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The modulatory effect of acupuncture on amygdala functional connectivity: narrative review of the clinical research

O efeito modulatório da acupuntura sobre a conectividade funcional da amígdala: revisão narrativa de pesquisas clínicas

El efecto modulador de la acupuntura en la conectividad funcional de la amígdala en pacientes: revisión narrativa de ensayos clínicos

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Abstract
The amygdala is a brain area crucial for emotional, behavioural and visceral sensitivity/motor signals processing. To exert these functions, the amygdala is reciprocally connected with cortical and subcortical regions. Some studies have showed that acupuncture modulates the activity of the amygdala and its circuits. However, there is no literature review synthesizing and evidencing the actual research status about this subject. Thus, the aim of this paper is to present and discuss the newest evidence about the effect of acupuncture on the amygdala resting-state functional connectivity (rsFC) in the context of clinical research. The narrative review of clinical research was focused on published clinical trials (controlled and randomized) designed to analyze the effect of acupuncture on the modulation of the amygdala rsFC in clinical conditions. The search was conducted on Pubmed, ScienceDirect and Scielo databases up to March, 2022. The studies found were about patients with major depressive disorder, functional dyspepsia and premenstrual syndrome, which demonstrated that acupuncture significantly decreases its symptoms. In addition, this therapeutic effect were correlated with the modulation of the amygdala rsFC with a range of brain regions. According to the data reviewed, it can be concluded that the brain action's mechanisms of acupuncture is related, at least in part for the clinical conditions analyzed, to its modulatory effect on the amygdala network. However, the studies about this theme are rare, and more studies should be done to clarify the amygdala involvement in the effect of the acupuncture.
Keywords: Acupuncture; Functional magnetic resonance imaging; Clinical research.

Resumo
A amígdala cerebral é crucial para o processamento emocional, comportamental e de sinais sensitivos e motores viscerais. Para exercer essas funções, a amígdala se conecta reciprocamente com regiões corticais e subcorticais. Alguns estudos mostraram que a acupuntura modula a atividade da amígdala e seus circuitos. No entanto, não há revisão de literatura sintetizando e evidenciando o atual estado de pesquisa sobre o assunto. Assim, o objetivo deste artigo é apresentar e discutir as mais recentes evidências sobre o efeito da acupuntura na conectividade funcional em estado de repouso (*rsFC*) da amígdala no contexto da pesquisa clínica. A revisão narrativa da pesquisa clínica foi focada em ensaios clínicos (controlados e randomizados) projetados para analisar o efeito da acupuntura na modulação da *rsFC* da amígdala em condições clínicas. A busca foi realizada nas bases de dados Pubmed, ScienceDirect e Scielo até março de 2022. Os estudos encontrados foram sobre pacientes com transtorno depressivo maior, dispepsia funcional e síndrome pré-menstrual, os quais demonstraram que a acupuntura diminui significativamente os sintomas. Além disso, este efeito terapêutico foi correlacionado com a modulação da *rsFC* da amígdala com uma gama de regiões cerebrais. De acordo com os dados revisados, pode-se concluir que os mecanismos de ação cerebral da acupuntura estão relacionados, ao menos em parte para as condições clínicas analisadas, ao seu efeito modulador sobre a rede cerebral da amígdala. No entanto, os estudos sobre esse tema são raros, e mais estudos devem ser feitos para esclarecer o envolvimento da amígdala no efeito da acupuntura.
Palavras-chave: Acupuntura; Amígdala; Ressonância magnética funcional; Pesquisa clinica.

Resumen
La amígdala cerebral es crucial para el procesamiento emocional, conductual y de señales sensoriales y motoras viscerales. Para realizar estas funciones, la amígdala se conecta recíprocamente con regiones corticales y subcorticales. Algunos estudios han demostrado que la acupuntura modula la actividad de la amígdala y sus circuitos. Sin embargo, no existe una revisión bibliográfica que resuma y evidencie el estado actual de la investigación sobre el

tema. Por lo tanto, el propósito de este artículo es presentar y discutir la evidencia más reciente sobre el efecto de la acupuntura en la conectividad funcional en estado de reposo (*rsFC*) de la amígdala en el contexto de la investigación clínica. La revisión narrativa de la investigación clínica se centró en los ensayos clínicos (controlados y aleatorizados) diseñados para analizar el efecto de la acupuntura en la modulación de la *rsFC* de la amígdala en condiciones clínicas. La búsqueda se realizó en las bases de datos Pubmed, ScienceDirect y Scielo hasta marzo de 2022. Los estudios encontrados fueron en pacientes con trastorno depresivo mayor, dispepsia funcional y síndrome premenstrual, que demostraron que la acupuntura reduce significativamente los síntomas. Además, este efecto terapéutico se correlacionó con la modulación de la *rsFC* de la amígdala con una variedad de regiones cerebrales. De acuerdo con los datos revisados, se puede concluir que los mecanismos de acción cerebral de la acupuntura están relacionados, al menos en parte para las condiciones clínicas analizadas, con su efecto modulador sobre la red cerebral de la amígdala. Sin embargo, los estudios sobre este tema son escasos y se deben realizar más estudios para aclarar la participación de la amígdala en el efecto de la acupuntura.
Palabras clave: Acupuntura; Amígdala; Resonancia magnética funcional; Investigación clínica.

1. Introduction

The amygdala is comprised of multiple interconnected nuclei nestled deep in the temporal lobe (Janak & Tye, 2015). This brain region is critical for emotional processing and motivated behavior (Murray, 2007). Despite this important role, the amygdala is a relatively small region including the basolateral complex of the amygdala (BLA) made up of the lateral (LA), basal (BA), and basomedial (BM) cell groups and the central nucleus (CeA) with lateral (CeL) and medial (CeM) subdivisions (Janak & Tye, 2015). The BLA is the major sensory input subregion of amygdala and CeA, the output amygdala subregion (Zeng et al., 2019).

The amygdala receives direct sensory input from sensory thalamus and cortical regions to integrate sensory information from the internal and external environment with aversive and/or rewarding outcomes (Smith et al., 2021; Lalitha et al., 2016). The BLA is reciprocally connected with cortical regions, especially the midline and orbitofrontal cortex (OFC), and the hippocampus (HIPP), as well as sensory association areas (McDonald, 1998). Hence, the BLA transmits information widely throughout cortical regions, but its neuronal processing is greatly affected by excitatory projections from these regions. Predominantly unidirectional outputs of the BLA include the striatum, especially the nucleus accumbens (NAc), and the bed nucleus of the stria terminalis (BNST) and the CeA. In turn, the striatum, BNST and CeA have been considered to mediate the translation of BLA signals to behavioural output (Corbit & Balleine, 2005)

Studies has showed that amygdala may be modulated by acupuncture (Quin et al., 2008). Acupuncture is an ancient energy based traditional Chinese medicine technique, popular in the East but still recent in Western countries. 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).

Accumulating evidence has indicated that acupuncture modulates the functional connectivity of brain networks (Yu et al., 2019; Cai et al., 2018; Quin et al., 2008). These studies have used the resting-state functional connectivity (rsFC) method from functional magnetic resonance image (fMRI) to analyze the synchronized temporal activation of spatially separated brain regions in patients at rest. In this technique, when two spatially different brain regions are activated at the same time, form a functional connectivity between these regions, which can be quantify by computational and statistical methods (Heuvel, 2010). More specifically, seed-based rsFC is a method of functional brain imaging that can assess the temporal dependency of brain regions (seeds) during rest (Biswal et al., 1995). This method allows for the study of the function of one or several brain regions in relation to its functional network and how the network contributes to brain procedures, been able to reveal the underlying mechanisms of different diseases (Hwang et al., 2015; Sun et al., 2012). However, there is limited rsFC studies on the involvement of the amygdala, as seed, in the effect of acupuncture on human diseases. Thus, the aim of this review is to present and discuss the newest evidence about the modulatory effect of acupuncture on amygdala brain networks in patients with major depressive disorder, functional dyspepsia and premenstrual syndrome.

2. Methodology

A narrative review was carried out, 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 March, 2022, to find publications correlating the following search terms: ("acupuncture" or "electroacupuncture" and "amygdala" and "fMRI" or "rsFC"). According to this search process and considering the amygdala as seed in the rsFC studies, it was found the following articles: two studies on major depressive disorder (Wang et al., 2016; Duan et al., 2020), one on functional dyspepsia (Sun et al., 2018) and one on premenstrual syndrome (Pang et al., 2021). Based on these retrieved articles, it was done the data extraction considering the modulation of amygdala rsFC, promoted by acupuncture, on the diseases cited above. This data was summarized in the figures related to each disease, described in the following topics.

3. Results and Discussion

3.1 Major Depressive Disorder

Major depressive disorder (MDD) is a common disorder that affects a large proportion of the population by significantly impairing their occupational, social, and academic functioning (Lehtinen & Joukamaa, 1994). Many brain regions including the amygdala, HIPP, insula (INS), ventral striatum, ventral anterior cingulate gyrus, and prefrontal cortex (PFC) are involved in the neural pathology and development of MDD (Phillips et al., 2015). Studies showed that compared with healthy controls, MDD patients showed abnormal elevated activity in the amygdala when presented with negative stimuli (Phillips et al., 2015; Sheline et al., 2010).

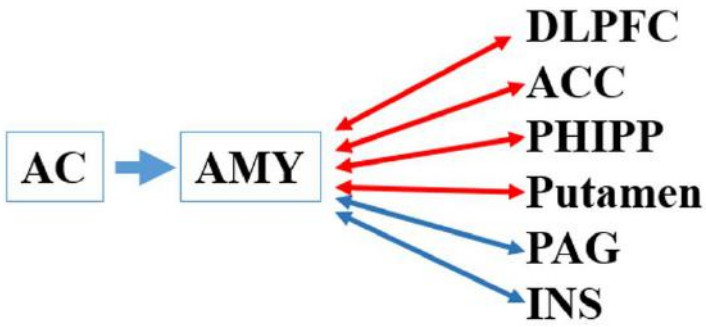
One study compared the effect of verum acupuncture plus fluoxetine with sham acupuncture plus fluoxetine in MDD patients (Wang et al. 2016). The results showed that verum acupuncture plus fluoxetine promoted greater clinical improvement as indicated by Montgomery–Åsberg Depression Rating Scale (MADRS) and Self-Rating Depression Scale (SDS) scores, as compared with sham acupuncture. The rsFC increased between the left amygdala and subgenual anterior cingulate cortex (sgACC)/preguenual anterior cingulate cortex (pgACC), and between the right amygdala and left parahippocampus (PHIPP)/putamen. The amygdala-sgACC/pgACC rsFC was negatively correlated with corresponding clinical improvement. The sgACC is implicated in automatic behavioral control, and the pgACC is involved in automatic attentional control based in part on their functional interaction with the amygdala (Salvadore et al., 2010). Thus, we can consider that the increased connectivity between the amygdala and the sgACC/pgACC has an antidepressant effect. The increased connectivity of the PHIPP with the amygdala probably decreased the depression by mediating contextual processing and emotion, thus facilitating emotion understanding and expectations of the environment (Aminoff et al., 2013). Regarding to putamen, the antidepressant effect could be related to reward and motivation functions of this structure (Felger et al. 2015). The authors concluded that the additive effect of acupuncture to antidepressant treatment and suggest that this effect may be achieved through the limbic system, especially the amygdala and the ACC.

In another study, the amygdala network (AN) of the MDD patients was compared with healthy subjects and was analyzed whether electroacupuncture (EA) at *Baihui* (GV20) acupoint could modulate the abnormal AN of patients with the first-episode, drug-naïve MDD by using rsFC-fMRI method (Duan et al., 2020). The results showed that, compared to healthy subjects, MDD patients had aberrant intrinsic AN which mainly showed increased rsFC between amygdala and HIPP, precuneus, precentral gyrus and angular gyrus, as well as decreased rsFC between amygdala and OFC. Moreover, the results indicated that EA at GV20 induced increased rsFC between amygdala and dorsolateral prefrontal cortex (DLPFC) and decreased rsFC between amygdala and periaqueductal gray (PAG) and INS in MDD patients (Figure 1).

In general, the PFC is responsible for executive functions. The OFC, being a portion of PFC, has a vital role in executive control of information processing and behavioral expression by inhibiting neural activity associated with contextually irrelevant, unwanted, or uncomfortable information, sensations, and actions (Shimamura, 2000). The DLPFC is a critical area for performing executive function and is associated with voluntary emotion regulation (Connolly et al., 2017). Thus, these characteristics of PFC can explain, at least in part, the mechanism of action of EA at GV20 in MDD patients.

The PAG is involved in pain perception by descending modulation of the spinal cord neurons (Yu et al., 2014). This region has close anatomical connections with amygdala and INS, providing a circuit for pain perception and modulation, and emotion processing (Zhuo, 2016; Truini et al., 2016). The decreased rsFC between amygdala and PAG/INS, could modulate these pain-related regions associated with emotion perception and regulation, that also might be another therapeutic mechanism of EA at GV20 for MDD patients.

Figure 1: Acupuncture (AC) in MDD: AC promotes modulatory effect on amygdala (AMY) rsFC with dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), parahippocampus (PHIPP), putamen, periaqueductal gray (PAG), and insula (INS). Bidirectional arrows represent reciprocal AMY connectivity. Red color: increased rsFC; Blue color: decreased rsFC.



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3.2 Functional Dyspepsia

As one of the most common categories in functional gastrointestinal disorder, functional dyspepsia (FD) is characterized by postprandial fullness, early satiation, epigastric pain or burning, the symptoms of which could not be explained by organic, systemic, or metabolic disease (Tack & Talley, 2013).

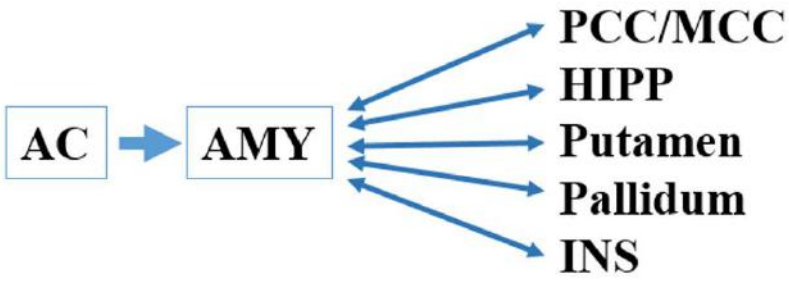
The amygdala is considered the key region in the central pathogenesis of FD (Nan et al., 2015). Its function is related to the processing of afferent and efferent visceral signals of food intake (Lalitha et al., 2016), gastric distention (Wang et al., 2008), and emotion arousal reactions (He et al., 2016).

It has been reported that acupuncture can improve the symptoms of FD due to its action on the amygdala (Sun et al., 2018). In this study, the acupuncture decreased the left basolateral amygdala (BLA) rsFC with bilateral INS, putamen and middle/posterior cingulate cortex (MCC/PCC), right pallidum and HIPP. The reduction of the patient's symptoms were positively correlated with the left BLA rsFC with left INS and with right HIPP. In addition, the reduced symptoms were negatively correlated with increased right centromedial amygdala (CMA) rsFC with left medial prefrontal cortex (mPFC), after treatment (Figure 2).

Compared with healthy subjects, the FD patients present the following rsFC patterns: increased BLA rsFC with the right anterior INS and significantly decreased BLA rsFC with the mPFC and PCC. Regarding to CMA, FD patients showed significantly decreased rsFC with the bilateral right precuneus/cuneus and anterior INS (Zeng et al., 2019).

The INS and amygdala are important cortical and subcortical regions in the salience network (SN). The SN is a network that contributes to detecting sensory and visceral afferents, and self-awareness through the integration of this information (Zeng et al., 2019). The mPFC, HIPP and PCC belong to the default mode network (DMN), which is active in internal mentalization and de-active in certain goal-oriented tasks (Brewer et al., 2011). The mPFC has reciprocal connections with the amygdala, and receives and processes sensory, affective, motivational, and cognitive information of visceral sensation directly from the amygdala projections (Aziz et al., 2000). The PCC receives the internal and external information, which is integrated and gathered by the mPFC, and regulates the affective and sensory process together with the mPFC and amygdala (Northoff et al., 2006; Fox et al., 2005). The HIPP/PHIPP is involved not only in different aspects of pain and visceral sensations processing, but also recall of past visceral pain/discomfort memories of sensations (Andresen et al., 2005). In conclusion, the acupuncture exerts its effect probably by modulating the functional connectivity of the SN, and participate in the adaptive modulation of disrupted relationship between the SN and DMN in FD.

Figure 2: AC in FD: AC promotes modulatory effect on amygdala (AMY) rsFC with posterior and middle cingulate cortex (PCC/MCC), hippocampus (HIPP), putamen, pallidum and insula (INS). Bidirectional arrows represent reciprocal AMY connectivity. Blue color: decreased rsFC.



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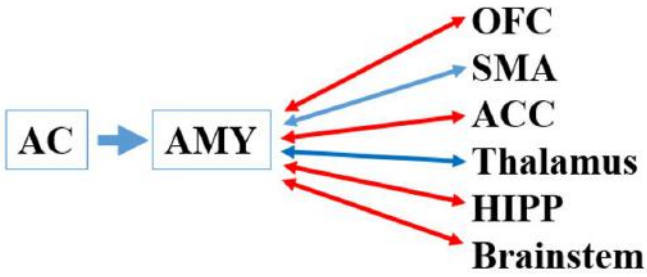
3.3 Premenstrual Syndrome

Premenstrual syndrome (PMS) is associated with a series of cyclical and relapsing emotional, behavioral and physical symptoms that appear in the late luteal phase of menstrual cycle and disappear soon after the onset of menses (Greene & Dalton, 1953). Previous study found that aberrant amygdala functional networks were involved in PMS (Deng et al., 2018). In one study (Pang et al., 2021), the results showed that EA at *Sanyinjiao* acupoint (SP6) induced increased rsFC between the left amygdala and brainstem, right HIPP, and decreased rsFC between the left amygdala and left thalamus, bilateral supplementary motor area (SMA). Moreover, the results also showed that EA at SP6 induced increased rsFC between the right amygdala and brainstem, right HIPP, right OFC, bilateral ACC, and decreased rsFC between the right amygdala and right SMA (Figure 3).

Amygdala, OFC, HIPP, belong to the affective network (AfN), which plays a vital role in emotion regulation and processing (Bayer et al., 2014). In addition, ACC belongs to DMN, and abnormal connection between the amygdala and DMN in psychopathology have been well described (Gusnard et al., 2001). Regarding to physical symptoms of PMS, such as, bloating, breast tenderness and headache, the EA could have improve it through the modulation of rsFC of amygdala with brainstem, ACC, thalamus and SMA, which are brain regions related to pain processing (Schweinhardt & Bushnell, 2010). Thus, in this study, it was concluded that the SP6-related acupuncture can modulate the connectivity between amygdala and AfN/DMN in PMS patients, which might partly explicate the neural modulatory mechanisms of EA on PMS.

Figure 3: AC in PMS: AC promotes modulatory effect on amygdala (AMY) rsFC with orbitofrontal cortex (OFC), supplementary motor area (SMA), anterior cingulate cortex (ACC), thalamus, hippocampus (HIPP) and brainstem. Bidirectional arrows represent reciprocal AMY connectivity. Red color: increased rsFC; Blue color: decreased rsFC.



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4. Concluding Remarks

Nowadays, its increasing the number of fMRI studies analyzing the modulation of the amygdala rsFC with other brain regions in pathological conditions. Nevertheless, there is a lack of studies verifying how acupuncture affects the amygdala rsFC in the vast majority of diseases. For FD and PMS, only one study for each condition was found in literature review. For MDD, just two articles were found. In these studies, the results showed that acupuncture has the potential to modulate the amygdala rsFC and this modulation is associated with improved symptoms. However, more studies are needed to clarify the precise effect of acupuncture on the amygdala network, under pathological conditions. Future studies analyzing the effect of different acupuncture protocols on the modulation of brain circuits linked to the amygdala should be done in order to elucidate the brain action's mechanisms of acupuncture in the clinical setting.

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