

Acupuncture and anxiety: possible neural mechanisms

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Abstract

Anxiety disorders are among the most common mental disturbances around the world, and they can negatively impact a patient's quality of life and disrupt important activities of daily living. Recent studies have shown that the psychopathology of anxiety involves altered neural circuits and the normalization of these circuits would be the key factor for therapeutic effects. Acupuncture has an anxiolytic effect recognized in the treatment of anxiety. However, neural mechanism underlying the anxiolytic acupuncture effect is unknown. Some studies have shown that brain circuits related to the control of the autonomic nervous system, emotional, memory and cognitive processing are modulated by acupuncture. These circuits overlap the circuits related to psychopathology of anxiety. Thus, in this paper, we presented a hypothesis about how the acupuncture can reduce anxiety through modulation of brain circuits. In conclusion, the consulted literature showed that acupuncture has the potential to modulate the brain regions implicated in the anxious behaviors. Nonetheless, future studies should be done to elucidate the neuroendocrine mechanisms of acupuncture in the anxiety disorders.

Keywords: Acupuncture; Anxiety; Brain plasticity; Brain network.

Resumo

Os transtornos de ansiedade estão entre os distúrbios mentais mais comuns em todo o mundo e podem afetar negativamente a qualidade de vida de um paciente e interromper atividades importantes da vida diária. Estudos recentes mostraram que a psicopatologia da ansiedade envolve circuitos neurais alterados e a normalização desses circuitos seria o fator chave para os efeitos terapêuticos. A acupuntura tem um efeito ansiolítico reconhecido no tratamento da ansiedade. No entanto, o mecanismo neural subjacente ao efeito ansiolítico da acupuntura é desconhecido. Alguns estudos mostraram que circuitos cerebrais relacionados ao controle do sistema nervoso autônomo, do processamento emocional, da memória e do processamento cognitivo são modulados pela acupuntura. Esses circuitos se sobrepõem aos circuitos relacionados à psicopatologia da ansiedade. Assim, neste artigo, apresentamos uma hipótese sobre como a acupuntura pode reduzir a ansiedade através da modulação de circuitos cerebrais. Em conclusão, a literatura consultada mostrou que a acupuntura tem potencial para modular as regiões cerebrais implicadas nos comportamentos ansiosos. No entanto, estudos futuros devem ser feitos para elucidar os mecanismos neuroendócrinos da acupuntura nos transtornos de ansiedade.

Palavras-chave: Acupuntura; Ansiedade; Plasticidade cerebral; Rede cerebral.

Resumen

Los trastornos de ansiedad se encuentran entre los trastornos mentales más comunes en todo el mundo y pueden afectar negativamente la calidad de vida de un paciente e interrumpir actividades importantes de la vida diaria. Estudios recientes han demostrado que la psicopatología de la ansiedad involucra circuitos neuronales alterados y la normalización de estos circuitos sería el factor clave para los efectos terapéuticos. La acupuntura tiene un efecto ansiolítico reconocido en el tratamiento de la ansiedad. Sin embargo, se desconoce el mecanismo neural subyacente al efecto ansiolítico de la acupuntura. Algunos estudios han demostrado que los circuitos cerebrales relacionados con el control del sistema nervioso autónomo, el procesamiento emocional, de la memoria y cognitivo son modulados por la acupuntura. Estos circuitos se superponen a los circuitos relacionados con la psicopatología de la ansiedad. Por lo tanto, en este artículo, presentamos una hipótesis sobre cómo la acupuntura puede reducir la ansiedad a través de la modulación de los circuitos cerebrales. En conclusión, la literatura consultada mostró que la acupuntura tiene potencial para modular las regiones cerebrales implicadas en las conductas ansiosas. No obstante, se deben realizar estudios futuros para dilucidar los mecanismos neuroendócrinos de la acupuntura en los trastornos de ansiedad.

Palabras clave: Acupuntura; Ansiedad; Plasticidad cerebral; Red cerebral.

1. Introduction

Anxiety can be defined as a future-oriented condition, characterized by apprehension related to the perception of not being able to control or predict potentially aversive events. In addition, the patients present body symptoms of physical tension and a shift in focus of attention to potentially aversive events or to affective responses elicited by them (Craske et al., 2009). Anxiety is an essential and natural condition for human life, responsible for preparing the individual for situations of threat and danger. These conditions involve cognitive, behavioral, affective, physiological and neurological factors that, together, modulate the individual's perception of the environment, provoking specific responses and directing some type of action (Craske et al., 2009). In some cases, however, an individual may present disproportionately high anxiety to the situation that elicits it or in situations in which it is not adaptive, often persisting and leading to impairments in its functioning, characterizing anxiety disorders (Kessler et al., 1994).

Anxiety disorders, including panic disorder with or without agoraphobia, generalized anxiety disorder, social anxiety disorder, specific phobias, and separation anxiety disorder, are the most prevalent mental disorders and are associated with immense health care costs and a high burden of disease (Bandelow & Michaelis, 2015). According to large population-based surveys, up to 33.7% of the population are affected by an anxiety disorder during their lifetime (Wittchen & Jacobi, 2005).

Considering the psychopathology of anxiety, several studies have shown the implication of brain circuits, distributed between cortical and subcortical regions (Downar et al., 2000). These circuits are involved in assessment and expression of behaviors related to environmental threat (Apps, 2018). Thus, the connectivity disturbance in these circuits will give rise to errors on judgments about what is dangerous or not, creating the neurological condition to anxiety symptoms.

Nowadays, several studies have demonstrated that acupuncture has anxiolytic effect on anxiety disorders (Tong et al., 2021; Yang et al., 2021). In addition, one great advantage of acupuncture on conventional treatments is that acupuncture does not cause side effects in the vast majority of patients (Yang et al., 2021). However, the neural mechanism underlying the anxiolytic acupuncture effect is unknown. In this context, we hypothesized that acupuncture could exert its anxiolytic effect through modulation of brain circuits related to the psychopathology of anxiety. Therefore, the aim of this study is to present the empirical data supporting our hypothesis and the perspectives for future studies.

2. Methodology

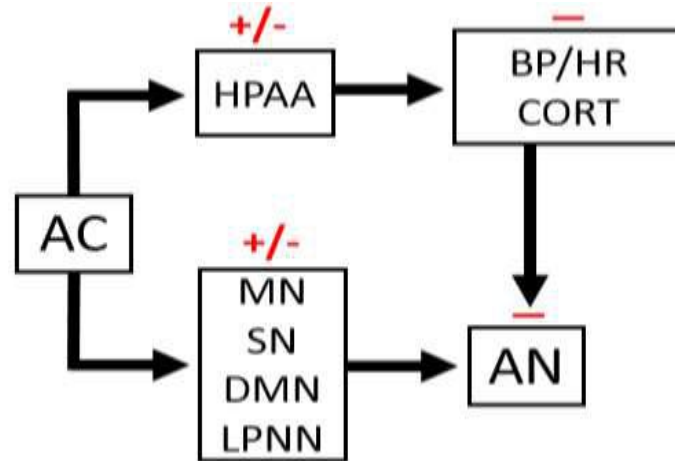
This study is a narrative review, where the criteria used in the evaluation and selection of the consulted studies do not follow systematic search methods (Bernardo et al., 2004). It was conducted a computer-based search of articles through PubMed, ScienceDirect and Scielo databases, up to April, 2022, to find publications with the following search terms: ("acupuncture" or "electroacupuncture" and "anxiety" or "anxiety disorder" and "neural circuits" or "Brain networks"). Based on these retrieved articles, it was done the data extraction with the goal to support the hypothesis formulated.

3. Hypothesis

From a mechanistic point of view, the hypothesis is that the anxiolytic effect of acupuncture on anxiety may occur due to the regulation of brain regions involved in emotional, cognitive and memory processing, via modulation of memory network (MN), salience network (SN), default mode network (DMN) and limbic-paralimbic-neocortical network (LPNN). In addition, the acupuncture decreases the cortisol production, via modulation of the hypothalamic-pituitary-adrenal (HPA) axis. (Figure 1).

Figure 1. Hypothesis about the acupuncture's mechanism of action on anxiety:

Acupuncture (AC) promotes the modulation (+/-) of the hypothalamic-pituitary-adrenal axis (HPAA) and the decrease (-) of variables (BP/HR/CORT) related to anxiety (AN) symptoms. AC also promotes modulation (+/-) on the brain areas responsible for memory (MN), cognitive (SN, DMN) and emotional processing (LPNN), leading to decreasing AN. BP: blood pressure; HR: heart rate; CORT: cortisol; MN: memory network; SN: salience network; DMN: default mode network; LPNN: limbic-paralimbic-neocortical network.



Fonte: Authors.

4. Foundation of the hypothesis

4.1 Neural circuits of anxiety

According to studies of unpredictable shock threat and high-resolution functional magnetic resonance imaging (MRI), several brain areas are involved in the psychopathology of anxiety. The dorsolateral prefrontal cortex (dlPFC) regulates emotion and attention control and is related to anxiety (Bishop, 2009). When the individual is engaged in cognitive tasks that activate the dlPFC, this activation inhibits anxiety caused by the unpredictable threat of shock (Vytal et al., 2012). Patients with psychiatric disorders show hypoactivation of dlPFC during tasks that cause anxiety (Balderston, et al., 2017). These studies demonstrate that normal dlPFC activity is crucial in controlling pathological anxiety. Anxious patients also have a cognitive deficit due to low dlPFC activation, which impairs working memory (Balderston, et al., 2017).

The dorsomedial prefrontal cortex (dmPFC) regulates conscious threat assessment and worry (Mechias et al., 2010). This region, together with the anterior (ACC) and posterior (PCC) cingulate cortex, are overactive in psychiatric patients, acting in the social response, interoception, assessment and expression of behaviors related to environmental threat (Etkin et al., 2011; Apps, 2018). Functional neuroimaging studies demonstrate a circuit formed between the dmPFC and the amygdala. Connectivity between the dmPFC and the amygdala increases when healthy subjects are subjected to the unpredictable threat of shock, and this increase is greater in subjects with high dispositional anxiety (Robinson et al., 2016). Thus, these studies indicate that the dmPFC/ACC/PCC/amygdala circuit is involved in the pathogenesis of anxiety. The anterior part of the insula is also associated with the dmPFC/ACC circuit. This cortical region has the function of integrating interoceptive information, making them conscious and, via ACC, allocating attention and initiating appropriate action (Paulus & Stein, 2006). The anterior insula is also involved in anticipating aversive events, being responsible for sustaining anxiety during such events (Alvarez et al., 2011).

In addition to the functions mentioned above, the medial portion of the prefrontal cortex (mPCF) is also involved, together with the anterior hippocampus, in consolidation and retrieval of memories (Preston & Eichenbaum, 2013). The hippocampus is involved in anxiety, probably, due to its role in learning and memory (Phillips & LeDoux, 1992). A positive correlation has been shown between activation of the anterior hippocampus, measured with magnetoencephalography, and increased level of anxiety in humans (Cornwell et al., 2012). Thus, dlPFC, mPCF and the anterior portion of the hippocampus form a memory network (MN) that, when altered, contributes to the pathogenesis of anxiety.

In addition to MN, the other brain regions mentioned above make up other functional brain networks, such as the salience network (SN) and the default mode network (DMN). Changes in these networks are also related to anxiety disorders, as described below.

The cortical nodes of the SN are the dlPFC, ACC, PCC and anterior insula (Yeo et al., 2011). These nodes are activated by sensory stimuli that attract attention because they are unexpected, new or behaviorally relevant. Cortical activations are accompanied by subcortical activations during active and voluntary involvement of cognitive control, response selection, or response inhibition (Downar et al., 2000; Corbetta et al., 2000). Thus, the hyperactivation of these circuits are relevant to anxiety disorders due to their integral role in emotional, cognitive and behavioral self-regulation (Marsh et al., 2009).

The DMN is a resting state network responsible for an introspective self-referential state (Imperator et al., 2019). This network is composed of the dmPFC, PCC, precuneus and medial and lateral parietal cortex. A study with electroencephalography showed that individuals with high trait anxiety fail to synchronize DMN during the resting state, reflecting a possible deficit in top-down cognitive control. In these individuals, there was a decrease in connectivity between dmPFC and ACC / PCC / retrosplenial cortex. Furthermore, the strength of functional DMN connectivity was negatively related to the total State and Trait Anxiety Index (STAI-T) score (Imperator et al., 2019). Taken together, these studies indicate that the main goals of therapies for anxiety disorders are to increase emotional regulation in dlPFC and decrease the emotional reactivity implicit in other areas of the brain in the anxiety neural circuit.

4.2 Acupuncture anxiolytic effect

The acupuncture has been used to treat various diseases for at least 2500 years in China. According to oriental medicine theory, acupuncture is defined as the insertion of needles into the skin and underlying tissues, at specific locations known as acupoints, for curative or preventive purposes (Kavoussi & Ross, 2007). Systematic reviews have shown that acupuncture has been used to control generalized anxiety in preoperative, pre-exam conditions and other conditions (Amorin et al., 2018; Kwon & Lee, 2018; Li et al., 2019). In these studies, in addition to the significant results in decreasing anxiety, there were no relevant side effects. Among the 360 points of acupuncture, located in the main energy channels (meridians), the points PC6 (*Neiguan*), HT7 (*Shenmen*), L3 (*Taichong*) and *Yintang*, are the points that the scientific literature indicates as the most effective in controlling anxiety.

From a mechanistic point of view, the anxiolytic effect of acupuncture can occur through the reduction of cortisol production (Hsieh et al., 2001), via modulation of the hypothalamic-pituitary-adrenal axis, and regulation of brain regions involved in cognition, memory, and emotion (Hui et al., 2010; Cai et al., 2017). Numerous studies have shown that regions of the brain modulated by acupuncture largely overlap with regions related to the anxiety neural circuit (Chae et al., 2013). These studies, brought together in a meta-analysis of brain activities associated with acupuncture stimulation, reveal activation in the sensorimotor cortical network (insula, thalamus, ACC and primary / secondary somatosensory cortex) and deactivation of the limbic-paralimbic-neocortical network (LPNN) composed of mPCF, caudate, amygdala, PCC and parahippocampus. This "LPNN" terminology was given by the authors for the network of brain regions involved in the acupuncture response (Hui et

al., 2009). The LPNN is composed of the main nodes of the DMN, amygdala and hypothalamus. The activation and deactivation patterns cited in these studies suggest that hemodynamic responses in the brain simultaneously reflect sensory, cognitive and affective modulation after acupuncture stimulation.

Another meta-analysis also conducted in healthy individuals showed that acupuncture increases the connectivity of the DMN and the sensorimotor network with brain areas related to pain, affectivity and memory (periaqueductal substance, ACC, left posterior cingulate cortex, right anterior insula, limbic / paralimbic and pre-cuneiform). It has also been shown that acupuncture can adjust the LPNN, brainstem, cerebellum and hippocampus. The authors concluded that the functional connectivity network is closely related to the acupuncture mechanism and central integration plays a critical role in the acupuncture mechanism (Cai et al., 2017).

5. Future perspectives and Conclusion

According to the literature reviewed, the acupuncture has a significant anxiolytic effect and can modulate the neural circuits related to psychopathology of anxiety. This ancient technique is a low-cost therapy with no side effect in the vast majority of the cases. Pharmacotherapy and psychotherapy are the conventional treatments for anxiety (Bandelow et al., 2012). In relation to psychotherapy, this is insufficient when used alone, in most cases. In pharmacotherapy, anxiolytics, antidepressants or monoamine oxidase inhibitors are used, with benzodiazepines being the most used as anxiolytics. However, these drugs can cause habituation, serious adverse effects and drug interactions (Arranz, et al., 2007; Goyata et al., 2016).

Considering this acupuncture characteristics and possible advantages in relation to conventional treatments, future studies elucidating the neuroendocrine mechanisms of acupuncture could establish new treatment protocols, with the more suitable acupoints to modulate the neural circuits altered by anxiety.

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