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# Chapter 11

[AU1]

# Psychotherapy Increases the Amount of Serotonin Receptors in the Brains of Patients with Major Depressive Disorder

**Hasse Karlsson**

**Keywords** Fluoxetine • Major depressive disorder • Positron emission tomography • Serotonin receptors • Short-term psychodynamic psychotherapy



## Introduction

The effects of psychotherapy have traditionally been measured by change in core symptoms, psychological abilities (personality, defenses, cognitions, etc.), or social functioning. With the advent of functional brain imaging methods (such as SPECT, PET, fMRI, and MEG), it has become possible to include a new dimension in the measurements, namely changes in brain functions after psychotherapy. Several studies investigating change in cerebral blood flow or metabolism have been published, and they have showed that different forms of psychotherapy indeed lead to brain changes [1, 2]. These studies have been usually performed with patients suffering from depressive or anxiety disorders, and the treatments have in the majority of the studies been cognitive-behavioral therapy (CBT) or interpersonal psychotherapy (IPT).

In addition to measuring blood flow and metabolism, positron emission tomography (PET) can also be used to investigate changes in receptor densities in the synapses. In depression, especially the serotonin system has been intensively investigated, and serotonergic medications are currently widely used in the treatment of depression. We have focused on the serotonin 5-$HT_{1A}$ receptor system, which is implicated in the pathophysiology of depression [3, 4]. It has also been directly shown that patients with depressive illness have a widespread decrease in the density of serotonin 5-$HT_{1A}$ receptors during the illness period [5–9].

## Psychotherapy and the Serotonin System

There are only very few studies using brain imaging and utilizing psychodynamic therapy as the treatment. All of the published studies have focused on the serotonin system, and they are performed by two separate groups in Finland. The other group has investigated changes in serotonin transporter

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(SERT) density after psychotherapy using single photon emission computed tomography (SPECT). The first published study was a case study showing that SERT densities increased in the medial prefrontal area and thalamus after 1 year of psychodynamic psychotherapy and recovery from depression in a patient suffering from major depressive disorder and borderline personality disorder [10]. Another case study from the same group reported a subject with mixed mania and six depressed controls [11]. The patient with mixed mania had an elevated SERT availability in the midbrain compared to depressed patients who had decreased levels. All received psychodynamic psychotherapy (the mixed mania case for 8 months and the depressed patients for 12 months). After treatment, the SERT availability decreased in the single case by 9.9% and increased in the depressive controls by 12.5%. Finally, this group has reported recently that in a group ($N=19$) of depressed patients, midbrain SERT density increased after 12 months of psychodynamic psychotherapy in patients suffering from atypical depression, but no change was found among typically depressed patients [12]. The main problems with these studies are that they are not randomized and that the most recent study lacks a control group.

As far as I know, only one randomized comparative study on receptor level changes after psychodynamic psychotherapy has been published [13]. In this study, we measured changes in serotonin 5-$HT_{1A}$ receptor densities after psychotherapy and compared them with changes after fluoxetine pharmacotherapy. PET scanning with the 5-$HT_{1A}$ radiotracer [*carbonyl*-$^{11}$C]WAY-100,635 was performed before and after the intervention.

The patients with symptoms of depression were recruited through five occupational health service units providing primary health care. All of the included subjects were help-seeking patients, and they gave their written informed consent for the study. All the subjects were interviewed by a psychiatrist, using the Structured Clinical Interview for DSM-IV axis-I disorders. The severity of the depression was assessed by the psychiatrist using the 17-item Hamilton Depression Rating Scale (HDRS), and the subjects were also asked to fill in the Beck Depression Inventory (BDI).

The inclusion criteria for the study were:

1. Mild or moderate episode of major depressive disorder
2. HDRS score of 13 or more
3. Age 20–60 years
4. No psychotherapeutic or psychopharmacological treatment during the preceding 4 months
5. No DSM-IV axis-I or axis-II co-morbidity
6. No severe somatic illnesses

After fulfilling the criteria of the study, the patients were randomly allocated to receive either psychodynamic psychotherapy or fluoxetine medication.

The psychotherapy was short-term psychodynamic psychotherapy (STPP), and it consisted of 16 weekly sessions with experienced psychiatrists or psychologists ($n=5$) who had training in psychodynamic psychotherapy and work experience of over 10 years as a psychotherapist. Additionally, all of them had completed the same 2-year training program in STPP with teachers from Finland, Sweden, Norway, and the UK.

The pharmacotherapy with fluoxetine also lasted 16 weeks. The initial dose was 20 mg/day and the dose could be increased to 40 mg/day if there was no response in 3–4 weeks. The medication was supervised by a general practitioner, who was a member of the research team. The general practitioner met the patients once or twice a month. Plasma fluoxetine and norfluoxetine levels were measured at the 4-month follow-up.

In a previous paper, we reported that both treatments functioned equally well and were highly effective [14]. According to the DSM-IV criteria, a total of 68% ($n=13$) of the completers in the fluoxetine group, and 71% ($n=15$) in the psychotherapy group were clinically in remission at the 4-month follow-up ($p=0.84$). The corresponding figures for all randomized patients ($n=51$) were 52% and 58%.

In the subgroup of patients who underwent PET imaging ($N=23$), the clinical outcome in both treatment groups was also similar in terms of standard symptom ratings: the average Hamilton depression

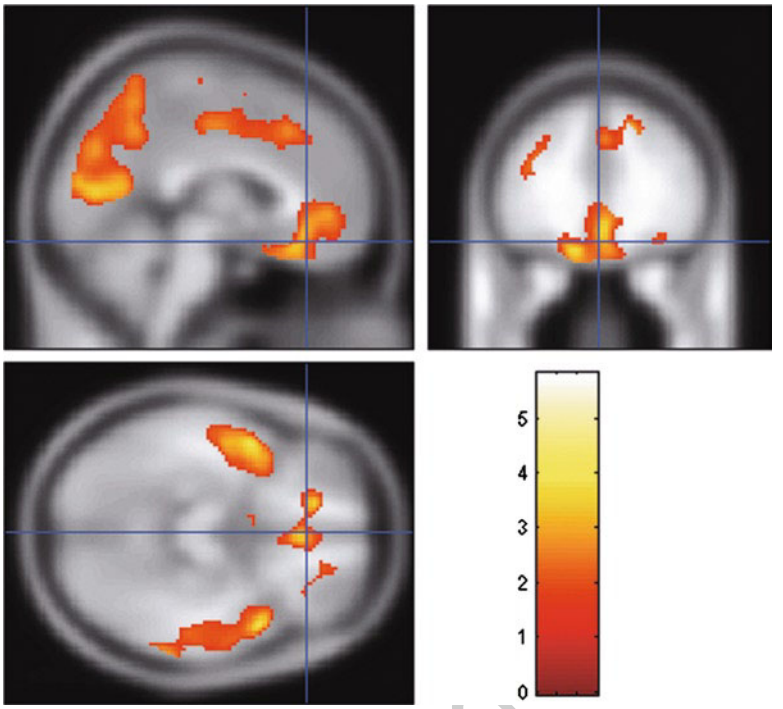


**Fig. 11.1** Results from the SPM analysis shows two large clusters ($k_E = 9{,}515$, $T_{max} = 5.82$ at [−26, 0, −38] and $k_E = 18{,}231$ voxels, $T_{max} = 4.10$ at [−46, −20, 42]) located mainly in frontal, temporal and parietal cortex. These clusters represent significantly increased BP in the psychotherapy group as compared with the fluoxetine group. The results are visualized on a T1-weighted MRI template in stereotactic standard space, and color bar represents the *T* statistic at voxel level (Reprinted with permission from Ref. [13]. Copyright © Cambridge Journals)



total score decreased in the STPP group from 19.9 to 5.6 ($p < 0.001$) and in the fluoxetine group from 18.1 to 7.3 ($p < 0.001$). The average BDI total score decreased from 22.4 to 8.8 ($p = 0.001$) and from 24.9 to 11.5 ($p < 0.001$), respectively. Thus, there was a substantial treatment response as 59% of the subjects reached remission and 77% of the subjects met the criteria for response at 4 months.

Additionally, there were no differences between the treatment groups in the baseline HDRS or BDI scores, in the reduction of HDRS or BDI, or in the proportion of patients in remission or those classified as responders following treatment.

Preparation of the radioligand [*carbonyl*-$^{11}$C]WAY-100,635 and PET scanning procedures have been previously described in detail [15]. Regarding the technical details concerning the imaging, quantification, and data analysis, I refer to the original publication [13].

Analysis of the change in the 5-$HT_{1A}$ receptor density in the treatment groups revealed a significant increase in the STPP group as compared with the pharmacotherapy group (rmANOVA: group × repetition, $p = 0.014$). When compared with healthy controls, patients in the STPP group demonstrated significantly increased 5-$HT_{1A}$ density after treatment (group × repetition, $p = 0.003$), whereas patients receiving fluoxetine did not differ from healthy control subjects in terms of the change (group × repetition, $p = 0.222$).

When we restricted the analysis only to responders, the difference between the groups was still evident (group × repetition, $p = 0.063$) and the same applied to those in remission (group × repetition, $p = 0.027$). When the main analysis was covaried with both response and remission status (group × repetition, $p = 0.028$), first-episode/recurrent status (group × repetition, $p = 0.029$), or level of education (group × repetition, $p = 0.037$), the main result was still unchanged.

The voxel-based analysis of parametric [*carbonyl*-$^{11}$C]WAY-100,635 BP confirmed the results from the main analysis (Fig. 11.1) and demonstrated two large clusters in frontal, parietal, and

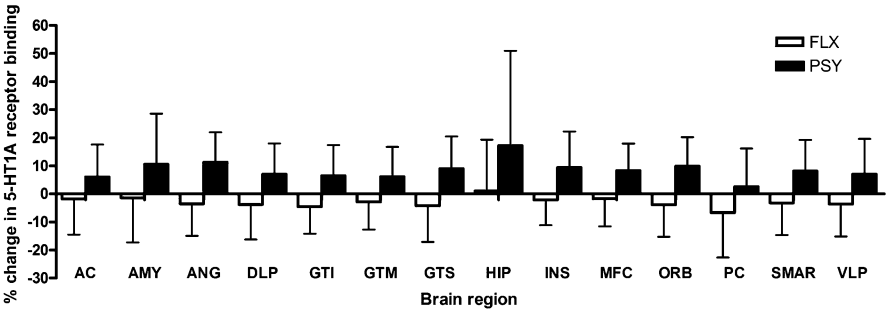


**Fig. 11.2** Average percentual changes in $5HT_{1A}$ receptor density in different brain areas in the fluoxetine (*white bars*) and psychotherapy (*black bars*) groups (Reprinted with permission from Ref. [13]. Copyright © Cambridge Journals)

temporal cortex representing significant increase in 5-$HT_{1A}$ density in the STPP group as compared with the fluoxetine group.

To investigate which brain regions contributed most to the overall analysis, regional rmANOVA models were also applied. Average percentage changes in different brain regions in 5-$HT_{1A}$ receptor density in the treatment groups are shown in Fig. 11.2.

## Psychotherapy Increases Serotonin 5HT-1A Receptor Densities: So What?

In this randomized study, we found an increase in the density of serotonin 5-$HT_{1A}$ receptors in multiple cortical regions after psychotherapy among patients suffering from major depressive disorder. A similar change was not seen among patients receiving fluoxetine medication. What do these results mean?

The first very general conclusion from this study is that the artificial separation between interventions targeting either brain or mind is outdated. Psychotherapy clearly changes brain functions, and there is evidence that medication changes abilities traditionally considered to belong to the mind as distinct from the brain.

Secondly, there is previous evidence that treatment with SSRI medication does not increase the densities of 5-$HT_{1A}$ receptors among patients suffering from major depressive disorder [6, 16], and our results are in line with these. The study by Bhagwagar et al. [7] additionally showed that recovery from depression is not accompanied by increase in brain 5-$HT_{1A}$ receptors. However, the patients in that study suffered from recurrent depression and had used antidepressant medication earlier.

Thus, it has been suggested that the lower level of 5-$HT_{1A}$ receptors in patients could be a trait marker of depression that increases the risk of future depression. If this is true, one important implication of our study would be that this brief psychodynamic psychotherapy may lead to a change in this trait. This possibility is indirectly supported by a finding showing that the relapse rate among patients suffering from major depressive disorder is lower among those treated with psychotherapy compared with those treated with antidepressant medication [17].

However, another possibility is that the decreased amount of 5-$HT_{1A}$ receptors is a state marker of major depression, but that currently widely used methods for symptom quantification (such as BDI, HDRS) do not wholly reflect the function served by this receptor system. It could be that the change in the 5-$HT_{1A}$ system is related to something else in the depressive state than symptoms (e.g., functional ability, quality of life, change in defenses, or interpersonal relations). We are currently exploring some of these possibilities.

The main finding was that different molecular changes are associated with the two treatments despite the fact that clinically both treatments functioned equally well. A highly simplistic view of the

function of the serotonin system in relation to these treatments would suggest that the two treatments could lead to similar outcomes both clinically and in the functions of the serotonin system, because fluoxetine enhances serotonergic neurotransmission by increasing the amount of the neurotransmitter in the synaptic cleft and psychotherapy by increasing the density of postsynaptic receptors.

Why, then, does psychotherapy increase the amount of serotonin receptors? The mechanisms involved remain unknown. There is evidence from animal studies that the development of the serotonin system is influenced by environmental factors, such as maternal separation in rats. For example, Vicentic et al. [18] have demonstrated that a 180-min separation from the dam (the rat mother) during postnatal days 2–14 resulted in a change in the forebrain 5-$HT_{1A}$ receptor levels compared to non-handled pups. Also, environmental factors later in life, such as mild chronic stress, may induce changes in the 5-$HT_{1A}$ system in rats [19]. However, all the previous studies showing that environmental factors modulate the serotonin system have been animal studies and have shown changes induced by stress or other "negative" events. This study included patients and the environmental intervention aimed at a "positive" change, and it reversed the downregulation associated with major depression and led to plastic molecular level changes in the synapse.

Given the importance of CNS serotonin in cognitive and emotional processes and the fact that psychotherapy is probably a form of emotional learning, the increase in 5-$HT_{1A}$ receptors in the psychotherapy group could reflect a top-down modulation of the serotonin system based on increased emotion regulation and learning. Along these lines, Kandel [20] has hypothesized that psychotherapy could lead to changes in gene expression through learning by altering the strength of synaptic connections and inducing structural changes that alter the anatomical pattern of interconnections between nerve cells of the brain. Our study clearly supports this hypothesis.



## Where to Go from Here?

The findings of this study should of course be replicated. In the future, it would also be important to find out if there are differences in the relapse rate of patients that have recovered from depression with the help of different treatments, but who exhibit different changes in the serotonin system after the treatment. An important aspect is also to find out if the 5-$HT_{1A}$ system really represents a state or trait marker of depression. Future studies should also investigate the effect of different psychotherapies and of spontaneous remission on the changes in the 5-$HT_{1A}$ system. A plausible thought is that different psychotherapies target different brain systems and, thus, would show different change patterns in the brain. No direct comparisons, however, between different psychotherapies in this regard have been performed. At this stage, we also do not know if the brain changes seen so far using different psychotherapies reflect changes that are specific for the therapies or just the recovery process in the brain (which could be similar across different therapies).

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| AU1 | Please check if the chapter title should be edited as "Psychotherapy: Increased Amount of Serotonin Receptors in the Brains of Patients with Major Depressive Disorder", since a chapter title cannot be a complete sentence. | |