent or previous experience with musical settings seems to be required to derive benefits from this type of therapy [32].

When music is defined within a theoretical framework, it is best to refer to its physical definition as the production of varying pitches inside a rhythmic framework. It has long been known that this simple harmonic motion can have an abundance of psychological and physical effects [34,35]. From the moment an auditory stimulus is perceived a cascading series of events is set in to motion. Hence, music enters the body mostly through the ears, and nerve fibers transport the sound information from there (via the cochlear nerve) to the brainstem. In the brainstem, 'music' gets filtered and analyzed for the first time. For example, pitch and direction of sounds are examined [32]. The thalamus, the 'door to the cerebrum' or 'guardian of consciousness', decides upon the further fate of music within the brain. This gating effect of the thalamus is important for the valuation of music information, and it protects from overwhelming 'sound attacks' [33]. The primary cortex areas for hearing perception and analysis in the temporal lobe (auditory cortex), getting input from the thalamus, send further information throughout the brain in associative fields and wired areas of importance for the processing of music [36,37]. Thereby, the right hemisphere works on the rough structure of music, whereas the left hemisphere conducts the more subtle analysis [38]. Also, close connec-

tions to evolutionarily older (and deeper) areas of the brain like the limbic system exist [38,39].

For a long time, music is known for its close association with emotion, i.e., initiation of emotional responses [33]. However, research has just begun to thoroughly investigate this connection, mainly using neuroimaging techniques. For example, different research groups have examined whether music processing in the brain subjectively depends on positive or negative music perception [34–38]. Hence, subjective/individual music preferences have a strong impact on the physiological effects of music. When teenagers listen to music of their preference, parts of the frontal and temporal lobe in the left hemisphere of the brain get activated [36,38]. In contrast, when they listen to music they dislike the same areas on the other side (i.e., right brain) are active. Further, deeper CNS structures get involved: Pleasurable music not only stimulates the frontal (left-anterior) brain, but also activates parts of the limbic system like the cingulate gyrus [36]. Dissonant or unpleasant music, on the other hand, activates right parahippocampus and amygdala (related to fear and anxiety) [38,39]. Finally, music-associated positive body sensations (e.g., 'happy chills') are often result of brain reward circuitry stimulation [32,38]. Hence, pleasant or unpleasant, the decision upon the quality of music not only depends upon individual or subjective but also upon different cultural backgrounds [32,33].

When pleasant music is heard, as described, the brain's motivation and reward pathways are reinforced with positive emotion mentally linked to the music. This emotionalized memory may include 'somatic markers' (sensations) that potentially accompany emotion [39]. Evolutionarily, these sensations may remind us of the significance and advantages of music for early humans: Music may have developed from early separation cries that served the goal of keeping contact between mother and child [38]. Also, music may create feelings of social support, protection, and community. Clearly, music and feelings are interconnected, and the emotion it imparts can be viewed as a process of reinforcing a positive belief so that rational thought can not hinder the strength of the belief [39]. Thus, music is a powerful tool to elicit an emotional response (i.e., limbic activation) and fulfill expectations without the use of rational information processing. Hence, music perception is rooted in the present moment, although the processing of music mirrors past experiences, e.g., an acquired belief system [32,33].

Music has the capacity to influence the autonomic-emotional integration system (involving limbic pathways) [39]. Here, the autonomic nervous system and emotions are wired together. Furthermore, sympathetic activity and stress hormone production are imbedded in the underlying autoregulatory circuits [17,18,32]. An association of music with emotions, neurotransmitter and stress hormone production, autonomic responses, behavior, and mood states becomes obvious. The influence of music on vital functions such as breath, respiratory rate, blood pressure, and cardiac output (a result of the autonomic-emotional integration) may lead to a different self- and body-experience, a different 'consciousness' or altered state of mind [33] (Figure 1).

Although rhythm and music are not entirely synonymous terms, rhythm constitutes one of the most essential structural and organizational elements of music: Time structure of music is the essential element relating music specifically to motor behavior [32]. Thus, the motor system appears to be strongly sensitive to auditory priming. This may be due to evolutionary processes, since rhythm represents an ancient form of music and some of the basic auditory-motor arousal connections may have their basis in adaptive processes related to survival behavior, e.g., in fight-or-flight reactions [40]. These important ancient connections may lead to a deep and even unrealized (instinctive) impact of rhythm upon our feelings and behaviors. Musical healing may use this path to affect various disease states positively [33]. In addition, the repetitive character of rhythm movements may enhance the capacity to elicit the relaxation response [32,39]. Music and rhythm, different from verbal language, may be able to reach patients even when no other access exists. Hence, evolutionarily old mechanisms and neuroanatomic structures may fit together in a healthy way here and yet establish contact on a deep, non-cognitive level [32,33].

In healthy individuals, music therapy is often recommended as part of stress-management programs or accompaniment to physical exercise [32]. This may be due to the fact, that music has been shown to possess the ability to decrease stress hormone levels in stressful (challenging) situations and further enhance blood concentrations of endorphins and endocannabinoids, eventually facilitating relaxation and feelings of well-being [41]. Hence, music may be used as an effective calming and stress-reducing intervention [33]. Clearly, listening to favorite music can be a suitable way to 'unwind'. But the soothing and therapeutic properties of music can obviously do more than just help to relax at the end of a busy day: Music therapy is a branch of health care dedicated to the use of music for emotional, physical, functional, and educational improvement in a broad range of settings and conditions [32]. With many psychiatric/psychosomatic diseases (and additionally, in pain management), for example, music has been applied successfully in conjunction with standard medical care to improve patients' overall well-being, mood, and actual disease states [42–45]. Thereby, music is well tolerated, inexpensive, with good compliance and few side effects [32,33]. Also, music helps patients to gain control over movement patterns, stimulates memory, self-esteem, and social interaction [46,47]. Thus, the use of music with severely disabled patients – including geriatric/neurodegenerative, psychiatric, and psychosomatic patients – has been proven to be especially fruitful [33].

In clinical medicine, several studies have shown analgetic and anxiolytic properties of music that have been used in intensive care units, both in diagnostic procedures like gastroscopy and in larger operations, in preoperative as well as post-operative phases, reducing the need for medication [41]. Additionally, subjective stress levels and stress hormone production have been lowered [32,41]. Hence, music has the ability to induce positive emotions and diminish stress, as does the relaxation response [18,32,41]. Moreover, stress has been shown to potentially have an impact upon neurodegen-

erative diseases and mental disorders [17]. Thus, as shown here, musical healing may represent a powerful tool to treat psychiatric/psychosomatic patients, similar to the relaxation response. Further, music may be used as a means for elicitation of the relaxation response [33].

Music listening has the power to lower blood pressure, i.e., stimulate peripheral vasodilation, decrease heart rate, and create an overwhelming sense of relaxation and well-being [35,39,48,49]. In examining a potential mechanism for the music-induced relaxation, besides the over-riding CNS output via the autonomic nervous system, peripheral neurovascular processes would appear to be important [39]. With regard to trust and belief, linkages between music listening and belief system – and how they share commonalities within CNS circuitries – have been examined. Briefly, music and its calming effects have a large emotional component, which involves the brain's motivation and reward pathways [39,50]. In addition, the ability of music to calm and reduce blood pressure, for example, can be initiated at the level of the cerebral cortex and may involve insular as well as cingulated, amygdalar, and hypothalamic processes [35,39]. The hard-wiring of emotion/music and cardiovascular neural systems probably involves many subcortical descending projections from the forebrain and hypothalamus [39]. The insular cortex in cardiac regulation is important because of its high connectivity with the limbic system, suggesting that the insula is involved in cardiac rate and rhythm regulation under emotional stress. [39]. Again, the interconnectedness of music physiology and limbic processing becomes obvious.

Taken together, music is a complex phenomenon. Listening to music and playing music are different in many aspects. However, the physiological and emotional responses that music elicits may very well be comparable and equally important for the alleviation of clinical symptoms. In music, all senses get activated. This, presumably, is one of the reasons why musical healing obviously works on a deep level. Music keeps people 'in the moment', and clearly, there is no room for day-to-day worries, a condition that resembles a state of 'flow' described by Csikszentmihalyi in the 1970s (and the years after). Furthermore, the flow experience seems to be closely related to the relaxation response. Yet, the path of music within body and CNS starts with the sensory organ's stimulation (when music 'hits' the body), possibly accompanied by the pure and naïve sensation of music (e.g., 'resonance'). The elicitation of emotions associated with music perception may be followed by 'somatic markers' – secondary bodily sensations, i.e., mind/body reactions. These depend on memories (emotional memory) and limbic system involvement. Thus, music-related brain's reward circuitry stimulation may introduce feelings of wholeness and wellness, i.e., 'remembered wellness.' Subsequently, music reduces stress and promotes naturally occurring health processes.

MASSAGE THERAPY

Massage therapy (MT) is an ancient form of treatment that is now gaining popularity as part of the complementary and alternative medical therapy movement [51]. Thereby, three types of commonly used classical MT

techniques exist: Moderate massage, light massage, and vibratory stimulation [52]. Differences depend on pressure used and type or level of body contact performed. Special forms of MT are, for example, acupoint massage/acupressure, healing touch, Reiki (with or without body contact), and others. However, moderate MT may be viewed as the most common classical approach [53].

For a long time, typical indications for MT within the CAM framework have been chronic pain conditions [51,53–55]. MT has been successfully conducted on patients with pain in cancer, inflammation, following medical procedures or operations, and other painful conditions [51,53,55–57]. However, besides reducing pain, further indications for MT followed over time. MT or therapeutic touch decrease symptoms of anxiety, depression, and mood disturbance [51–53,56–58], may lower fatigue and sleep disturbance/insomnia (as MT, for example, may improve sleep and quality of life especially in patients with severe disease states [56,57]), reduce agitated behavior in persons with dementia syndromes [59], or down-regulate elevated blood pressures as well as heart rates [51, 52, 56]. Also, MT may alter stress hormone levels, i.e., neurohormonal responses, and autonomic nervous system activity [59,60]. Besides reduction of stress-associated symptoms and subjective stress levels, MT may decrease hyperresponsiveness to stress or detrimentally high endogenous cortisol production [52, 59,60]. Nonetheless, the largest MT effects have been observed for pain control (i.e., antinociceptive effects), anxiety, and depression reduction. Interestingly, many of the positive results achieved by MT lasted for longer periods of time even when the treatment ended. This may particularly be true for psychiatric/psychosomatic symptom reduction, thus indicating, for example, behavior change in the course of MT [51,53,54].

With regard to affect, belief, limbic system involvement, and positive emotional memory (i.e., reward circuitry stimulation, 'remembered wellness') as part of the MT physiology, studies have indicated a particular participation of the frontal brain [58]. In contrast to left-anterior activation of the brain related to positive affect (as described), EEG asymmetry with greater relative right frontal activation is associated with negative affect [27,58]. Thus, depressed adults show stable patterns of this asymmetry [58]. As music therapy attenuates frontal EEG asymmetry, so does MT: In a recent study, adolescents with greater relative right frontal EEG activation and symptoms of depression were given either MT or music therapy. Hence, frontal EEG asymmetry was significantly attenuated during and after both procedures [58]. In addition, MT may induce feelings of well-being and relaxation, as indicated, for example, by induction of a hypometabolic/relaxed physiological state, resembling the relaxation response [52,56]. Moderate MT has the potential to lower blood pressure, respiratory rate, and heart rate [56]. Thus, the stress-antagonizing quality of MT may be related to RR autoregulatory pathways, i.e., elicitation of the RR.

Subjective and objective CNS parameters change during MT: Moderate massage increases delta and decreases

alpha and beta EEG activity, suggesting a RR pattern [52]. Simultaneously, moderate MT increases positive affect with a shift towards left-frontal EEG activation [52]. In contrast, light massage or vibratory stimulation may increase arousal and trigger a stress response instead, as indicated by decreased delta and increased beta activity, accompanied by an accelerated heart rate [52]. Taken together, moderate MT may represent a suitable tool to positively affect body and mood states, thereby involving left-anterior brain activation. This type of brain activity pattern seems to be related to meditative states and feelings of wellness or wholeness (illustrated above), possibly including limbic or reward circuitry pathways. Positive subjective therapy expectations may further support beneficial MT effects.

DISCUSSION

The CNS plays a major role in CAM physiology and autoregulation. Obviously, CNS activity patterns detectable in CAM – mainly through EEG and neuroimaging techniques – show commonalities between different therapeutic approaches, since similar structures get involved. Thereby, left-anterior (i.e., frontal) and limbic structures of the brain seem to be of particular interest. This may be due to positive affect or reward circuitry stimulation in connection with CAM as well as associated memory processing and emotion-related behavior change. In addition, autonomic centers located in the brain (e.g., hypothalamus) are of importance. Hence, the brain is a crucial component of CAM effects.

With reference to the CAM techniques examined here, a close association regarding analogies in CNS activity has been demonstrated for acupuncture, meditation/RR techniques, music, and massage therapy. In general, all these approaches revealed an overall decreased brain metabolism, whereas particular regions like limbic and frontal/prefrontal areas of the brain showed an increased activity. CAM may therefore involve RR-related physiological pathways, possibly facilitating positive emotional memory, feelings of well-being, and relaxation, i.e., 'remembered wellness.' Further, subjective experiences of comfort, protectedness, and flow occurred [32,33]. With regard to physiological modifications in consequence of CAM therapy, secondary bodily reactions with cardiovascular, respiratory, and other autonomic changes are involved: Somatic markers, i.e., positive or pleasurable sensations and body perceptions ('signals'), may accompany complementary and alternative medical experiences. Thus, we can speak of profound mind/body reactions closely related to various CAM therapeutic approaches. These physiological and psychological responses – in connection with a certain therapy – resemble the placebo response [4]. Like CAM, the placebo response also relies on trust, belief, and positive therapy expectation, and additionally, similar brain structures like limbic and prefrontal/frontal regions are involved [4,61–64]. Yet, the brain's reward and motivation circuitries seem to be a major player in placebo physiology and CAM pathways likewise [4,61,63]. Clearly, subjective and objective CNS phenomena have been demonstrated in the course of CAM.

Acupuncture is a complex and 'multi-task' method. Effects depend on a huge variety of constituents, e.g., different needling techniques or type of stimulation [9]. Particularly, varying patterns of acupuncture points chosen for each single subject plus individual compositions of concrete therapeutic strategies, possibly modified from session to session, can make it difficult to compare acupuncture treatment with other – potentially more 'standardized' – CAM approaches. With regard to CNS effects observable in acupuncture, the same structures seem to be involved as in other CAM therapies (illustrated here). However, the concrete pattern may be different, 'individual,' or 'unpredictable'. Thus, the interpretation of particular CNS activity patterns found in acupuncture is still open. Nonetheless, acupuncture – as other CAM therapies – reaches cortical and subcortical CNS structures like the deep limbic and paralimbic areas (including reward and motivation circuitries) and may thereby coordinate a neuronal network involved in the regulation of emotion and autonomic, endocrine, or vegetative functions [7–12].

On the molecular level, concrete physiological pathways responsible for CAM effects are still a matter of discussion. However, some analogies obviously exist here as well: Nitric oxide, endocannabinoid, and endorphin/enkephalin autoregulatory signaling have been demonstrated or discussed in association with acupuncture [6,8, 65–67], RR [4,18,19], music [32,33,39], and massage therapy [54,55] (also preliminary data Stefano et al.). These molecules that possess a strong CNS affinity may also be involved in the placebo response (besides dopamine and serotonin) [61–63] and facilitate positive CAM effects or subjective feelings of well-being and relaxation. Moreover, they own a stress-antagonizing capacity – like CAM [18–22,32,39,41,48–55,59,60,68,69]. The relief of stress or detrimental effects related to stress, i.e., stress-associated diseases, may be due to the CAM-connected reduction of norepinephrine reactivity/turnover or a decreased autonomic nervous system hyperresponsiveness (e.g., see [18,32,59,68]). This ability has been demonstrated for various CAM therapies, as for the RR [18,70]. However, many of the CAM effects occur almost instantaneously. Thus, some of the molecular pathways described above may not be fast enough to be held responsible for all the observed results (e.g., inducible nitric oxide pathways or endorphin signaling). The same may be true for the placebo response. Hence, constitutive nitric oxide mechanisms and endocannabinoid autoregulation represent rather fast acting signaling pathways [19,71].

Taken together, common CNS activity patterns found in CAM may represent shared physiological pathways, indicating general or non-specific (subjective) CAM effects. This non-specific overlapping autoregulation may be complemented by additional specific (objective) effects in certain cases: Subjective and objective mechanisms may be associated with various CAM approaches likewise. For example, a recent study on acupuncture working with anesthetized volunteers, thereby avoiding subjective conscious cognition and interaction, showed a specific analgesic effect [67]. However, trust and belief in a therapy/therapist may activate naturally occurring self-healing capacities (→ self-care), especially when positive

qualities like pleasurable sensations, touch, attention, feelings of well-being or protection are involved. These subjective qualities may be utilized by CAM therapies. The mind/body that wants to be cared for and participates in his/her health care as a self and respected being, believing in a remedy or 'resonating' with a method and its unique sociocultural background, feeling in control and giving up resistance – clearly, CAM addresses individual, i.e., subjective, beneficial mind/body physiological pathways. Thus, personal history and former experiences (e.g., 'remembered wellness') as well as therapy expectations may play a role, although CAM is based on specific and non-specific components together, obviously. Every approach may make use of these two components that correspond with each other. This 'holistic' interpretation of CAM with a particular focus upon shared CNS functions and common brain-located innate healing capacities still has to be investigated further and may be critically questioned. Nonetheless, a common psychoneuroendocrinologic explanation for many observable CAM effects may be found, presumably, within the brain.

As noted earlier, several CNS signaling processes with known neurotransmitters may be involved in this process. Besides endocannabinoids and others, recent information suggests that morphinergic signaling should be part of this hypothesis as well. Endogenous morphine, both biochemically and immunocytochemically, has been found in various neural tissues as well as in limbic structures [72–82]. Additionally, these reports demonstrate the presence of morphine precursors in various mammalian tissues, including brain. Furthermore, an opiate receptor subtype, designated mu3, has been cloned, which is opiate alkaloid selective and opioid peptide insensitive [83], strongly supporting the hypothesis of an endogenous morphinergic signaling system. The psychiatric implications of this system have been examined as well, including brain reward circuitry [50]. Thus, morphine, given its reported effects and those exerted via constitutive nitric oxide stimulated nitric oxide release, may form the foundation of this common signaling among these complementary medical methodologies. In general morphine exerts immune, vascular, and neural down-regulating activities [84,85]. Opiate compounds are part of the reward system. Indeed, morphine may additionally represent signaling that allows one to make rationale short cuts, since being rationale may be too time consuming, i.e., emotional motivation [86]. Taken together, endogenous morphinergic signaling would appear to be an important missing component linking the factors that make complementary medical therapies important. Additionally, the evolutionary survival strategies that do occur because of morphinergic signaling [86] make this hypothesis important.

Placebo treatments have no intrinsic pharmacological potential but nonetheless alter brain activity patterns – especially those of deep brain structures [87]. Hence, belief and expectations are, by nature, important ingredients of the placebo response. In particular, multiple component expectation-induced placebo effects may involve morphinergic signaling, since a reduction of

placebo effects by the opioid selective antagonist naloxone has been demonstrated [87,88]. In placebo experiments [87] increased brain activity was found. This was determined by fMRI (functional magnetic resonance imaging) during the anticipation of pain relief in the midbrain in the vicinity of periaqueductal gray matter (PAG), which contains high concentrations of opiate neurons involved in the descending pain inhibitory pathway. Neurons immunoreactive for morphine are largely present all along the extension of PAG and in brainstem raphe nuclei (Figure 2), implicating morphinergic neural pathways in the placebo response. Importantly, this process also may be active in altering the experience of pain. The presence of endogenous morphine has been confirmed by gas chromatography coupled to mass spectrometry in the brainstem and cortex [74]. Additionally, the prefrontal cortex (particularly the dorsolateral aspect) has been shown to be involved in the representation of cognitive control, goal determination, and expectation – and thus plays a crucial role in the placebo response [87]. Moreover, the prefrontal cortex possesses close neural connections to limbic components such as the hippocampal formation and cingulate cortex where morphine immunoreactivity is largely present in neurons and fibers (Figure 2) [78]. These limbic areas play a major role in memory processes and also mediate motivational, affective and autonomic responses often accompanying pain. Additionally, endogenous morphine appears to modulate memory processes playing a role in weakening the memory of a nociceptive experience [89]. Limbic areas also are connected to the prefrontal cortex, which integrates emotion, memory, belief, expectation, motivation and reward processing, i.e., affective and motivational responses [4,90]. Also, prefrontal mechanisms may trigger opiate release in the midbrain [87]. It also has been demonstrated that endogenous morphine can be released in a chemically detectable form from rat brain slices in a Ca^{2+} and K^+ dependent manner, suggesting a role for morphine as a neurotransmitter or neuromodulator in the mammalian CNS, further supporting its involvement in these processes [80]. Recent studies demonstrate that morphine release nitric oxide from rat limbic tussues, i.e. hippocampal "plugs", suggesting further that endogenous morphine processes are involved since this results indicates a m3 presence [91]. Taken together, prefrontal cortex activation in placebo as well as CAM treatments may reflect a form of – mainly – externally elicited top-down CNS control, possibly involving morphinergic autoregulatory pathways.

CONCLUSIONS

The CNS is involved in CAM, which holds specific and non-specific qualities. Common brain structures like frontal and limbic regions get activated in various CAM approaches, indicating a crucial role of affect and belief. Thereby, CAM therapies – acting via common brain pathways – also possess a stress-reducing capacity that may be addressed in self-care-oriented medical procedures, some of them accepted for their low-cost (although effective) way of acting in the healing process. Yet, CAM is rapidly becoming popular. While medical knowledge and technical abilities are expanding, they still have to be affordable.
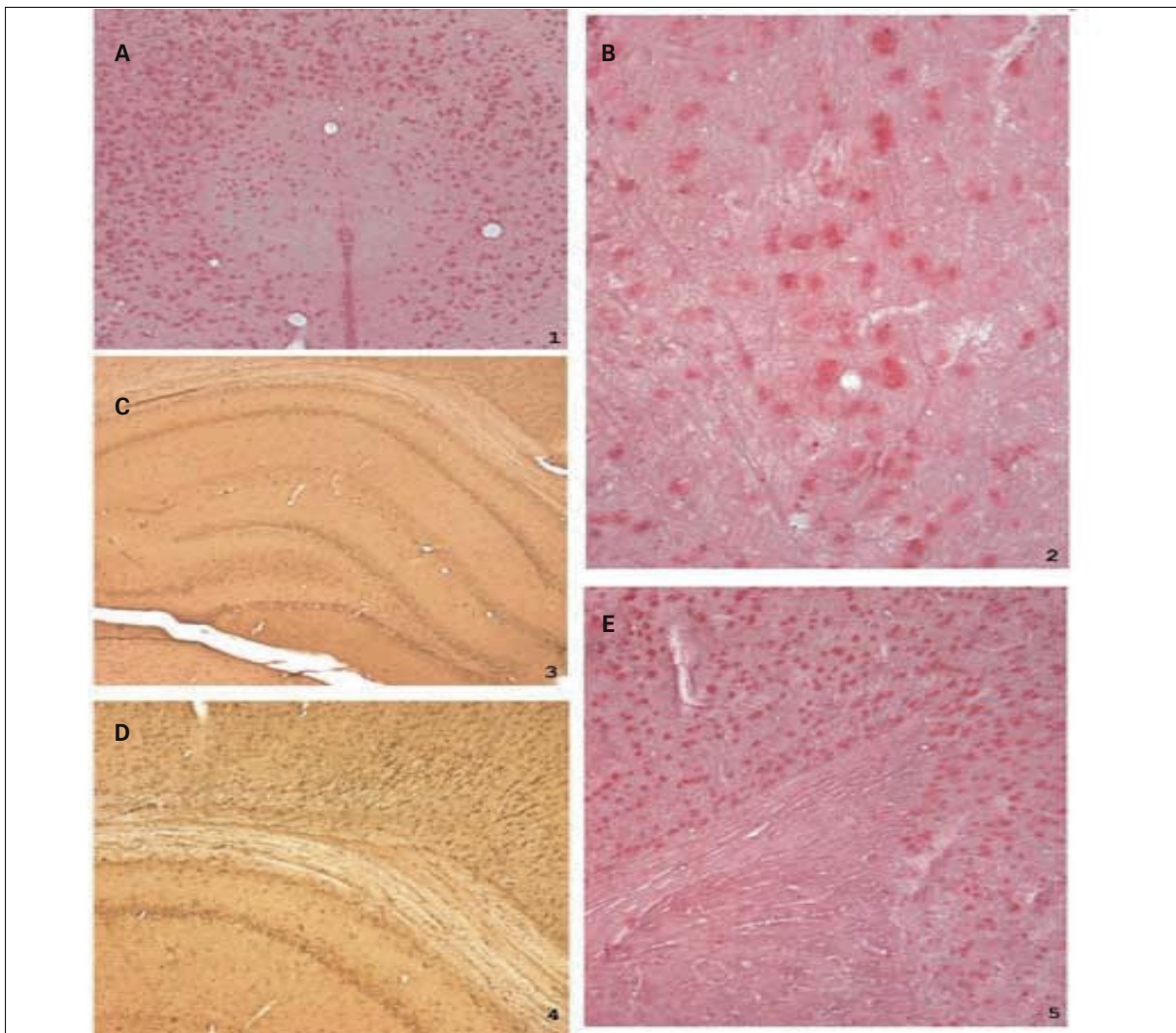
Figure 2. Immunohistochemistry localization of morphine-like immunoreactivity in rodent brainstem, hippocampal formation and cingulated cortex- Immunoreactive neurons are visible in rostral PAG (**1**), linear raphe (**2**), dorsal hippocampus (**3**) and cingulated cortex (**4,5**). The images in **1**, **3** and **5** were obtained from coronal paraffin sections and immunostained with an alkaline phosphatase immunoenzymatic method. Peroxidase-anti-peroxidase method was used in coronal vibratome sections for images **2** and **4**. An affinity purified anti-morphine IgG, which exhibited minimal cross-reactivity with codeine and other peptides, was used in this study [93].

CAM may help to solve this problem. However, knowledge about mechanisms involved in CAM is often fragmentary. This deficit has to be reduced before CAM becomes part of the regular and scientific medicine.

Sensations that may accompany CAM therapy (e.g., stimulation of the sensory organs) may activate limbic or other areas of the brain related to the reward and motivation circuitry (limbic-cortical circuits). Secondary physiological changes and bodily reactions may follow, i.e., autoregulatory mind/body reactions. Besides specific effects, non-specific reactions may evolve in the course of different CAM approaches, possibly involving analogous brain compartments. Thus, the existence of subjective CNS phenomena and commonalities in CAM may emphasize the significance of naturally occurring health processes and general self-care capabilities. Trust and belief may increasingly become part of future therapeutic strategies and regular medicine [92].

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