Higher cortical modulation of pain perception in the human brain: Psychological determinant

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Abstract: Pain perception and its genesis in the human brain have been reviewed recently. In the current article, the reports on pain modulation in the human brain were reviewed from higher cortical regulation, i.e. top-down effect, particularly studied in psychological determinants. Pain modulation can be examined by gene therapy, physical modulation, pharmacological modulation, psychological modulation, and pathophysiological modulation. In psychological modulation, this article examined (a) willed determination, (b) distraction, (c) placebo, (d) hypnosis, (e) meditation, (f) qi-gong, (g) belief, and (h) emotions, respectively, in the brain function for pain modulation. In each, the operational definition, cortical processing, neuroimaging, and pain modulation were systematically deliberated. However, not all studies had featured the brain modulation processing but rather demonstrated potential effects on human pain. In our own studies on the emotional modulation on human pain, we observed that emotions could be induced from music melodies or pictures perception for reduction of tonic human pain, mainly in potentiation of the posterior alpha EEG fields, likely resulted from underneath activities of precuneus in regulation of consciousness, including pain perception. To sum, higher brain functions become the leading edge research in all sciences. How to solve the information bit of thinking and feeling in the brain can be the greatest challenge of human intelligence. Application of higher cortical modulation of human pain and suffering can lead to the progress of social humanity and civilization.

Keywords: pain modulation; brain; will; distraction; placebo; hypnosis; meditation; belief; qi-gong; emotions

1 Introduction

The pain control system in the human brain was early articulated by Wakers and Mayer over 30 years ago^[1], while the physiology of pain and pain modulation described by Fields on the endogenous system^[2] were largely based on small animal research. The early work was largely focused on the brainstem descending system in regulation of nociception.

In the last decade or so, the advent of neuroimaging in

studying human brain functions non-invasively opens up a brand new vista of pain research in experimental healthy subjects and patients inflicted with pain^[3,4]. The activation of pain perception in the human brain has been well reviewed^[5-7] and this article is focused on the pain modulation in the human brain. However, the techniques and modalities for pain modulation cover a wide field, from genetics to mind regulation. In fact, it can be organized in a systematic schema as listed in the following Table 1.

This paper addresses only the class-D. psychological modulation of human pain in the brain. Psychological pain modulation encompasses over inherently across most of pain treatment, either in physical modulation types or pharmacological types. Among them, 8 subtypes were specifically selected for discussion. Since psychological modulation de-

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Table 1. List of pain modulation modalities and techniques

A. Gene Therapy:	Mostly in animal models.
B. Physical M.	1. Massage; 2. Acupuncture; 3. TENS; 4. TMS.
C. Pharmacological M.	1. NSAIDs; 2. Opiates; 3. Anesthetics.
D. Psychological M.	1. Determination; 2. Distraction; 3. Placebo; 4. Hypnosis; 5. Meditation; 6. Qi-gong; 7. Belief; 8. Emotion.
E. Pathophysiological M.	1. Alzheimer's disease; 2. Depression; 3. Schizophrenia.

Note: M: modulation; TENS: transcutaneous electrical neurostimulation; TMS: transcranial magnetic stimulation; NSAIDs: nonsteroidal antiinflammatory drugs.

notes higher cortical function in top-down mechanisms of brain action, it is of special importance and interest.

2 Psychological modulation

2.1 Determination Determination is a willed act, which is focused on endurance and bearing to tolerate pain, such as during child birth in labour pain. Yet, no research paper has been found in this profound higher cortical regulation of human pain in the brain.

However, the protocol of studying self-regulated noxious stimulation vs external stimulation may bear hint to self-determination of pain endurance/coping in the brain. Self-regulated painful stimulation showed increased activation at the perigenual anterior cingulate cortex (ACC), equal activation from both self- and other- activation at the mid-cingulate cortex, and no activation in self- but clear activation by other- at the posterior ACC^[8]. Furthermore, SI was modulated in the

self-regulation but not SII or Insular cortex during noxious perception^[9]. In addition for thermal hyperalgesia, a stronger pain-related activity increase during self-administered stimuli the posterior insula was shown. In contrast, stronger increase to uncontrollable external heat stimuli in prefrontal cortex was noted. All of these studies may help to understand self-regulation of human pain from cognitive strategies^[10].

2.2 Distraction Distraction can be said as the most primitive form in pain regulation, possibly from the dawn of human race. It is based on the act of distraction of attention from painful source or event. On the physiological level, pain as aversive sensation and nociception demand our attention, and brain mechanisms involved in noxious experience are of critical interest. In a study from the intracranial recording of 3 major nociceptive-receiving areas, over primary somatosensory, parasyllian, and cortices medial frontal cortex, during attending for and distraction from noxious laser stimulation was examined. Distraction attenuated the field activity particularly at the parasyllian cortex during pain processing^[11].

The effect of distraction and decreased arousal in pain-related laser-evoked potentials, whose amplitude at vertex, likely of ACC source, was observed to be reduced by 38% during distraction task and by 42% in stage-2 sleep. Thus, distraction can markedly modulate brain function in human pain^[12].

In the human electroencephalography (EEG) study of distraction, its effects on frontal alpha activities related to expectancy of pain indicated that distraction during the expectancy of pain could result from reduced neural desynchronization of fronto-central midline alpha rhythms^[13].

2.3 Placebo As an act of human mind, placebo is defined as an innocuous or inert medication or effort, given as a pill/powder to the control group in experiments for pain modulation. Thus, placebo effect has been concluded by the action of human psyche, through some neurochemical and neurophysiological functions. Pain requires the integration of sensory, cognitive, and affective information. So is this in placebo. Since placebo must result from processes in a higher order, it is influenced by cognitive and affective dimensions of the pain experience.

The study of placebo in human brain has drawn major interest recently. Placebo analgesia is taken as contribution of attention, expectation and reappraisal as 3 basic mechanisms participate in the cognitive modulation of pain^[14]. Placebo analgesia involves the prefrontal and anterior cingulate cortices to exert influence down-ward in the descending control system to modulate the ascending incoming noxious input, largely via activation of the endogenous pain modulatory circuit in the brainstem periaqueductal gray structures^[15]. The endogenous pain control in placebo analgesia encompasses the rostral anterior cingulate cortex (rACC), with bilateral amygdalae and the periaqueductal gray (PAG), riched in opiate receptors. The interactions of these brain areas mediate PIA by way of descending inhibitory mechanism and often in conditioning learning^[16]. Other network of interconnected brain areas has been suggested in PA^[17], including the anterior and posterior insula (A-Ins, P-Ins), dorsal anterior cingulate cortex (DACC), dorsolateral prefrontal cortex (DLPFC), and the supplementary motor area (SMA).

This leads to the contention that PIA treatment may exert 3 stages of pain processing, by (1) expectation of pain relief, (2) modulating pain perception, and (3) distorting pain experience. The effects of PIA may vary by circumstances and individuals. Brain areas of these pivotal role include the prefrontal cortex, ACC, anterior insula, and PAG^[18].

The individual difference in PIA was further supported in that in the placebo responders (nearly 50% of all subjects), regional cerebral blood flow (rCBF) in the medial prefrontal cortex (MPFC), posterior parietal cortex (PPC), and inferior parietal lobe (IPL) increased in PIA, while rCBF in the MPFC, PPC and IPL also increased under the resting conditions without any sensory stimulation. This PET study suggests that placebo analgesia has its effect under the resting conditions. MPFC, IPL and PPC play critical roles in placebo analgesia^[19].

In an intra-individual study, the expectancy combined with innovative selective placebo intervention and pain modulation was shown on the placebo-treated side, with significant differences in the bilateral rACC, lateral prefrontal cortex, right anterior insula, supramarginal gyrus, and left inferior parietal lobule. In addition, significant negative correlation was observed in the bilateral lateral/orbital prefrontal cortex,

rACC, cerebellum, right fusiform, parahippocampus, and pons. Also, decreased activity in pain-sensitive regions such as the thalamus, insula, and ACC suggests that placebo analgesia may be configured through multiple brain pathways and mechanisms^[20].

From a broader perspective, placebo, as expectation of symptom improvement, can have effects on the psychological dimension of physical diseases, such as depression, pain, or even Parkinson's disease. Brain areas in frontal cortical areas, particularly the dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices are associated with rewarding system and emotional regulation capacity^[21].

2.4 Hypnosis: suggestion, dissociation, relaxation, and sleep The original connotation of hypnosis is a state of reversible act in deep sleep by suggestion of induced effect, while suggestion comes from sequential mental process commanded with both physical/mental relaxation and strong dissociation of the sense of pain from body feelings. Hypnotic pain modulation certainly is carried out by the brain functions. However, the interaction complexity of suggestion, distraction, relation, mental transformation, and even light sleep during hypnosis requires indepth and systematic evaluation.

Hypnotic state examined by Positron Emission Tomography (PET) neuroimaging suggests that pleasant states demonstrate activations of a widespread set of cortical areas involving occipital, parietal, precentral, premotor, and ventrolateral prefrontal and ACC as similar to that in mental imagery with relative deactivation of precuneus^[22]. And hypnotic analgesia could induce only 50% of pain perception.

With modulation of the activity in the midcingulate cortex (area 24a') and its connectivity to frontal cortical areas, more extensive networks associated with increased functional connectivity with ACC include (1) left insula, (2) right insula, (3) perigenual cortex, (4) pre-supplementary motor cortex, (5) superior frontal gyrus, (6) right thalamus, (7) right caudate nucleus, (8) midbrain/brainstem^[23].

Given the experimental heat pain stimulation, hypnotic suggestion on modulation of pain unpleasantness induced hypnosis-related decreases in rCBF in the right inferior parietal lobule, the left precuneus, and the posterior cingulate

gyrus, while hypnosis-with-suggestions produced additional widespread increases in rCBF in the frontal cortices on the left side^[24]. Increased rCBF at the occipital area was associated imagery during hypnosis. Modulations of pain expectation and pain affects largely attenuate pain perception, via the ACC and associated suffering and autonomic arousal^[25].

Another study attempted to correlate the morphology of corpus callosum with the hypnotizability and efficacy of pain control. In that study, the highly hypnotizable subjects showing effective attentional and inhibitory capabilities had a significant enlargement of rostrum by nearly 32%, a corpus callosum area implicated in the allocation of attention and transfer of information between prefrontal cortices^[26], an interesting hypothesis in hypnotic analgesia.

Finally, Derbyshire *et al.* have demonstrated the bi-direction effect of hypnosis in the human brain. Many patients with chronic pain are burdened with significant psychological uncertainty and unproven physical causes. Hypnotical pain, such as painful experience induced through suggestion and imagery by hypnosis, activated areas within thalamus and ACC, insula, prefrontal, and parietal cortices^[27], in the conventional pain matrix. In a further study of fibromyalgia patients^[28], both suggestion with or without hypnosis could activate similar brain regions in the midbrain, cerebellum, thalamus, midcingulate, primary and secondary sensory, inferior parietal, insula and prefrontal cortices, which correlated with reported changes. However, suggestion with hypnosis activated additional cerebellum, anterior midcingulate cortex, anterior and posterior insula, and the inferior parietal cortex.

2.5 Meditation As a mental act, meditation describes the continuous and profound contemplation or musing on subject or series of subjects of a deep or obstruce nature. Often, it is associated with religion during contemplation of spiritual matures or philosophical issues. As in religion, meditation is often associated with doctrine of practices. Among them, Christian chants are known in the West, while citation of Budha sutra, silent Zen meditation, or body transformation in Yogi are appreciated in the East. How these exercises alter brain functions is of scientific interest in pursuit of higher brain modulation of human pain. From a PET study of yoga

nidra relaxation meditation, meditation was to activate a relatively increased perfusion in the sensory-imagery system (hippocampus and sensory and higher order association regions) along with decreased perfusion in the executive system (dorsolateral prefrontal cortex, anterior cingulate gyrus, striatum, thalamus, pons, and cerebellum). During meditation, increased striatal dopamine binding to D2 receptors in striatum indicated the involvement of dopaminergic system in human meditation. Furthermore, meditation of mental self during self-reference task activated medial prefrontal-precuneus/posterior cingulate cortex, thalamus, and cerebellum as in covert memory retrieval^[29].

In a report on how meditation affects the brain responses to pain, the activities of thalamus, prefrontal cortex and total brain in the long-term TM practitioners were reduced to 50% of those in the control subjects without meditation practice and a 25% reduction of pain rating was shown a thermal pain study^[30]. In the study of a Yogi Master^[31], MEG alpha-activity was much increased over occipital, parietal and temporal regions, and evoked MEF activity at SI and SII were weak during meditation, while fMRI showed marked changes in thalamus, SII-insula (mainly the insula) and cingulate cortex. However, no study of pain was conducted in this report.

Aside from these 2 limited pain-related meditation reports, there still lacks in-depth research in this field. Nevertheless, the nature of meditation in human brain becomes a pivot research focus in the higher brain regulatory function.

In the most comprehensive review^[32], EEG studies indicated a proficiency of meditation in theta and alpha but a overall slowing after meditation. Sensory ERP studies indicated meditation-related changes in some peak latency and amplitude. Cognitive ERP indicated attention allocation under meditation. fMRI studies, however, showed increased cerebral blood flow at certain brain areas. As a whole, meditation has been shown to exert some specific brain modulations.

Practice seems to make difference. In a mindful meditation of breathing and mental effort, meditators shower higher activation in the rACC and mPFC, with the formed taken as stronger ability for distraction from external event and the latter the higher capacity in engagement of internal event^[33].

In studying the compassion meditation^[34], a loving-kindness-compassion meditation state and a form of meditation enhance affective processing, in particular in response to sounds of distress, the novice and expert showed distinct brain activation patterns. The distress of the emotional sounds was associated with increased pupil diameter and activation of limbic insula and cingulate cortices, while the experts showed increased activation in amygdala, right temporo-parietal junction (TPJ), and right posterior superior temporal sulcus (pSTS) in response externally imposed distress.

2.6 Qi-gong Qi-gong, literally means “breath-exercise” as a long tradition in martial art and a cultural symbol of China, has developed into a health regime. Some say that it takes years to practice qi-gong. Mental regulation accounts far more than the body exercise and can be considered as a higher brain regulatory function. Broadly, it refers to the type of exercise that manages the health of mind, body and breath.

In the rare scientific research on the brain study of pain reaction under state of qi-gong^[35], 4 masters with over 30 years of qi-gong discipline were examined before and 15 min after qi-gong practicing under noxious potassium infiltration on the arm. Noxious painful stimulation activated the classical “pain matrix”: SI and SII-insula regions, many other Brodmann areas, the cingulate cortex, the thalamus, and the cerebellum. The practice of qi-gong could significantly reduce the pain-related SII and insular activation by 66%. Given no control subjects were compared, the central effects of qi-gong remain to be fully validated.

2.7 Belief Belief is often a vague idea temporary or persist in mind so that some confidence is placed. Belief also holds that certain cognitive content shall be true in subjective contention. It is the psychological state in which one holds a proposition or premise to be true. Religious belief in God and religious ritual in praying certainly have been inheritive in human races and in all cultures for centuries.

Brain rewording system is shown to be related to the firm religious praying, such that interpersonal trust and loving can activate certain brain areas^[36]. The power of praying for God in the brain has been recently reported^[37], and the activated brain areas include (A) precuneus, (B) temporo-

parietal junction, (C) anterior medial prefrontal cortex, (D) temporopolar region. These regions are in a greater context of belief and religion. Religion has been grounded into religious belief on the perceived level of involvement, the perceived emotion, and the doctrinal/experiential religious knowledge. Each may also involve the individual’s intent and emotion, abstract semantics, and imagery, while the neuroimaging results have been interpreted as to support contemporary psychological theories that ground religious belief within evolutionary adaptive cognitive functions^[38].

It has been reported that brain areas in the dorsal medial prefrontal cortex (dmPFC) exert influence of religious belief in Christian while those in the ventral medial prefrontal cortex (vmPFC) are responsible for non-religious belief on self-reference^[39]. Furthermore, Chinese Buddhist doctrine of no-self is characterized by weakened neural coding of stimulus self-relatedness in the vmPFC, and yet enhanced evaluative processes in the dmPFC by monitoring the conflict between the doctrine of no-self and self-focus thinking in belief^[40].

Belief is considered as a probability of confidence in exerting behavior. In the confidence of expectancy of pain modulation of emotional distress, brain areas in right anterior insula, posterior midcingulate and inferior parietal cortices during the anticipation of pain predict a greater influence of anticipation cues on pain perception, whereas activity in right inferior parietal cortex predicts a decreased influence of anticipatory cues^[41].

In studying the effect of religious conviction *vs* non-conformist during pain modulation^[42], the right VLPFC was considered specific to the religious conviction while the ventral midbrain area activation was associated with fondness of the picture along, during pain modulation. This result can be used to contend that religious belief is involved in pain-regulatory brain processes.

2.8 Emotions All of the above higher cortical regulation modalities represent some deliberate cognitive, cool, strategies in pain modulation. Equally, higher cortical regulation shall also address some more innate and inherent affective, hot, strategies in human pain modulation. Emotion can be easily defined as any strong feeling aroused by external stimuli and internal perception, involving subjective qualities, co-

vert brain processes with bodily reaction, and overt or likely overt facial expressions/bodily gestures. In general, emotion is a mental and physiological state, often associated with a wide variety of feelings, thoughts, and behaviour, along with mood, temperament, personality, and disposition.

Emotional modulation of human pain in the human brain can be reviewed in several major reports^[43-45]. In our recent studies, we have examined the effect of music and pictures of emotional tones on human pain modulation. Females are considered more sensitive to emotional effects than male subjects. In the music study, we examined 15 university female subjects when they listened to the violin concerto of the famed Chinese folk music “Butterfly Lovers” in a fast episode vs a slow melody. The fast melody was rated happy, free, and light while the slow melody as sad, heavy, *etc.* (Fig. 1)^[46].

However, both melodies showed pain modulation in a tonic thermal pain model. Apparently, both happy and sad music can modulate human pain and induce some pleasant emotions. The spectral alpha EEG field power at the parietal side of posterial area (Fig. 2) showed a greater reduction

Fig. 1 Subjective rating on the affective perception of the fast melody and slow melody, respectively termed “happy” and “sad” in coresponding to the subjective differentiation of the experienced emotions. The control was a speech featuring social-economic reform in China (adopted from Zhao H *et al.*, 2009)^[46].

compared to the resting baseline state, while the frontal mid-line theta EEG power exhibited a significant correlation between the EEG power and subjective rating of affective scale.

In the picture perception of both arousal and valence dimensions from a set of 150 animal pictures, ranging from

Fig. 2 EEG effects of alpha-2 spectral fields power mappings dominant at the posterior area in listening to the fast happy and slow sad melodies differentiated from baseline quiet condition. Both affective music melodies induced significantly larger areas and field powers when compared to those at baseline stage, all at eyes-closed condition (unpublished data).

Fig. 3 Affective pictures varying in valence of emotional perception resulted in topographic ERP mapping at the late 350 ms stage (unpublished data).

negative, neutral (control) to positive valence. It was hypothesized that negative pictures should enhance pain while positive pictures could attenuate pain if the valence hypothesis was correct. In the results, the opposite turned out to be true in that both negative and positive pictures reduced pain endurance in the tonic thermal pain test, owing to the observations that both negative and positive pictures incurred higher arousal ratings than the control pictures. The event-related potentials indicated a faster activation in the negative pictures than that in the positive pictures at the late positive stage around 350 ms (Fig. 3). Meanwhile, the scalp field activities of the negative and the positive pictures were centered at the parietal field of the posterior area. In the music study, the subjects were listening to music episodes while their eyes were closed, and in the picture study, the eyes of the subjects were open, without a transition from either state. The observed posterior parietal activation in both studies can be interpreted as scalp reflection from the underneath neural activation from precuneous cortex, which has been contended recently in conscious awareness function^[47] and

confirmed indirectly by our study results.

3 Conclusion

Top-down regulation of brain functions, such as the higher cortical modulation of human pain in the brain, is becoming a dominant branch of neuroscience research of great clinical interest and importance. This article could be the first major review on a broad modalities of human repertoire attempted for understanding higher brain functions. These repertoires are of great interest in and out of academic research. The studies reviewed may only scratch the surface of phenomena. Using non-invasive imaging techniques, our ability to probe the mystery of human mind, demonstrated in the studies cited recently within the past 5 years, still leaves quite a vacuum in our knowledge. These studies can largely achieve accurate quantifications of brain activations and locate the activities of these activations. However, these studies on a whole cannot measure the dynamics of brain function, or scrutinize the quality of subjective experience. Neither could they delineate the working principle, or even inquire

how and why the top-down mechanisms work. The information bit carried out by the top-down processing in human mind remains elusive.

Nevertheless, the documented studies clearly point out 2 principles: (A) One-acts-Many, and (B) One-takes-Many. In the former, one stimulation may act on many separate but often inter-related brain areas. In the latter, one brain response is likely to be encompassed by many divergent stimuli. Noxious activation of pain experience can act in both specific and non-specific brain areas termed neuromatrix of pain, while each brain area, for example, ACC, can be activated by a diversified external and internal events.

This article, nevertheless, achieves one major goal. The diversified higher cortical regulation modalities seem to recruit some common brain structures for pain modulation, in addition to each own specific functions.

To sum, higher brain functions have become the leading edge research in all sciences. How to solve the information bit of thinking and feeling in the brain can be the greatest challenge of human intelligence. Application of higher cortical modulation of human pain and suffering shall be in humanity of enlightening civilization.

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人脑痛知觉的高级皮层调节：心理要素

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摘要：最近的研究报道了痛知觉和它的人脑起源。本文综述了人类疼痛的高等皮层调节(下行调节)，尤其强调了心理要素。疼痛调节可包括基因治疗、生理、药理、心理和病理生理调节。在心理学调节中，本文从脑功能变化对疼痛的调节分别阐述了以下方面：(a)意志,(b)分心,(c)安慰剂,(d)催眠,(e)沉思,(f)气功,(g)信念,(h)情绪。本文系统详实地描述了操作定义、皮层处理、脑成像和疼痛调节。尽管并非所有研究均集中于疼痛调节的进展，但它们证明了人类疼痛调节的潜在方法。在对情绪调节疼痛的研究中，音乐旋律和图片认知对人持续性疼痛的调节作用已逐渐被发现。脑电量定位研究显示其机理主要为α波的增加，这可能与侧顶叶皮层对意识的调节和疼痛感知有关。总之，高等脑功能正成为最顶端的科学研究领域。如何解开思维及情绪在脑中的编码是人类崇高的智慧挑战。应用高等脑功能解脱人类的痛苦是人道的文明进展。

关键词：疼痛调节；脑；意志；分心；安慰剂；催眠；沉思；信念；气功；情绪

Erratum to Vol. 25, No. 4, 2009

Page	Line from bottom	Error	Correction
204	13, 14	LSPC and BIL were all purchased from Sigma-Aldrich (St. Louis MO, USA).	LSPC and BIL were provided by Huazhong Agricultural University.