

## Neurobiological Correlates on Psychotherapy in Depression

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### Abstract

Psychotherapy (PT) is as effective and important as antidepressant treatments (ADT) for patients with depression. However, the neurobiological mechanism of PT has not been well understood. In this study, the known biological mechanism of PT is introduced, and its importance is reviewed.

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**Received:** March 08, 2016; **Accepted:** March 09, 2016; **Published:** March 14, 2016

### Introduction

Treatment mechanism on depression have focused on antidepressant treatment (ADT) rather than Psychotherapy (PT), because the neurobiological fundamentals of PT were not sufficient despite the empirical evidence that it could improve the brain dysfunction in patients with depression. Consequently, ADT has typically been accepted as a form of biological intervention, whereas PT is a form of psychosocial intervention. However, the development of functional neuroimaging technologies has made it possible to examine the patients' brain and corresponding circuit changes and to understand the neurobiological underpinning on PT.

Both ADT and PT are effective in the treatment of depression. The main concern of researchers has been whether the treatment mechanisms of ADT and PT are neurobiologically same or different from each other. Depression is considered as a network disorder with a pathologic functional connectivity [1]. Patients with depression have an increased resting metabolism level of amygdala [2] which is activated by aversive stimuli [3], but the resting metabolism of the prefrontal cortex (PFC) decreased [4]. In the functional MRI, patients with depression showed an increased amygdala reactivity when they carried out emotion-processing tasks, and decreased dorsolateral prefrontal cortex (DLPFC) reactivity with cognitive tasks [5]. Based on these findings, it is concluded that patients with depression showed an increased bottom-up emotional reactivity and a decreased top-down regulation of emotions, suggesting a decreased functional connectivity between the amygdala and DLPFC. Previous researchers have explained the phenomenon as 'cortico-limbic dysregulation model' [6, 7]. Importantly, the difference in the treatment mechanism between ADT and PT can be explained using the network dysfunctions. In briefly, ADT can weaken the subcortical (limbic-amygdala) bottom-up emotional reactivity, while PT can reinforce the cortical (PFC-DLPFC) top-down regulation of emotion [7]. However, other studies have reported

that these simple mechanisms of bottom-up / top-down regulation were not applicable to depression [8]. Moreover, limitations in event-related functional MRI were confirmed. PFC activity changes depending on the tonic and resting states. Event-related response changes based on PT and ADT [9]. Thus, it is not sufficient to explain the difference between ADT and PT by simply using the difference in the stimulus-dependent neural mechanism. Nevertheless, these theories have significantly helped in understanding the biological mechanism of PT.

Amygdala is regarded as an important structure for implicit memory [10]. When exposed to aversive stimulation, amygdala is activated, and fear reactions developed. Neocortex is not necessarily required in fear reaction development, but is essential in removing the fear reaction [11]. PT reinforces the neocortex functions to regulate the implicit memory of the amygdala. The circuit from the cortex to the amygdala is weaker than the circuit from the amygdala to the cortex [12]. Accordingly, a long term interval is required for new connectivity formation from the cortex to the amygdala. This is why it takes a long time to confirm the effects of PT.

PT commonly normalizes the dysfunction of the cortico-limbic circuit regardless of the type of PT. Currently; slightly different neural circuits are known to be activated according to the type of PT (e.g., psychodynamic PT, cognitive behavioral therapy (CBT), and behavioral therapy (BT)). The free association in

psychodynamic PT is based on random memories rather than episodic memories. In contrast, the process of collecting clinical information from a patient by a clinician is based on the patient's episodic memories. Random memory is associated with a specific area in the brain, such as the frontal, parietal, and temporal cortex. Episodic memory is associated with specific verbal areas, such as the Broca's area and the left frontal operculum [13]. Hence, free association is a less-censored process and is associated with the extensive cortex network. In psychodynamic PT, clinicians explore patients' depression symptoms through these extensive cortex activations. Therefore, the free association activates the implicit memories of the amygdala, meaning that patients play active roles in psychodynamic PT. In summary, the progression in psychodynamic PT contributes to additional activations of the extensive cortex and amygdala to further strengthen their connectivity. Consequently, the pathologic association between emotion and cognition is improved. The psychodynamic PT is not a passive, conditioned reflex but an active learning process in patients with depression.

In cognitive behavioral therapy (CBT), patients with depression are asked to recall bad or sad memories, and then requested to re-evaluate them, and finally to re-interpret their negative memories more positively. Moreover, the states before and after the re-interpretation are rated. The negative emotions are associated with limbic and ventral prefrontal cortex. Researchers have observed the increased activity of dorsolateral and dorsomedial PFC, the decreased activity of amygdala and the orbitofrontal cortex during CBT [8]. Hence, CBT is a process of re-interpreting negative emotions to become positive through these biological models.

Behavioral therapy (BT) is used to desensitize the stimuli that cause

anxiety and extinguish learned responses. The desensitization and extinction processes are associated with ventral PFC, and the conditioned fear responses are associated with the amygdala [14]. Animal experiments demonstrated that the fear-conditioned responses disappeared when the amygdala was removed, or drugs inhibiting amygdala activation were administered [15]. Similarly, in human experiments conducted through functional neuroimaging, the amygdala was activated with conditioned fear responses [16]. Therefore, BT is a process that involves repetitive practice, which continues until the fear-conditioned responses formed in the amygdala are fully controlled by PFC.

In conclusion, it is now important to understand the neurobiological underpinning on psychotherapy in depression. There are four main reasons for that: firstly, since ADT has been developed based on biological evidence, PT also requires a scientific basis for further development. Secondly, treatment priority can be determined between ADT and PT based on the biological subgroups in patients with depression. Furthermore, the most efficient type of psychotherapy can be determined. Third, clinicians and researchers can easily rate the effects of PT and compare with them or ADT. Fourth, when combining ADT and PT, which is common in depression treatment, the contribution of each method can be evaluated. This means that the optimal treatment for patients with depression can be formulated. Psychotherapy holds a key position in depression. However, biological evidence pertaining to such an important form of PT has not been proven yet. In the near future, the most advanced technologies, including brain neuroimaging, can demonstrate the treatment mechanisms of various PT which has been understood based on empirical evidence to date.

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