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Review

Effects of acupuncture on the brain hemodynamics

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ABSTRACT

Acupuncture therapy has been applied to various psychiatric diseases and chronic pain since acupuncture stimulation might affect brain activity. From this point of view, we investigated the effects of acupuncture on autonomic nervous system and brain hemodynamics in human subjects using ECGs, EEGs and near-infrared spectroscopy (NIRS). Our previous studies reported that changes in parasympathetic nervous activity were correlated with number of de-qi sensations during acupuncture manipulation. Furthermore, these autonomic changes were correlated with EEG spectral changes. These results are consistent with the suggestion that autonomic changes induced by needle manipulation inducing specific de-qi sensations might be mediated through the central nervous system, especially through the forebrain as shown in EEG changes, and are beneficial to relieve chronic pain by inhibiting sympathetic nervous activity. The NIRS results indicated that acupuncture stimulation with de-qi sensation significantly decreased activity in the supplementary motor complex (SMC) and dorsomedial prefrontal cortex (DMPFC). Based on these results, we review that hyperactivity in the SMC is associated with dystonia and chronic pain, and that in the DMPFC is associated with various psychiatric diseases with socio-emotional disturbances such as schizophrenia, attention deficit hyperactive disorder, etc. These findings along with the previous studies suggest that acupuncture with de-qi sensation might be effective to treat the various diseases in which hyperactivity in the SMA and DMPFC is suspected of playing a role.

Contents

1. Introduction

Acupuncture has been used for more than three thousands of years to treat a wide variety of disorders, including cardiovascular, psychiatric diseases, chronic and acute pain, etc., but its mechanism of action are not well understood. The process of acupuncture therapy includes 2 main steps; the first is puncture of the skin with a needle, and the second is subsequent manipulation of this needle. The acupuncture manipulation stimulates nerve receptors both directly and indirectly through mechanical coupling via the connective tissue surrounding the needle (Langevin et al., 2002). In general, this acupuncture manipulation induces autonomic, endocrine and systemic behavioral responses. These empirical results suggest that acupuncture therapy beneficially affects a whole body even if it stimulates only limited sites of the body using fine needles (Sandberg et al., 2003; Samuels et al., 2008; Kim et al., 2009). These findings further suggest that acupuncture exerts its effect through not only local reflexes but also through the central nervous system. Indeed, recent studies reported that acupuncture affected brain activity

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(Esch et al., 2004; Hui et al., 2005; Sakai et al., 2007; Fang et al., 2008; Samuels et al., 2008).

In this paper, we review autonomic and cerebral hemodynamic changes induced by acupuncture manipulation based on our recent findings, and discuss about a possibility that acupuncture can be applied to various diseases related to the central nervous system.

2. Specific acupuncture sensation “de-qi” and its correlation with autonomic functions

Clinical acupuncturists are required to induce a specific sensation so called “hibiki” in Japanese or “de-qi” in Chinese. Effective acupuncture treatment usually induces de-qi sensations described as aching, soreness, pressure, heaviness, fullness, warmth, cooling, numbness, tingling, or dull pain around the acupuncture point. Recent noninvasive imaging studies reported that de-qi sensations are particularly important among the different effects of acupuncture stimulation when they occur in the central nervous system. For example, peripheral pain induced limbic activation, while activity in the limbic system decreased when a de-qi sensation was achieved by acupuncture treatment (Hui et al., 2005).

It is generally believed that de-qi is essential for producing acupuncture analgesia and anesthesia. Chiang et al (1973) showed correlations between analgesia and de-qi sensations (of numbness, fullness, and sometimes soreness). The results suggest that de-qi is an indispensable component of acupuncture analgesia. Takeda and Wessel (1994) investigated the effect of real and sham acupuncture on osteoarthritis (OA), and found that the experience of de-qi can be used as a predictor for significant improvement. We investigated relationships among specific sensations induced by acupuncture manipulation, effects on sympathetic and parasympathetic autonomic functions, and EEG changes (Sakai et al., 2007). An acupuncture needle was inserted into the right trapezius muscle of the subjects, and acupuncture manipulation was repeated to induce specific acupuncture sensation repeatedly while the needle was left in the muscle. Acupuncture manipulation significantly decreased heart rate (HR), and increased systolic blood pressure (SBP). Spectral analysis indicated that acupuncture manipulation significantly decreased low-frequency components (LF) of both HR variability (HRV) and SBP variability (SBPV), and significantly reduced ratio of LF to high frequency component (HF) of HRV (LF/HF, index of sympathetic activity). Furthermore, there was a significant negative correlation between changes in LF/HF ratio of HRV and the number of specific acupuncture sensations reported, and a significant positive correlation between HF (index of parasympathetic activity) of HRV and the number of acupuncture sensations (Fig. 1). Analyses of EEG data indicated that acupuncture manipulation nonspecifically increased power of all spectral bands, especially for theta and alpha band of EEG (Fig. 2 for theta band). Furthermore, changes in HF and total power (overall activity of the autonomic nervous system) of HRV were positively correlated with changes in theta, alpha, and gamma power, while changes in LF of SBPV and LF/HF of HRV were negatively correlated with changes in power of all spectral bands. These results are consistent with the suggestion that autonomic changes induced by acupuncture manipulation inducing specific de-qi sensations might be mediated through the central nervous system, especially through the forebrain as shown in EEG changes. These findings suggest that acupuncture stimulation is beneficial to relieve chronic pain by inhibiting sympathetic nervous activity through the forebrain.

However, other studies showed no significantly difference between real and sham acupuncture treatments, and further concluded that de-qi sensation did not result in marked effect (e.g., Scharf et al. 2006). Furthermore, except acupuncture analgesia and anesthesia to acute pain, evidence indicating a significant relationship between de-qi and therapeutic effect has been rare (Kong et al. 2007). These findings might suggest that therapeutic effects of de-qi sensation might be specific to pain. Nevertheless, some of studies reporting that there were no significant differences in therapeutic effects between real and sham acupuncture did not check presence of de-qi sensation in the sham acupuncture (e.g., Linde et al. 2010). Further detailed studies are required to examine these discrepancies.

3. Hemodynamic changes induced by acupuncture with de-qi sensation

It is reported that stimulation of specific points on the body surfaces (called “acupoints”) during acupuncture therapy could effectively ameliorate general pain, visceral pain, psychoneurotic disorders, as well as other ailments (Esch et al., 2004). However, stimulation of both acupoints and non-acupoints has been shown to induce de-qi sensations. In addition, there was no apparent difference in brain activity between these two locations (Fang et al., 2008). Furthermore, the exact anatomical locations of the acupoints have not been clearly identified.

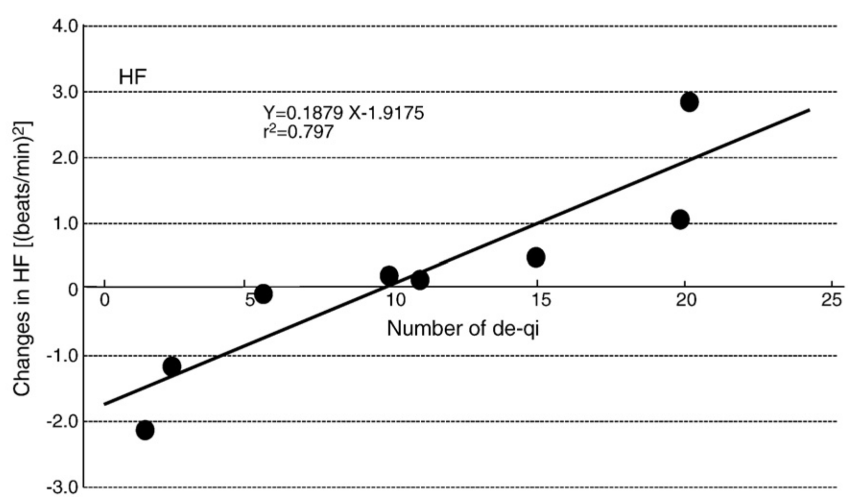

Fig. 1. Correlation between number of de-qi sensation and high frequency (HF) component of heart rate (HR) variability. Subjects were required to press a button when they felt de-qi sensation during acupuncture manipulation. The ECGs were recorded before, during and after acupuncture manipulation, and HR variability was analyzed. Note a significant positive correlation between number of de-qi sensation and changes in HF component. HF component of HR variability reflects the activity of parasympathetic nervous system. The results indicate de-qi sensation and parasympathetic nervous activity is highly correlated. Ordinate, changes in HF component of HR variability between pre-acupuncture control and post-acupuncture period; abscissa, number of button pressing indicating de-qi. The figure is modified from that by Sakai et al. (2007).

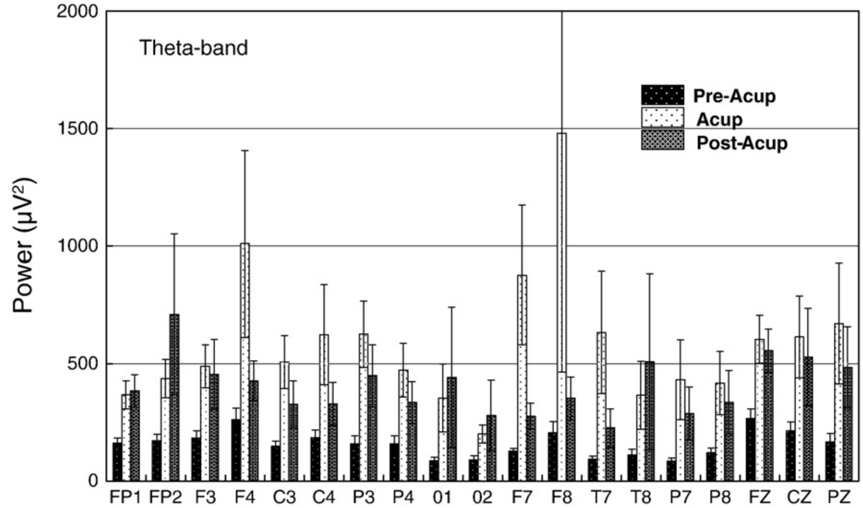

Fig. 2. Changes in θ band power of EEGs by acupuncture stimulation. The EEGs were recorded before, during and after acupuncture manipulation. The results indicate θ power increased during acupuncture stimulation and post-acupuncture stimulation period. Abscissa indicates EEG channels recorded according to the international 10–20 system. Pre-Acup, control period before acupuncture stimulation; Acup, acupuncture stimulation period; Post-Acup, period after acupuncture stimulation. The figure is modified from that by Sakai et al. (2007).

The term "trigger points" (TPs), on the other hand, has been coined in the West, instead of acupoints, when referring to the points targeted during acupuncture needling. Identified TPs (71%) correlated anatomically with acupoints (Melzack et al., 1977). Acupuncture needling at TPs is widely utilized for the treatment for myofascial pain syndrome (MPS), fibromyalgia, chronic fatigue, secondary muscular strain accompanying other diseases, as well as other conditions. TPs are specific sites on the body surface exhibiting tenderness, which is one of the characteristics of MPS. It is reported that a sensation similar to de-qi was obtained by acupuncture stimulation at TPs (Kong et al., 2001). However, the effect of de-qi sensations resulting from acupuncture stimulation at TPs on the central nervous system has not been investigated.

We recently investigated relations among acupuncture stimulation on TPs, de-qi sensation and brain activity (Takamoto et al., 2007, in press). Acupuncture needles were manipulated using a standard vertical back-and-forth movement between the 2 points 1.0 and 1.5 cm from the skin (length of the movements, 0.5 cm; 1 movement/sec) for 15 s, followed by a resting period 60 s. The needle remained there during the resting period. The procedure was repeated eight giving eight cycles. Brain hemodynamic responses were recorded using functional near-infrared spectroscopy (fNIRS) during acupuncture stimulation at TPs and non-TPs of the right extensor muscle in the forearm. Changes in the Hb concentration [Oxy-Hb, Deoxy-Hb, and Total-Hb (Oxy-Hb ± Deoxy-Hb)] from the baseline were estimated based on a modified Lambert–Beer law (Seiyama et al., 1988; Wray et al., 1988). During fNIRS recording, the subjects were asked to report their subjective de-qi sensation by pressing a button. The behavioral results indicated that acupuncture stimulation to the TPs always induced de-qi sensations while stimulation to non-TPs only sometimes induced de-qi sensations.

The fNIRS results indicated that Oxy-Hb concentration was decreased in the supplementary motor area (SMA), pre-supplementary motor area (pre-SMA) and anterior dorsomedial prefrontal cortex (DMPFC) during acupuncture stimulation only if de-qi sensation was induced regardless of the stimulation sites (TPs or non-TPs) (Fig. 3). Fig. 4 shows the T-value maps of the Oxy-Hb data following non-TP acupuncture manipulation (A) and TP acupuncture

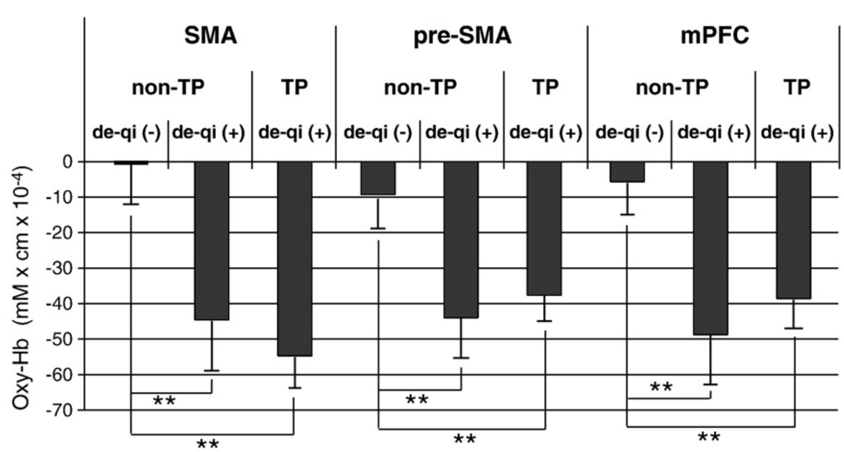

Fig. 3. Effects of de-qi sensation on cerebral hemodynamic responses (changes in Oxy-Hb concentration). The hemodynamic changes were compared among three conditions (acupuncture stimulation to TP and non-TP. The non-TP condition was further divided into two conditions, with and without de-qi sensation). The Oxy-Hb concentration in the SMA, pre-SMA, and mPFC decreased significantly during non-TP and TP stimulation with de-qi sensation when compared with non-TP stimulation without de-qi sensation. Data are expressed as mean ± SEM. **, $p < 0.01$. non-TP, acupuncture stimulation to non-trigger point; TP, acupuncture stimulation to trigger point. de-qi(+), acupuncture stimulation with de-qi sensation; de-qi(-), acupuncture stimulation without de-qi sensation. The figure is modified from that by Takamoto et al. (in press).

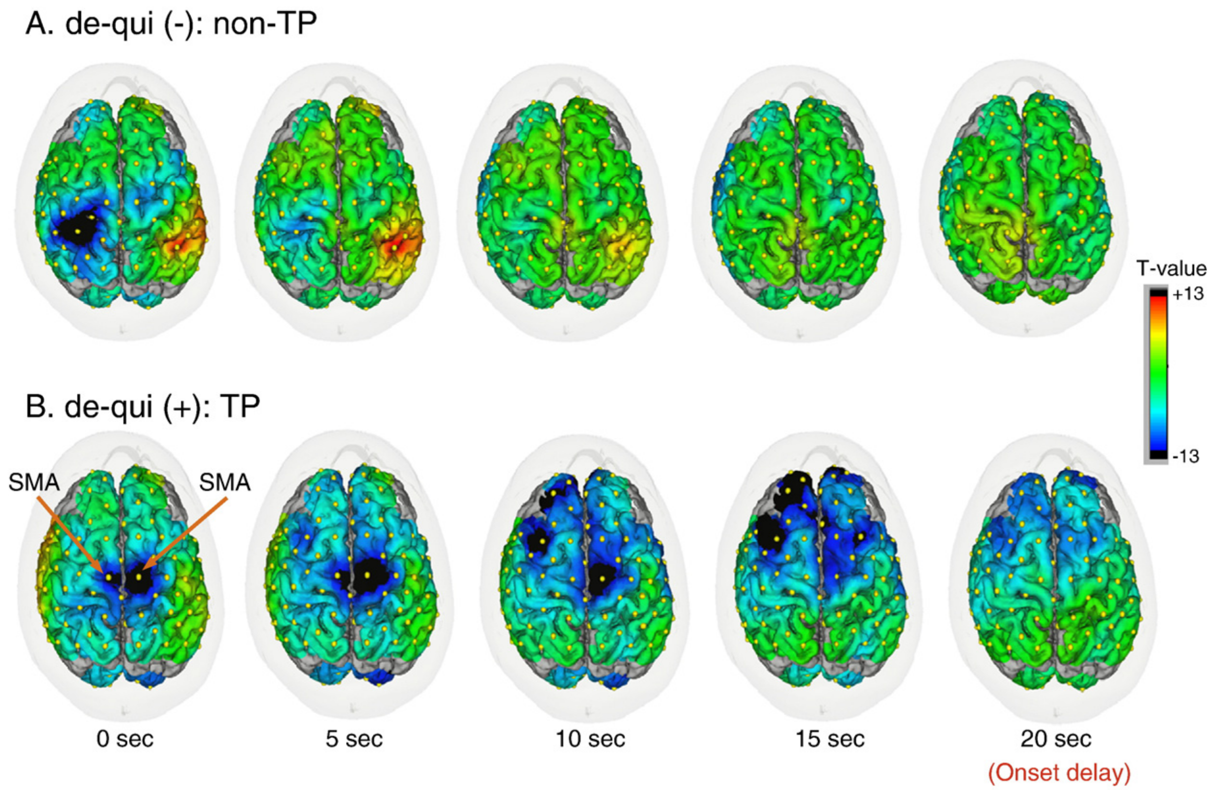

Fig. 4. Examples of T-value maps of hemodynamic responses in non-TP stimulation without de-qi sensation (A) and TP stimulation with de-qi sensation (B) in a typical one subject. Note that the T values decreased prominently in the bilateral SMA, and that the brain regions with lower negative T values moved from the SMA to the more anterior parts of the prefrontal cortex.

manipulation (B) in a typical one subject. The hemodynamic responses were statistically analyzed using a general linear model (GLM) and a boxcar function approximating the hemodynamic responses (Takeuchi et al., 2009; Takamoto et al., in press). In this analysis, the start of the boxcar function was gradually delayed up to 20 s. Negative T-values indicated that the Oxy-Hb concentration significantly decreased from the measured baseline level. In TP stimulation, the T values decreased to the greatest extent in the SMA when a 0 s delay was applied. When the delay was gradually increased up to 20 s, we observed that the T values in the SMA decreased most when the start of the boxcar function was delayed by 10 s. It is noted that this subject felt a de-qi sensation an average of 10 s after the beginning of the TP needling manipulation. That is, the latency of the moment when the subject felt a de-qi sensation was coincident with the delay of the boxcar function when the T value showed the largest decrease in the GLM analysis. This suggests that hemodynamic responses were approximated by a boxcar function once the subject began to feel a de-qi sensation.

Furthermore, onset latencies of these hemodynamic responses in the SMA were significantly correlated with those of subjective de-qi sensations (Takamoto et al., in press). These results suggest that the effects of acupuncture stimulation with de-qi sensation were mediated partly through the central nervous system. In the next sections, we discuss about a possibility that acupuncture manipulation with de-qi sensation could be applied to various psychiatric diseases as well as chronic pain because of its inhibitory effects on the supplementary motor complex (SMC) and medial prefrontal cortex (MPFC).

4. SMC responses to acupuncture manipulation

The SMC including the SMA and pre-SMA is located on the medial aspect of the brain in humans (Picard and Strick, 2001). Previous studies reported that the SMC was implicated in intentional or voluntary action (see reviews by Haggard, 2008; Nachev et al., 2009; Tanji et al., 2009). Lesions of the SMC in humans lead to alien-limb syndrome in which patients demonstrate involuntary actions such as grasping nearby objects without any intention to do so (Feinberg, et al., 1992). Some other patient demonstrates utilization behavior in which they unable to resist the impulse to use an object that has been placed within their reach, even when the object is not needed (Ghosh and Dutt, 2010). Hyperactivity in the SMC has been observed in tardive dystonia (Thobois et al., 2008), writer's cramp, or focal hand dystonia (Murase et al., 2005) and epilepsy associated with ADHD (Inaba et al., 2000). To reduce hyperactivity in these patients' SMC, GPi stimulation (Thobois et al., 2008) or subthreshold low-frequency transcranial magnetic stimulation (TMS) (Murase et al., 2005) has been applied. These findings suggest that inhibition of the SMC induced by acupuncture stimulation with de-qi sensation might be effective for therapy of these patients, although there is no such a report.

Furthermore, the SMA is reported to be implicated in not only motor control but also somatosensory (Stancak et al., 2007) and/or pain-related (Farrell et al., 2005.) information processing; 1) noxious stimulation such as heat stimulation increased SMA activity (Hsieh et al. 1995; Kwan et al., 2000; Farrell et al., 2005), 2) SMA activity was correlated with intensity of pain (Coghill et al., 1999) or an unpleasant sensation (Drzezqa et al., 2001), 3) SMA activity increased in patients experiencing phantom pain (Dettmers et al., 2001; Willoch et al., 2000) or allodynia (Peyron et al., 2004), and 4) the SMA receives information from the anterior cingulate gyrus, which is involved in the emotional evaluation of pain (Morecraft and Van-Hoesen, 1992, 1993; Wang et al., 2001). These results suggest that inhibition of the SMA activity induced analgesia. Therefore, analgesia induced by acupuncture with de-qi sensation might be mediated through its inhibitory effects on the SMA. In addition, our findings suggest that de-qi sensations predict the success of acupuncture therapy.

5. MPFC response to acupuncture manipulation

The MPFC contributes to various higher brain functions such as decision making for goal-directed behaviors (Rushworth et al., 2005; Volz et al., 2006; Rushworth and Behrens, 2008; Venkatraman et al., 2009; Balleine and O'Doherty, 2010), outcome evaluation (Bush et al., 2002; Gehring and Willoughby, 2002), a form of reasoning (Volle et al., 2010), evaluation of stimulus valence and emotional context (Viinikainen et al., 2009; Zaretsky et al., 2009), regulation of emotions (Etkin et al., 2006; Modinos et al., in press) and social interactions (Amodio and Frith, 2006; Behrens et al., 2008, 2009). These findings reasonably suggest that human appropriate and adaptive behaviors in various psychological situations depend on normal functioning of the MPFC, and consequently that activity changes in the MPFC would induce various behavioral disturbances. Consistently, activity in the MPFC was increased in schizophrenia (Taylor et al., 2007), social phobia (Blair et al., 2008), panic disorder (Sakai et al., 2006), attention deficit hyperactive disorder (Fassbender et al., 2009), etc. Previous clinical studies reported that acupuncture has been applied to some of these disorders (Rathbone and Xia, 2005; Pilkington et al., 2007). As mentioned above, acupuncture manipulation with de-qi sensation reduced activity in the DMPFC in our previous study (Takamoto et al., in press). Therefore, therapeutic effects of acupuncture on these disorders might be attributed to inhibitory effects of acupuncture stimulation on DMPFC activity.

Furthermore, neuropsychological studies reported that activity in the MPFC including the DMPFC was increased in the resting period, and this resting state activity has been termed the default mode of brain activity (Raichle et al., 2001; Sonuga-Barke and Castellanos, 2007). Obstinate and/or hyper default mode activity is observed in a stressed condition (Gianaros et al., 2009) and various psychiatric disorders such as attention deficit/hyperactivity disorder (ADHD) (Sonuga-Barke and Castellanos, 2007; Fassbender et al., 2009), and schizophrenia (Zhou et al., 2007), etc. (see a review by Broyd et al., 2009). These obstinate activities in the MPFC might interfere with brain functions for goal-directed behaviors (Sonuga-Barke and Castellanos, 2007). Therefore, acupuncture stimulation with de-qi sensation, which reduces activity in the DMPFC, might be also effective to treat these disorders.

On the other hand, the DMPFC sends its efferents to the lower level autonomic outflow regions such as the periaqueductal grey and hypothalamus in monkeys (An et al., 1998; Ongür et al., 1998). Previous noninvasive brain imaging studies have reported that activity in the DMPFC is increased by mental and physical stress loading such as that associated with mental arithmetic and exercise, and that activity in the DMPFC is positively correlated with 1) changes in blood ACTH concentration (Liberzon et al., 2007), 2) skin conductance responses, which reflect sympathetic nervous activity (Critchley et al., 2000a), and 3) increase in heart rate (Critchley et al., 2000b, 2003; Williamson et al., 2003; Kimmerly et al., 2005; Macefield et al., 2006). In addition, a noninvasive study reported that the dorsal anterior cingulate cortex (dACC), which has close neuroanatomical connections with the dorsal region of the medial prefrontal cortex, is involved in output to the sympathetic nervous system (Critchley et al., 2003). Furthermore, our recent study reported a direct evidence that changes in Oxy-Hb in the anterior–dorsal region of the MPFC were significantly and negatively correlated with those in parasympathetic nervous activity (Yasui et al., in press). The above findings suggest that the DMPFC is involved in controlling responses of the sympathetic nervous system to various stresses. Therefore, acupuncture stimulation might decrease sympathetic activity and increase parasympathetic activity through its inhibitory effects on DMPFC activity, which might be beneficial to treat chronic pain in which hyperactivity of the sympathetic nervous system is suspected (Janig, 1992; Schott, 1999; Passatore and Roatta, 2006).

6. Conclusions

The NIRS study revealed that acupuncture stimulation reduced Oxy-Hb concentration in the SMA in the human subjects. This suppressive effect might be effective to treat dystonia and chronic pain. Furthermore, acupuncture manipulation decreased sympathetic activity while it increased parasympathetic activity, and it also reduced Oxy-Hb concentration in the DMPFC. Therefore, its inhibitory effects on the sympathetic nervous system might be mediated through its inhibitory effects on the DMPFC. These findings suggest that acupuncture stimulation might be effective to treat chronic pain by affecting pain information processing through its inhibitory effects on SMC activity, and by inhibiting sympathetic nervous activity through its inhibitory effects on DMPFC activity. On the other hand, it has been reported that activity in the DMPFC is increased in various psychiatric diseases with emotional and social disturbances. The present results also suggest that acupuncture could ameliorate these emotional and social disturbances.

Taken together, the present data along with the previous reports suggest that acupuncture stimulation could be effective to treat various brain-mediated disorders, although its transduction mechanisms in the skin or muscles still remain unclear. Further studies are required to elucidate how de-qi sensation is induced during acupuncture stimulation.

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