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The Effects of Psychotherapy on Brain Function — Major Depressive Disorder

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1. Introduction

Functional neuroimaging technologies have played an important role in the observation and characterization of the change in the brain function during depression. Various treatment techniques for depression related to brain function changes have been investigated based on research on functional neuroimaging technologies. However, the development of such technologies has focused more on the effect of the pharmacotherapy neural mechanism than on the effect of psychotherapy on depression treatment. This has led to an unbalanced approach to depression treatment, which emphasizes pharmacotherapy more than psychotherapy even if the treatment cost and depression treatment efficacy of the former are similar to those of the latter.[1, 2] This imbalance was caused by the traditional perception of pharmacotherapy as a biological intervention and of psychotherapy as a psychosocial intervention. [3] However, the recent development of functional neuroimaging technologies proved that the changes in the affect/behavior/cognition after psychotherapy are caused by biological underpinning. Many recent studies on depression confirmed through neuroimaging that psychotherapy has neural correlations. These studies proved that psychotherapy is a biologically rigorous approach.[4]

The neurobiological change in, and the putative mechanism of, psychotherapy in depression have recently been highlighted.[5] These are very important mainly in two aspects. First, each psychiatric intervention should have a neuroscientific basis. Psychotherapy has been poorly supported scientifically until now. Its treatment efficacy on depression was empirical from history and experience. The effective development of pharmacotherapy requires a neuro-

scientific basis that enables estimation of the side effect or the concomitant effect of a drug. This is also the case for psychotherapy. Second, the relationship of psychotherapy and neurobiology would help provide neurobiological evidence of the efficacy of various therapies based on psychotherapy (e.g., cognitive behavior therapy (CBT) and neurofeedback). Scientific evidence of psychotherapy would promote its development.

The poor neurobiological evidence of psychotherapy was caused by difficulties in directly observing neural plastic changes in the human brain. Conventional methods of brain plasticity observation could be used only at the cellular level. The development of functional neuroimaging technologies enables non-invasive observation of plastic changes in the human brain. With these new technologies, training- and learning-related changes in the brain activation pattern could be observed [6] and applied in depression patients. In other words, changes in the brain function, especially in the neural mechanism, and changes in brain areas and circuits due to psychotherapy in depression, could be more closely observed. Moreover, the relationship between pharmacotherapy and psychotherapy could be investigated neurobiologically. By approaching the relationship between these two therapies neuroscientifically, an optimal therapy for depression can be chosen, and combined evidence of the efficacy of these two therapies can be prepared.[7, 8]

Most studies on functional imaging that analyzed the effect of psychotherapy on depression have used the nuclear medicine method. In such method, the brain metabolism and the blood flow on the pre- and post-treatment scans are compared using positron emission tomography (PET) or single photon emission computed tomography (SPECT). Functional magnetic resonance imaging (fMRI) is also very useful for measuring brain activation during depression treatment and the follow-up period with no exposure to radiation. However, fMRI is mainly useful for measuring the brain activation pattern during perceptual or cognitive tasks rather than for measuring the baseline brain metabolism. In measuring brain function changes using fMRI, two techniques are required: (1) one for provoking symptoms under MRI environments, and (2) the other for measuring the neural correlates of the psychopathology.[9]

In this chapter, the analysis of the relationship between psychotherapy and the brain function in neuroimaging studies for depression will be discussed. Systemic and critical reviews will be presented, and how psychotherapy changes the brain function of depression patients will be discussed.

2. Applications of neuroimaging for psychotherapy on depression

2.1. Understanding of consciousness and unconsciousness

It is common knowledge that unconsciousness is an integral part of the psychotherapy on depression. Recently, neuroimaging has made it possible to understand the unconscious process. According to several studies, subjects without depressive disorder have shown normal emotion and anxiety; however, the amygdala was activated after they have been

exposed to a scary facial expression. Despite the fact that the subjects were unconscious of the stimulation, the amygdala, which is associated with anxiety, was activated when they were quickly exposed to a normal facial expression after transitioning from a scary facial expression. [10, 11] This indicates that anxiety is expressed through the unconscious process in patients with depressive disorder, which has been verified by neuroimaging. In another study, an amygdala hyperactivation, as well as a medial prefrontal cortex and an anterior cingulate cortex hypoactivation, occurred after exposing the patients with depressive disorder to the stimulation, and then examined through the use of the fMRI. [12] This result has been verified by fMRI, and it shows that the unconscious anxiety, which appears through the activation of the amygdala, cannot be consciously controlled in patients with depressive disorder.

2.2. Prediction of the risk factors on depression

Normal subjects, who have never experienced depression, were divided into two groups, namely, a group with a family history of depression and a group without a family history of depression. After processing the comparison, the volume of the hippocampus and prefrontal cortex was significantly reduced in the group with a family history of depression. [13, 14] This result explains some of the hereditary aspects of depression, thereby indicating the association of the neuroimaging findings with the risk factors on depression. [15, 16] In a study on functional neuroimaging, there is a remarkable mood-down-regulation effect due to the increased task in the normal group with a family history of depression than in the normal group without a family history of depression. Furthermore, the activation of the amygdala significantly increased in the normal group with a family history of depression as compared to the other group. [17] The activation of the putamen and insula was significantly lower in the normal group with a family history of depression than in the other group without a family history of depression in a reward expected situation, whereas the activation of the anterior cingulate cortex was significantly higher in the normal group with a family history of depression than in the other group in a punishment expected situation. [18] The aforementioned results are expected to explain some of the hereditary and risky aspects of complex depression. For this reason, it is interesting that the report on the abnormality of the limbic system and prefrontal cortex was observed in normal subjects without clinically significant depression.

2.3. Comprehensive development

Studies have been conducted in order to investigate the association of abnormal neuroimaging findings with trauma that has been experienced during childhood, and environmental and individual risk factors of depression. A previous study reported that the hippocampus volume was more reduced in patients who suffered from depression due to sexual harassment below 11 years of age than in patients who did not experience any sexual harassment at a young age. [19] In addition, the volume of the dorsomedial prefrontal cortex was more reduced in the group with child maltreatment than in the normal group. [20] The aforementioned studies were conducted in order to investigate how biological and psychological developmental factors, such as psychological trauma during childhood, progressed into pathophysiology of depres-

sion. However, the same psychopathology of depression is not always observed even if the subjects grew up in the same environment with the same genetic background.[21] Personal coping strategy, personality, and resilience contribute to the occurrence of depression, which makes the pathophysiology of depression more complex.[22-24] It was reported that the right amygdala- dorsomedial prefrontal cortex connectivity increased and the left amygdala- anterior cingulate cortex connectivity decreased in the normal group after they were exposed to negative emotions, such as fear and fury, as the severity of neuroticism increased.[25] In another study, a high extraversion group and a high neurosis group were exposed to positive/negative stimulations, which resulted in the increased activity of the amygdala in the high extraversion group after they were exposed to a positive stimulation, as opposed to the high neurosis group after they were exposed to a negative stimulation.[25] The aforementioned studies were conducted in order to investigate how personality factors induce mood disorder by affecting the cognition and process of emotion.

2.4. Depressive disorder subgroups

The activities of each area of the brain can be assessed by neuroimaging, which makes the subgrouping of depressive disorders possible, according to the pathogenesis of depressive disorder. Depression has various disease etiologies, but expressive symptoms of depression are similar. It is also possible to subgroup depressive patients by neuroimaging based on their depression etiology. This explains why a specific treatment is effective on a depressive patient, but other treatments are ineffective on the same patient. For example, when elderly patients with depression were subgrouped into the white matter microstructural abnormality by the diffusion tensor imaging, the remission rate of depression was low.[26] As a result, the brain process of these patients can be understood by neuroimaging, which will make the personalized treatment possible.[27] Furthermore, the treatment course can be monitored by neuroimaging.

2.5. Prediction of the prognosis of depression

The prognosis of depressive disorder can be predicted by neuroimaging. For example, the prognosis was reported to be better in depressive patients with hypermetabolic rostral anterior cingulate cortex than in those with hypometabolic rostral anterior cingulate cortex when the depressive patients were examined by PET and fMRI.[28] In addition, the activation degree of the prefrontal cortex and orbitofrontal cortex by PET may vary in depressive patients depending on their treatment response.[29, 30] It was reported that depressive patients with hypometabolic orbitofrontal cortex responded better to pharmacotherapy, whereas those with hypermetabolic orbitofrontal cortex responded better to psychotherapy. Accordingly, studies on the prediction of treatment outcome by neuroimaging prior to therapy had been continuously conducted [31, 32] in order to investigate how new treatments of depression, such as mindfulness-based cognitive therapy and acceptance and commitment therapy, change the brain process [33, 34] by which the neuroimaging study will be closer to the actual clinical practice.

3. Neuroimaging study on depressive disorder

Many clinical, genetic, and biochemical studies reported that depression is not the manifestation of a single risk factor such as the abnormality of a single neurotransmitter, but instead, it is the overall abnormality of various genetic, environmental, and developmental risk factors. According to recent neuroimaging studies, depression is considered as an outcome of the abnormality of various interactions and systems rather than the abnormality of a single area of the brain.[35]

The cortico-limbic circuit is currently gaining attention due to its ability of mediating stress response and playing an important role in the regulation of emotions. In early neuroimaging studies, which investigated the role of the limbic area in depression, the structural abnormalities of the limbic area, such as the atrophy or bilateral loss of the amygdala [36, 37] and the volume reduction of the hippocampus [38, 39] and caudate nucleus [40], were consistently reported in depressive patients. In addition, functional neuroimaging studies reported that the increased activation of the amygdala [41] and the reduced connectivity of the amygdala-cingulate [42] were observed when the subjects were exposed to negative stimulation such as a scary facial expression. The limbic area, including the amygdala, recognizes and classifies the emotional stimuli consciously or unconsciously, and mediates autonomic nervous system responses according to the emotion.[43, 44] As a result, a constant report regarding the abnormality of the limbic area in depressive patients seems to be reasonable. However, the activation of the limbic area was more reduced when an emotional stimulation was presented in a conscious level than in an unconscious level.[45, 46] In addition, the reduced activation of the limbic area and the removal of the negative emotion were observed in healthy subjects through cognitive emotional control strategy such as reappraisal.[47, 48] Based on the aforementioned results, the hyperactivation of the limbic area alone is insufficient to describe depression.

Accordingly, neuroimaging studies have been mainly conducted on the frontal cortex, which mediates the cognitive emotional processing. The prefrontal cortex, which is a complex structure that mediates emotional control, attention, reward system, and response inhibition, is important as it interacts with the anterior cingulate cortex and the limbic area.[49] In early structural neuroimaging studies, anatomical abnormalities, such as the reduced frontal cortex volume [50, 51] and the reduced number and size of frontal cortex neurons [52] were reported in depressive patients. The functional neuroimaging studies reported that the reduced activation, blood flow, and metabolism of the dorsolateral prefrontal cortex and ventromedial prefrontal cortex were observed in depressive patients regarding the conduct of emotional task.[53, 54] Furthermore, the failure of processing the emotional stimulation, which was caused by the failure of controlling the activation of the limbic area due to the reduction of prefrontal cortex activation, resulted in the clinical symptoms of depression, such as negative emotion, rumination [55-57] and decreased execution function.[58] Based on the aforementioned results, the failure of controlling the hyperactivated limbic area, which is attributable to the decreased function of the prefrontal cortex that controls the recognition and process of emotional stimuli, is likely to be the most important neuroimaging finding on depression.

4. Neurobiologic mechanism of psychotherapy on depressive disorder

Many studies were conducted in order to investigate the importance of the amygdala in relation to depressive disorder. Studies related to fear were also conducted, and the results showed that fear acquisition occurred in the amygdala when a specific stimulation was presented. The acquisition of fear does not necessarily require the neocortex; however, it is necessary to eliminate fear.[59] Psychotherapy, including behavioral treatment, is effective in controlling implicit memory acquisition in the amygdala and prefrontal area. Dealing with symbolic factors in dynamic psychotherapy will also control the activation of the amygdala by the temporal lobe and neocortex. However, the circuit from the cortex to the amygdala is weaker than the circuit from the amygdala to the cortex.[60] This is the reason why a longer duration is required for a new connectivity formation from the cortex to the amygdala, which serves as an evidence of long-term psychotherapy requirement. Psychotherapy includes the intentional memory for explicit memory, and promotes implicit memory by free association. The patient's amygdala is activated during free association. This means that the patients may play active roles in psychotherapy, to which emotional and cognitive associations related to the original trauma can be treated. The process of psychotherapy on depression is not a passive conditioned reflex, but instead, it is an active learning process.[61]

There are some methods of biologically measuring abnormal cognitive and emotional patterns during psychotherapy using repression or unconscious forgetting.[62] A previous study used a method that requests a subject to remember a certain word and then forget it.[63] After the subject is requested to forget the word, the increase in the prefrontal cortex (PFC) activation and the decrease in the hippocampus activation were observed during the recall tasks.[64] Other previous studies showed similar results. The anterior cingulate gyrus is known to play an important role in the attempt to forget unwanted memories. As such, the PFC and the anterior cingulate play an important role in the intentional forgetting of words or memories: i.e., the biological measurement of repression in psychodynamic psychotherapy.

Psychotherapy is related to characteristic neural circuitries, and different neural circuits are activated in different types of psychotherapy. It has been confirmed that different types of psychotherapy, including psychodynamic psychotherapy, cognitive therapy, and behavioral therapy, have different activation processes. For example, in psychodynamic psychotherapy, the therapist collects information on the patient based on his episodic memory. However, if the therapist uses the free association method, which focuses more on random memories than on the episodic memory, when these random memories are induced, the areas in the brain such as the frontal, parietal, and temporal cortexes are associated. On the other hand, the episodic memory is associated more with specific verbal areas such as Broca's area and the left frontal operculum.[65] As such, free association is a less censored process with the use of the extensive cortex network. The therapist investigates the symptoms and personality of the patient based on the extensive cortex activation during psychotherapy.

When cognitive behavioral therapy (CBT) is applied in depression patients, the patients are reminded of bad or sad memories, and they re-evaluate their negative memories. They re-interpret negative memories more positively during CBT, and their emotions before and after

the re-interpretation are rated. Several studies have investigated the correlations among the re-interpretations of the negative emotions/emotions/brain activity patterns during CBT.[66] The patients felt better after they re-interpreted their negative memories during CBT, which was related to the increased activity of their dorsolateral and dorsomedial PFC and to the decreased activity of their amygdala and orbitofrontal cortex. These findings are the bases of the biological model of CBT. Negative emotions as a result of certain stimuli are produced in the limbic and ventral prefrontal structures, which are decreased or blocked by the dorsal prefrontal circuitry during CBT.[67]

Finally, behavioral therapy (BT) will be discussed. BT is related to desensitization of stimuli that cause anxiety or extinction of learned responses. The results of animal tests and human studies showed that the areas, including the ventral PFC and the amygdala, are related to desensitization and extinction responses.[68] The result of an animal test using mice showed that the lesions in the amygdala or the administration of drugs that inhibit the amygdala distracted fear conditioning.[69, 70] Also, the results of human studies that used functional neuroimaging showed that amygdala activation is related to conditioned fear response. These results mean that the ventral PFC is related to the extinction and retention of the conditioned fear response by inhibiting the amygdala.[71] As such, the important mechanism of extinction-based BT involves the strengthening of the PFC activation and the attenuation of the amygdala.

5. Variable methodology of the brain function for psychotherapy and depression

The variability of the limitations and results of studies on psychotherapy and neuroimaging for depression should be reviewed first before their relationship is investigated. Recently introduced technologies on neuroimaging and their rationales are variable, and there are different ways to evaluate the efficacy of psychotherapy. Manual therapy under a time-limited setting is used for psychotherapy, including BT, CBT, and interpersonal therapy (ITP). Even if the program designs of many types of psychotherapy are standardized, they are subjective, depending on their investigator, due to their manualized treatment design.[72] Previous studies showed that the therapeutic modality of some types of CBT seem more similar to that of BT, or vice versa. The inconsistency of the methodology is also caused by the number of therapists (one or many), the number of sessions performed, or the type of therapy (e.g., individual therapy or group therapy). As such, the aforementioned factors should be considered when reviewing the results of previous studies.

Neuroimaging also has various modalities, as does psychotherapy. Neuroimaging is designed to evaluate the glucose metabolism or the cerebral blood flow (CBF). Although the relationship between the glucose metabolism/CBF and the neuronal activity cannot be understood fully, the brain function in neuroimaging is described using terms such as 'metabolic activity' or 'hemodynamic activity'. Also, "brain activity" is a commonly used term for both metabolic activity and hemodynamic activity.[73] As mentioned, neuroimaging refers to various methodologies, including PET, SPECT, and fMRI. Each imaging technique has a different

mechanism, with different image resolutions and application limitations.[74] There are other methods of separately measuring the regional brain activity, such as voxel-based techniques (e.g., SPM) and region of interest (ROI)-based techniques. Multiple comparison is difficult for ROI-based techniques, but such techniques present clear anatomical borders. For voxel-based techniques, much data can be extracted, and clear functional connectivity can be achieved.[74]

Even if different neuroimaging and psychotherapy methods are used, they have a common and duplicate study design. Most imaging studies scan brain images before and after psychotherapy and compare the results with those of healthy control subjects to evaluate the treatment efficacy. A functional neuroimaging study measured the brain activity while a patient was resting, and another study measured the brain activity while a patient was exposed to anxiety stimuli or was performing cognitive or affective tasks. Understanding the differences between various neuroimaging methods can lead to accurate understanding of brain activity data.

6. Imaging neural effects of psychotherapy on depression

Various studies have been conducted in the last few decades on the neurobiological mechanism in depression and on its relationship with psychotherapy.[75, 76] Aaron Beck, the founder of CBT for treating depression, has continuously claimed that studies are required on the relationship between the psychological mechanism and the biological mechanism.[77] The recent controversy on whether or not the biological mechanisms of antidepressant medication (ADM) and psychotherapy are different has led to many studies on neuroimaging. Many previous studies have proven that ADM and psychotherapy have different neurofunctional mediators and different mechanisms. Moreover, the studies found that the therapeutic efficacy of ADM differs from that of psychotherapy between mild and severe depression [78], as do their relapse rates.[75]

Relatively consistent study results were shown on the brain function of the depression patients. The results showed that the resting metabolism of the amygdala increased in the depression patients [79], and that the amygdala activation increased while aversive stimuli were expected. [80, 81] On the contrary, patients with depression showed decreased prefrontal cortex (PFC) resting metabolism.[82, 83] The investigators proved, using fMRI, that the amygdalar reactivity in the depression patients was elevated during the emotion-processing tasks and that the dorsolateral prefrontal cortex (DLPFC) activation decreased during the cognitive tasks. The investigators also found that the functional connectivity between the amygdala and the DLPFC decreased in the depression patients.[54] These findings are the basis of the theory that the brain function of depression patients shows increased bottom-up emotional reactivity and decreased top-down regulation of emotions. This is called the 'cortico-limbic dysregulation model'. [84] The emotion regulation of healthy people is also modulated by the bottom-up/top-down interaction. This theological model best explains the mechanism of the neurofunctional mode and the dysfunctional network in depression hypothesized by Beck.[77]

Various experiment methods were used to discover the pathophysiological mechanism related to the neurofunctional mode and the dysfunction of a neural network in depression, using

neuroimaging. In the beginning, many studies observed the changes caused by pharmacotherapy. One such study was that of Anand et al. [85], in which sertraline was administered to 12 depression patients for six weeks. Ten of them showed depression improvement, as well as elevated functional cingulo-limbic connectivity and naturally decreased limbic reactivity when they were exposed to aversive stimuli. These changes in the depression patients after the pharmacotherapy showed that the patients had pathologic functional connectivity and that depression is a network disorder.

This concept of a network disorder was also confirmed in longitudinal studies that compared depression patients and a control group treated with fluoxetine. All the patients showed elevated activities of their DLPFC, ACC, premotor, parietal, posterior insular, and posterior cingulate cortices and decreased activities of their subcingulate, parahippocampus, and thalamus after fluoxetine treatment.[86] Additional changes in the subcortical and limbic activities were observed in the patients who showed good response to fluoxetine. The isolated increase in the activity in the cortical structure shown in the control group was considered a top-down mechanism which is regarded as a placebo effect.

The principle of psychotherapy for depression does not seem to follow this simple principle of a decrease in the bottom-up regulation and an increase in the top-down regulation, based on the results of previous studies. The activity change in the PFC also differs between the tonic and resting states, and from the event-related responses in psychotherapy and pharmacotherapy.[75] With the authors' insufficient understanding of event-related fMRI and of the theory of the stimulus-dependent neural mechanism, there is only empirical evidence of the improvement of the brain function with psychotherapy, but the neurobiological fundamentals of psychotherapy have not been proven yet.

7. Posttreatment neuroimaging changes in depression

7.1. CBT and depression

[Goldapple]

There was a functional neuroimaging study that used only CBT, without pharmacotherapy (Goldapple et al., 2004).[87] The neuroimages before and after the CBT were compared, and the patients were asked not to ruminate on one topic during the FDG-PET. A further study by the same investigators included a patient group that underwent pharmacotherapy using only paroxetine. Surprisingly, the group that underwent only CBT showed decreased metabolism in multiple frontal regions, including in the dorsolateral PFC. This result that showed decreased dorsolateral PFC activity from the baseline is contrary to the previous results that showed CBT-strengthened dorsolateral PFC activity. The authors of this study understood this decreased prefrontal metabolism as a therapeutic effect of CBT due to decreased active rethinking and reappraisal of emotional ideas. This interpretation is consistent with the study results of Paquette et al. that showed the decreased dorsal PFC of spider phobia patients when their treatment was successful.[88] On the other hand, this result is opposite that of the study

of Ochsner et al., which showed that the ability to reappraise effect-generating stimuli was enhanced after CBT in the depression patients.[66, 67, 89] In the study of Goldapple, the PFC metabolism was elevated after the pharmacotherapy in the depression patients who received only paroxetine. This proves that the biological therapeutic mechanisms of pharmacotherapy and CBT in depression are different even if they have similar degrees of efficacy.[87]

The study of Goldapple also measured the changes in the limbic and paralimbic activities after CBT treatment in depression patients apart from the change in the PFC. They found that different mechanisms were involved in the patients who underwent only CBT and in the patients who underwent only paroxetine treatment. The patients who underwent only CBT showed clearly elevated activities in their hippocampus, parahippocampus gyrus, and dorsal cingulate gyrus. On the other hand, the patients who received only paroxetine showed less elevated activity in their hippocampal and parahippocampal areas with decreased activity in their posterior cingulate and ventral subgenual cingulate. Goldapple claimed a modality-specific model depending on the therapeutic response of depression [87], based on their study results and the widely known functional and anatomic relationship theory.[90, 91] Anti-depressant agents produce a bottom-up effect by disengaging the ventral frontal and limbic region, whereas CBT produces a top-down effect by decreasing the cortical processing. These changes help process of personal emotions and environmental stimuli, and show a therapeutic effect on depression. The results and interpretation of Goldapple et al. are opposite those of the emotional and regulation model [66] of Ochsner et al. Ochsner understood that ventral frontal and limbic hyperactivity caused negative emotions. Seminowicz et al. [92] explained the difference between the theories of Goldapple and Ochsner according to the brain activation, depending on the treatment protocol and the underlying brain state. In other words, Goldapple et al. performed CBT on depression patients, whereas Ochsner used it on healthy control subjects. As such, future studies are required to investigate the change in the brain activity when a different type of psychotherapy apart from CBT is used for depression treatment.

[Kennedy]

Kennedy performed a study with the same design as that of Goldapple to analyze neuroimaging, after dividing the depression patients into two groups: the CBT group and the pharmacotherapy group treated by venlafaxine (Kennedy et al., 2007).[93] Kennedy hypothesized that the prefrontal activity would decrease due to top-down processing after the CBT, and that subcortical changes would appear due to bottom-up modulation after the administration of venlafaxine. The glucose metabolism of the patients was measured before the treatment, after the treatment, and 16 weeks after the completion of the treatment following the CBT and the venlafaxine administration. All the patients who responded to the treatment, regardless of the CBT or the venlafaxine administration, showed decreased activities in their orbitofrontal cortex and their left medial prefrontal cortex, and increased activity in their right occipito-temporal cortex. The patients who responded to the CBT showed increased activities in their posterior cingulate and thalamus, and decreased activity in their left inferior temporal cortex. On the other hand, the patients who responded to the pharmacotherapy (venlafaxine) showed increased activity in their left temporal cortex and decreased activity in their posterior cingulate. The authors of the study concluded that CBT is related to reciprocal modulation of

cortical limbic interactions, which was consistent with the results of previous studies. They also presented venlafaxine as related to the cortical and striatal region, which was not known before.

[FU]

Fu reported the effect of CBT on depression using fMRI (Fu et al., 2004).[94] In their study, the fMRI scans of 16 depression patients were compared with those of healthy control subjects. When the 16 depression patients were exposed to a sad facial expression before the CBT, the reactivity of their right amygdala and hippocampus relatively increased compared to that of the healthy subjects. They also showed decreased ACC activation at the baseline, unlike the healthy subjects.[94] These differences between the groups no longer appeared after 16 CBT sessions. This means the stimulus-dependent reactivity in the amygdala decreased and the ACC activation increased in the depression patients after the CBT. However, it is uncertain if this result is meaningful, as the evidence of the event-related fMRI methodology is still insufficient and the stimulus-dependent neural mechanism is not fully understood yet. It has been understood that psychotherapy does not change certain areas but rather, extensive areas in the brain, and generally modifies brain dysfunction.[95] However, the results of the investigation of how psychotherapy changes the metabolic or functional activity have been inconsistent. In particular, the effect of psychotherapy on the PFC metabolism is more controversial. This may be attributed to the differences in the methodologies of the studies.

7.2. ITP and depression

[Martin]

Martin [96] measured the change in the CBF after IPT in depression patients. The neuroimages of the depression patients who underwent IPT were compared with those of the depression patients who underwent pharmacotherapy. The patients who underwent pharmacotherapy received 37.5 mg of venlafaxine daily. Twenty-eight depression patients were treated for six weeks, and their CBFs were measured using ^{99m}Tc -HMPAOSPECT. All of them had not been treated with any drug in the last six months before they participated in the study. The patients in the IPT group underwent IPT for six weeks with the same therapist, and those in the pharmacotherapy group were administered venlafaxine every second week with a 15-minute consultation. The patients in both groups showed clinical improvement with increased blood flow in their right basal ganglia. The patients in the IPT group showed additional changes - increased right posterior cingulate activity - which was similar to the result of the study of Goldapple.[87] Martin had the same opinion of Goldapple's result and considered insignificant the changes in the limbic and paralimbic recruitment of the brain function related to psychotherapy. However, he also observed the change in the brain function in a specific paralimbic region. A study is required to interpret this result.

[Brody]

Brody [97, 98] conducted a study with a design similar to that of Martin for 12 weeks. The study was conducted on 24 patients, divided into two groups: the IPT group and the paroxetine group. Then their PET neuroimages were compared. The study also included a healthy control

group, unlike Martin's study. The patients chose which treatment they would receive. The results of the study showed that the symptoms of the patients who chose paroxetine treatment were milder than those of the patients who selected IPT, and showed greater improvement after the treatment. Even if there were differences between the groups, the results of the study showed that the dorsal and ventral prefrontal cortical metabolism decreased after the IPT. This result was consistent with that of the study of Goldapple.[87, 92] All the patients in both groups showed increased metabolism in their limbic and paralimbic regions, particularly in their right insula and left inferior temporal lobe. Unlike Goldapple's study, Brody's study reported that the patients treated with paroxetine showed decreased PFC activation.[97, 98]

Brody conducted a further study on 39 patients.[99] As in his previous study, the subjects were divided into two groups: the IPT group and the paroxetine group. Their neuroimages, obtained using PET, were analyzed. Unlike in Brody's previous study, however, the improvements in the specific mood symptom cluster and in the brain activity were compared. In all the patients, decreased ventral and dorsal frontal lobe metabolism was associated with reduction of symptoms such as anxiety/somatization, psychomotor retardation symptom, tension/anxiety, and fatigue. It was interesting that the improvement of the cognitive function was positively correlated with the degree of the dorsolateral PFC metabolism. This result differed from those of previous CBT studies. Some studies reported that the activity of the dorsolateral PFC was negatively correlated with the global depression score after the CBT. This difference was attributed to the reduction of over-thinking and rumination and the decrease in the dorsolateral PFC function with CBT, and the increase in the general cognitive ability and the strengthening of the dorsolateral PFC function with IPT. However, the difference should be verified with further repetitive studies. Brody's study had the following significant limitations: (1) the patients chose between IPT and paroxetine administration for the treatment type, which caused a difference between the groups, and (2) six symptom clusters, each with 12 ROIs (regions of interest), were used for the analysis without correction for multiple comparisons.

7.3. PDT (PsychoDynamicpsychoTherapy) and depression

The metabolic activities in the amygdala, hippocampus, and dorsal prefrontal cortex of the depression patients treated by PDT become similar to that of healthy people when the patients are exposed to attachment-related stimuli. The activation of the subgenual cingulate cortex has been known to decrease in depression patients after PDT, compared to healthy people [100], and this neural mechanism of PDT in relieving the symptoms of depression was proven through neuroimaging. Depression is believed to be a pathological state of the activity level of the brain circuit, and PDT is believed to normalize the brain circuit.

The designs of the studies on the neural mechanism of PDT through neuroimaging were similar to those of CBT or IPT, as previously stated. The change in the brain function was analyzed before and after PDT, and the results of the control and pharmacotherapy groups were compared.[101] However, the difference in the methodologies of the studies makes their comparison difficult. For example, Buchheim suggested that PDT was very effective in patients with subgenual ACC overactive depression [100], whereas CBT did not show any relevance. [102, 103] It was not completely understood if such result was because the neurobiological

mechanisms of PDT and CBT were different, or if their study methodology was different due to their significantly different therapy methods. As such, standardization of the methodology is crucial in analyzing imaging data.

[Buchheim]

The study examining the effect of psychotherapy on brain function in patients with depression was conducted to investigate the effect of long-term psychodynamic intervention (Buchheim et al., 2012).[100] Sixteen, un-medicated outpatients with depression who underwent 15 months of psychodynamic therapy were scanned twice, before and after treatment, during the presentation of attachment-related scenes with neutral descriptions alternated with descriptions containing personal sentences previously extracted from an attachment interview. The results showed increased activation in the left anterior hippocampus/amygdala, subgenual cingulate, and medial prefrontal cortex in patients compared to healthy controls before treatment, and a reduction in the same areas after treatment. Furthermore, this normalisation of brain activity was positively correlated with general symptom improvement.

[Hirvonen, Karlsson]

Two other PET studies also focused on changes in neurotransmission implicated in the pathophysiology of depression following short psychodynamic psychotherapy (Hirvonen et al., 2010; Karlsson et al., 2010).[104, 105] Karlsson et al. (2010) for example compared the effect of psychotherapy and Fluoxetine on the density of serotonin 5-HT_{1A} receptors, building on previous studies reporting a widespread decrease in the density of serotonin 5-HT_{1A} receptors in the disease.[106-108] Specifically, patients were randomly assigned to either pharmacotherapy or psychotherapy, with the subsequent groups comprising 15 and 8 subjects respectively. Binding potential (BP) values, representing the ratio of specific and non-displaceable binding, were estimated using white matter as reference region (BP is a crucial measure in the PET studies to measure the density of “available” receptors), [109] Although both groups showed comparable symptom improvement post-treatment, when pre- and post-treatment values were compared, only those who underwent psychotherapy showed increased serotonin 5-HT_{1A} binding in several cortical regions including dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, ventral ACC, inferior temporal gyrus, insular cortex, and the angular gyrus.

In a subsequent study by the same group (Hirvonen et al., 2010), the effect of short psychodynamic psychotherapy and Fluoxetine was compared in patients with major depression with a specific focus on striatal and thalamic dopamine D_{2/3} receptors.[104] Results showed that although both treatments led to a significant improvement in symptomatology, no effects on D_{2/3} receptor availability in the ventral striatum or other subdivisions of the striatum were found. Moreover, only Fluoxetine increased thalamic D_{2/3} binding, but this increase was not correlated with clinical improvement. Thus, the study does not support the involvement of ventral dopaminergic neurotransmission in the antidepressant effects of Fluoxetine or psychodynamic psychotherapy. However, statistical power may have been hindered by the relatively small sample size.

7.4. BATD (Brief Behavioural Activation treatment for depression) and depression

Dichter et al. also carried out 2 fMRI studies with the same sample (2009, 2010). The main goal of the first study (Dichter et al., 2009) was to elucidate the neural correlates of Brief Behavioural Activation Treatment for Depression (BATD) during reward processing in depressed patients. [110] BATD is a structured and validated psychotherapy designed to increase engagement with rewarding behaviours and reduce avoidance behaviours.[111] Brain activity was measured in 12 subjects with depression and 15 healthy controls, while they were engaged in a Wheel of Fortune task (WOF), a two-choice decision-making task involving probabilistic monetary outcomes, before and after BATD.

Following the BATD, patients showed increased activity in structures that mediate responses to rewards, including the paracingulate gyrus during reward selection, the right caudate nucleus during reward anticipation, and the paracingulate and orbital frontal gyri during reward feedback. In contrast, the main aim of the second study by Dichter et al. (2010) was to identify baseline fMRI predictors of response to treatment in depression.[112] Before and after BATD, they scanned patients and matched controls while they were performing a task requiring cognitive control in both sad and neutral contexts. The results showed that following treatment, there was decreased activity in prefrontal structures including the paracingulate gyrus, the right orbital frontal cortex and the right frontal pole in response to stimuli presented within a sad context. In addition, pre-treatment activity in the paracingulate gyrus was identified as a significant predictor of symptomatic improvement following treatment.

8. Conclusion

In summary, despite the heterogeneity of the studies in terms of neuroimaging technique, psychotherapeutic approach and experimental paradigm employed, the majority of the above results suggest that psychological treatment of patients with depression results in a normalisation of the activation pattern in fronto-limbic circuitry. Regarding the relationship between the effects of psychotherapy and medication, their mechanisms seem divergent based on the results of two independent studies.[84] To explain these different mechanisms of action, it has been suggested that while psychotherapy may exert its effects top-down, targeting mainly frontal cortical regions and reducing dysfunctional thought processes, pharmacotherapy may produce bottom-up changes by disengaging ventral and limbic regions mediating attention to personally relevant emotional and environmental stimuli.[87, 92]

Neuroimaging techniques have significantly contributed to biological psychiatry research in the last decades, but the investigation of the mechanism of psychotherapy for depression has still been limited. The neural mechanism of psychotherapy is widely recognized, whereas its process cannot be clearly described yet. As psychotherapy holds a key position in psychiatry, it will be continuously investigated and researched. Therapy without a neuroscientific basis is only empirical, and the possibility of its development is low. Also, the application of such therapy is difficult, with limited potential to develop towards a new therapy.

Study	Psychotherapy (Number of subjects)	Pharmacotherapy (Number of subjects)	Controls	Neuroimaging Methods
Goldapple et al.(2004)	CBT (14)	Paroxetine (13)		PET
Kennedy et al.(2007)	CBT (12)	Venlafaxine (12)		PET
Fu et al.(2008)	CBT (16)		16	fMRI
Martin et al.(2001)	IPT (13)	Venlafaxine (15)		SPECT
Brody et al.(2001)	IPT (14)	Paroxetine (10)	16	PET
Buchheim et al.(2012)	15month PDT (16)		17	fMRI
Hirvonen et al.(2010)	Short term PDT (8)	Fluoxetine (14)		PET
Karlsson et al.(2010)	Short term PDT (8)	Fluoxetine (15)		PET
Dichter et al.(2009,2010)	BADT (12)		15	fMRI

Table 1. Studies on the effects of psychotherapy on brain function in depressive patients.

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