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Acupuncture-Induced Pain Relief and the Human Brain's Default Mode Network – an Extended View of Central Effects of Acupuncture Analgesia

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Keywords
Acupuncture · CNS · Neurobiology · Default mode network

Summary
As a complementary medical procedure, acupuncture has a significant impact on the treatment of acute and chronic pain. Though the physiological mechanisms behind this method are still unclear, acupuncture has been claimed to rely also on changes in the central nervous system. Recent functional imaging studies indicate that the so-called default mode network (DMN) which consists of cortical midline structures and lateral parietal regions plays an important role in these processes. This brief overview describes the effects of analgesic acupuncture on the DMN architecture. The stronger interplay between systems dedicated to endogenous analgesia (periaqueductal gray), affective processing (anterior cingulate cortex, amygdala), memory (hippocampus), and self-projective thinking (DMN) following this therapy supports the notion that acupuncture is a mind-body therapy which helps to reintegrate important neural dimensions of inner life and to establish psychophysical pain homeostasis.

Schlüsselwörter
Akupunktur · ZNS · Neurobiologie · Default Mode Network

Zusammenfassung
Als komplentäres medizinisches Verfahren hat die Akupunktur einen signifikanten Einfluss auf die Behandlung von akuten und chronischen Schmerzen. Obwohl die physiologischen Mechanismen dieser Methode nach wie vor nicht hinreichend geklärt sind, scheint die Wirkung von Akupunktur auch auf Veränderungen im zentralen Nervensystem zu beruhen. Aktuelle funktionelle Bildgebungsstudien zeigen insbesondere, dass das sogenannte Default Mode Network (DMN), welches kortikale Mittellinienstrukturen und lateral-parietale Regionen umfasst, eine wichtige Rolle in der akupunkturinduzierten Schmerzbeeinflussung spielt. Diese Übersichtsarbeit beschreibt die Wirkung von schmerztherapeutisch intendierter Akupunktur auf die DMN-Architektur. Indem es im Anschluss an erfolgreiche Akupunktursitzungen zu einer stärkeren Wechselwirkung zwischen Systemen der endogenen Analgesie (periaquäduktales Grau), affektiven Prozessierung (anteriorer cingulärer Cortex, Amygdala), Gedächtnisbildung (Hippocampus) und selbst-projektivem Denken (DMN) kommt, mag die Vorstellung naheliegen, dass Akupunktur hilfreich sein kann, die wichtigen neuralen Dimensionen der Innenwelt zu (re)-integrieren und damit eine psychophysische Schmerzhomöostase wiederherzustellen.

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Introduction

Acupuncture has been used in China and other Asian countries for the past 3,000 years. In recent decades, this technique has gained increasing popularity among patients and physicians in the Western world as part of Traditional Chinese Medicine (TCM) [1]. A relatively mature literature suggests that acupuncture and other forms of acustimulation are effective in the short-term management of low back pain, neck pain, and osteoarthritis involving the knee. On the other hand, the 'German Acupuncture Trials' (GERAC), 'Acupuncture in Routine Care Studies' (ARC), and 'Acupuncture Randomized Trials' (ART) have shown that acupuncture and sham or minimal acupuncture were equally effective in reducing chronic pain symptoms [2, 3]. Data on the efficacy of acupuncture for intraoperative analgesia [4], colonoscopy pain, and dental pain are inconclusive. Finally, the effects of acupuncture on postoperative or cancer pain [5] are under debate and, last but not least, depend on the timing of the intervention and the patient's level of consciousness [6]. These results have prompted an ongoing discussion as to whether acupuncture exerts its effects through a placebo response [7]. In this context it has been proposed that acupuncture analgesia is manifested only when the intricate feeling (soreness, numbness, heaviness, and distension) of acupuncture in patients occurs following needle manipulation [8]. Nevertheless, it seems that – at least in some cases – the analgesic response observed during genuine acupuncture cannot be exclusively explained by a placebo effect and does not occur equally following sham acupuncture.

Peripheral Effects of Acupuncture Analgesia

The mechanism of acupuncture analgesia (AA) itself has been widely explored since the 1970s. AA is a manifestation of integrative processes at different levels in the peripheral and central nervous system between afferent impulses from pain regions and impulses from acupoints. First, in manual acupuncture, all types of afferent fibers (Aβ, Aδ and C) are activated. Second, many brain nuclei composing a complicated network are involved in processing acupuncture analgesia, including mainly the nucleus raphe magnus, periaqueductal gray, locus coeruleus, arcuate nucleus, preoptic area, nucleus submedius, habenular nucleus, accumbens nucleus, caudate nucleus, septal area, and amygdala. Early studies focussed on the relationship between acupuncture and endogenous opiates like β-endorphin, enkephalin, endomorphin, and dynorphin [9]. Thus, before 1990, most experts had agreed on the concept, based on animal models, that lower frequency electroacupuncture (EA) stimulates the release of β-endorphin, enkephalin, and endomorphin, which in turn activates the μ- and δ-opioid receptors, and that higher frequency EA stimulates dynorphin which activates the κ-opioid receptor. Results from experiments on the anti-hyperalgesia effect of EA have raised a new issue about the influences of EA on receptors to excitatory amino acids in the spinal cord level, because various studies have shown that these receptors play a role in the mechanism of AA. Since the late 1990s, research has turned to the different analgesic effects of EA between normal and hyperalgesic animal models as different pain conditions and types seem to respond differently to EA. Research on the autonomic nervous system (ANS) indicates its connection with acupuncture. The inflammatory reflex (via the ANS) might be a crucial component of anti-hyperalgesia elicited by acupuncture, and this reflex, which regulates the immune system in the organism [10], can elucidate not only the mechanism of AA, but also the mechanism of acupuncture applied to other inflammatory conditions.

Diverse other signal molecules contribute to mediating acupuncture analgesia, such as glutamate, 5-hydroxytryptamine, nitric oxide (NO) [11], adenosine [12] and cholecystokinin (CCK) octapeptide (e.g. CCK-8 antagonises AA). Furthermore, the individual differences of AA are associated with inherited genetic factors and the density of CCK receptors. One should remember here that the balance between the cholecystokinergic and opioidergic systems is crucial in placebo responsiveness to pain [13], and one might speculate about the presence of CCK type-2 receptor hyperactivity in acupuncture non-responders.

PTX-sensitive Gi/o protein- and MAP kinase-mediated signal pathways as well as NF-κB, c-fos, and c-jun also play important roles in EA analgesia. The effects of acupuncture on central glia metabolism in mental disorders are still under debate [14]. Moreover, EA analgesia is likely associated with its counter-regulation to spinal glial activation [15–18]. More recently, besides (neuro)transmitters like serotonin and cytokines indicating psycho-neuro-endocrino-immunological links [19], especially nerve growth factors have also been identified as possible mediators for specific acupuncture effects [20, 21].

Central Effects of Acupuncture Analgesia and the Default Mode Network

Restoring the patients' psychophysical equilibrium is one cornerstone of complementary medicine. Acupuncture is a prime example for such a holistic mind-body approach [22] and its undeniable clinical outcome in pain relief cannot solely be explained by peripheral effects alone. At present, functional neuroimaging studies via positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), in particular, enable us to analyze the responses of the cortex to acupuncture on the living human body. However, the results of these experiments are still controversial.

Over the last decade, research especially on the human brain's resting state and its relevance for disease has become one of the major topics in modern neuroscience [23, 24]. The intrinsic neural activity during a task-free period does not reflect random background noise, but represents a complex and energy-consuming system which consists of the prefrontal cortex, posterior cingulate cortex, and precuneus as well as lateral parietal and temporal regions [25–27]. Activation within this so-called default mode network (DMN) is decreased by externally oriented attention, but active whenever the organism comes to focus on its own inner status – e.g during a resting state, remembering the past, prospection, and reasoning about thoughts and feelings [28–30]. Synoptically describable as introspective and self-projective in the broadest sense, these processes seem to establish a neural 'self' in terms of a stable perspective of the individual in relation to its environment [31, 32].

Having said this, it is intuitively clear that a disruption of the integrity of the DMN caused by exo- and endogenous noxa such as pain will affect the individual's inner homeostatis and its ability to properly regulate internal experiences like body states, feelings, and emotions, which is especially true for chronic pain conditions [33, 34]. Very current evidence from functional imaging studies supports the position that acupuncture influences the human brain's resting state and changes the functional architecture of the DMN.

In this context, genuine acupuncture seems to more strongly functionally interconnect the DMN and regions linked to the anti-nociceptive, affective and mnemonic dimension of pain processing. As shown by Zyloney et al. [35], EA leads to enhanced functional connectivity between precuneus, which shows the highest glucose consumption within the DMN, and periaqueductal gray [31]. The former is related to self-referential processing, the latter plays an important role in endogenous analgesia and is stimulated by AA [8, 36–39]. Furthermore, acupuncture leads to a stronger interplay between DMN, anterior cingulate cortex (ACC) [40], and amygdala [41]. These regions are involved in the emotional dimension of painful experiences [42] in a gender-related way [43]. Activated by negative affect, pain, and cognitive control, the dorsal ACC/anterior middle cingulate is a neural hub [44] which is responsible for expressing affect and executing goal-directed behavior [45]. The amygdala is also activated by aversive stimuli such as pain and subserves several cognitive processes relevant for pain, such as the guidance of attention, emotional learning, and memory retrieval [46].

The hippocampus, which is of particular importance for mnemonic functions, also seems to be involved in the central effects of acupuncture [41]. Increased connectivity between the hippocampus and other regions of the DMN following acupuncture was associated with decreased sympathetic and increased parasympathetic modulation, which might explain the general relaxation and pain relief caused by this kind of treatment [47–51].

However, not only functional connectivity but also the activation pattern of the DMN is influenced by acupuncture. With reference to its typical response to external stimulation, DMN activity was diminished during needling. Interestingly, acupuncture seems to influence the extent of this deactivation. Bai et al. [52] and Hui et al. [53] report that genuine acupuncture leads to stronger DMN deactivation than sham acupuncture or tactile stimulation [54]. This finding calls for research on the clinical impact of acupuncture on diseases that are associated with attenuated DMN deactivation in response to an external task such as depression [33, 34, 55]. Indeed, preliminary results of recent studies indicate a positive effect on at least certain mental [56, 57] and neurological disorders [58].

Furthermore, when genuine acupuncture causes sharp pain, DMN deactivation was attenuated in comparison with cases of acupuncture without pain [53]. If attention to the stimulus solely accounted for the neural response, DMN deactivation would probably be stronger during painful needling than during its non-painful equivalent. This finding is remarkable because it provides further evidence for the claim that attentional processes do not fully explain DMN deactivation elicited by acupuncture.

In contrast to the aforementioned findings, Napadow et al. [59] found reduced DMN deactivation during genuine acupuncture as compared to sham acupuncture. The limited number of studies and partly contradictory findings should encourage further research.

Interestingly, the main effects of acupuncture seem to be specific to certain acupoints [60]. As shown by Liu et al. [61], acupuncture at GB-37, which is one of the important acupoints used to treat eye diseases based on TCM, led to enhanced functional connectivity between the DMN and visual areas. In contrast, acupuncture at KI-8, which is related to menstrual pain, irregular menstruation, and gonalgia, led to a stronger interplay between DMN, the hippocampus, and insula. In another study, the partial correlation approach was utilized to investigate whether or not EA at 3 acupoints (GB-37, BL-60, and KI-8) and 1 sham point on the left leg modulated the DMN and how the intrinsic connectivity of the DMN changed. The results indicate that the DMN could be modulated based on EA, and that different modulation patterns of the brain are time-dependent deployed by distinct acupuncture points [62]. Knowing that the posterior cingulate cortex and precuneus (PCC/pC) strongly interact with other nodes during the pre- and post-stimulation states, the correlation between the PCC/pC and ACC though was interrupted in these states. The orbital prefrontal cortex negatively interacted with the left medial temporal cortex (lMTC) after stimulation of the mentioned acupoints [63].

Conclusion

After more than 40 years of scientific acupuncture research, there are still many puzzles left to be solved regarding the mechanism of AA [8, 64–66]. It is recommendable for future clinical trials to at least include potential biomarkers of acupuncture, e.g. measures of the autonomic nervous system function, in order to verify that acupuncture and sham acupuncture are different despite similar clinical effects [67].

Although preliminary, the neurobiological findings of an enhanced functional connectivity between the DMN and hippocampus, periaqueductal gray, amygdala, and anterior cingulate in particular suggest that genuine acupuncture (but not sham acupuncture) is a mind-body therapy that reintegrates several aspects of inner life such as body states, emotions, memory, and self-projective thinking and restores the unity between the body and self. The results of the studies reviewed in this article show that pain caused by needling attenuates the deactivation of the aformentioned brain regions. Furthermore, there is first correlative evidence for the specificity of DMN connectivity to the stimulation of different acupoints. Even if one argues that acupuncture is 'only' a placebo procedure based on sensoric input, the aformentioned imaging results reinforce the significance of physical touch for inner balance. Thus, acupuncture might lead to an experience of psychophysical wholeness which is one feature of true health. It remains an open question, however, whether and, if so, how the dosage of the acupuncture-stimuli influences the intrinsic connectivity of the human brain's default mode. Moreover, the neurobiological underpinnings of long-term effects of acupuncture remain still unclear and are worth to be addressed by future imaging studies.

Disclosure Statement

The authors declare no conflict of interest.

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