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Chapter 10
Toward Molecular Psychotherapy of Depression?

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Keywords 5-HTTLPR polymorphism • Brain imaging • Depression • Dynamic psychotherapy • Serotonin transporters • SPET • Therapy outcome

Introduction

The 30–40% share of genetic factors in the disposition to unipolar major depression (MD) leaves an important role for psychosocial and developmental factors in the etiology and treatment of depression [1–3]. Moreover, it is likely that the biological and psychosocial factors are not independent. Their interaction in depression has been suggested in numerous studies, although the relevant mechanisms are not well understood [4–7]. Especially in the psychodynamic picture of depression, the role of somatic factors has been little illuminated due to the lack of a viable theory that would connect somatic signs with the psychodynamic profile of depression [8, 9].

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The psychosocial symptoms of depression range from minor inhibitions of mood and pleasure to major disability that affects the quality of life, social, and occupational functioning and human relationships. Factors such as prolonged stress, personal loss or rupture in interpersonal relationships, developmental deprivation, loneliness, and occupational adversities usually underlie these symptoms [10, 11]. Clinical depression follows when the hardships are accompanied by feelings of disappointment, poorly tolerated mental pain, helplessness, and anger turned inwards. The psychodynamic conception of depression particularly centers on the meaning of object loss, inhibited mourning, and internalization of feelings of frustration and anger, sometimes acquiring the dimensions of rage [12–15].

In parallel with the psychological and psychosocial problems, several somatic signs of depression often prevail, although to an individually varying degree [16]. They include a wide spectrum of symptoms such as fatigue, affective blunting, inhibition of pleasure, diminished psychological energy, lowering of sexual interest, psychomotor and memory retardation, loss of motivation, constraints of anger expression, sleep disturbances, pain and gastrointestinal symptoms, cardiac arrhythmias, appetite disturbance, and disposition to infections.

The Need for a Theory Linking Depression of the Mind and Brain

The bodily expressions of depression make a connection between the psychological and somatic signs plausible. The parallel increase during recent years of knowledge in both biological [17, 18] and psychological treatments [19, 20] of depression clearly calls for a model to combine these divergent dimensions in the study and treatment of depression.

The current biological theory of depression pinpoints two major neurobiological mechanisms behind the somatic and affective symptoms [18, 21–26] (1) prolonged stress-related over-activity of the hypothalamic–pituitary axis (HPA) with hypercortisolism, a disturbed circadian rhythm of sleep wakefulness and cortisol excretion and (2) hypo-activity of especially serotonin, but also of noradrenaline and dopamine transmitter functions.

These biological signs do not, however, provide understanding of how the disorders of body regulation are intertwined with psychological malfunction. Integration of the neurobiological and clinical aspects in depression has proved to be a complicated matter. From the point of view of neural network connectivity, evidence has been gained that serotonin transmission perhaps is just an intermediating factor in the etiology of depression. The processes regulating the formation of new synapses may be more central [27, 28]. The abandoning of an explanatory model based on causal one-factor or additive multifactor effects has been seen as necessary, and its replacement with a multidimensional model with nonlinear variables has been suggested [5].

Through these theoretical developments, a growing recognition is taking place of the complexity of the mind–brain relations and their reciprocal nature. These new explanatory models and their implications for treatment are also becoming increasingly relevant for the psychodynamic understanding of the functions of the mind. They open new vistas to evaluate the feasibility of the psychodynamic approach in researching and treating depression from a neurobiologically informed, multidimensional perspective [9].

Several researchers, perhaps most notably Damasio [29] and Panksepp [30], have recently created a framework for describing how the human consciousness arises in an intimate relationship with emotions and affects. Damasio considers that consciousness develops from primitive body-attached vague awareness towards emotions proper, further to the capacity to feel the emotions and eventually to symbolic and verbal consciousness.

The somatically anchored and multilayered view of consciousness proposed by these authors is wider than the traditional one and gives better space for biological aspects in the phenomenology of

consciousness and its disturbance in depression. A number of psychosomatic symptoms in depression points towards the low-level consciousness of homeostatic functions such as sleep, appetite, affective experience, and alterations in vitality such as fatigue and exhaustion. They represent signs that derive from the regulation of the general psycho-physiological ambience of the personality [29].

The wider conception is also consonant with the psychodynamic understanding of ego development. It is often forgotten that Freud [31] underlined the role of the body in ego development. He regarded the ego as first and foremost a bodily ego that is shaped by body surface experiences, such as are characteristic of interactions between the infant and the mother in nursing. In these early stages of individual life, the formation of connections between the different areas of the brain is based on the simultaneity of activated signals, which then also become neurologically wired together. Multimodal sensory stimulation provided by developmental interactions is thus able to organize the bodily forms of primary consciousness. However, due its immaturity, this continues to function outside volitional and verbal control [32].

This view of the somatically anchored consciousness has been adopted by several authors such as Panksepp [30], Solms and Turnbull [33], Damasio [29], Edelman [34] and Watt [35], who all primarily regard consciousness as an interoceptive perceptual function that aims to monitor and guarantee the internal homeostatic constituents of the self-consciousness and connect it with perceptions from external reality in order to choose the best momentary adaptive behavior.

The Different Levels of Consciousness in Depression

When wishing to understand how the consciousness, with its different levels of functioning, begins to take an organized form and how it can become affected in depression, several neurophysiological mechanisms need to be considered.

First, the neural tracts from the sense organs on their way, via thalamic relays, to their specific cortical projection areas send collaterals to non-modality-specific reticular formation nuclei in the brain stem [36]. The latter have rich reciprocal connections with hypothalamic and limbic structures such as the amygdala [37, 38]. Besides their specific information, the sensory signals convey an unspecific alerting and affective response, which variably influences the homeostasis of the body and triggers behavioral activity to maintain optimal internal and external adaptation. Thus, the primary layer of consciousness is based on these lower parts of the brain such as the reticular formation of the brain stem, the pons, mesencephalon, and the periaqueductal gray.

The monitoring of bodily consciousness and vital homeostasis takes place at this level conjointly with the HPA, whereas the monitoring of self-consciousness requires other structures beginning from the cingulate cortex of the limbic system and extending to the prefrontal and insular cortices. The striatal structures are also relevant in depression. They regulate automatic motor patterns and connect them with signals from homeostatic and affect modulating centers for the appraisal of adequate (or inhibited) behavior [17, 39, 40].

The associative cortex of the parietal lobe and the insula of the temporal lobe form the second level, where the sensory information from different sources is integrated [41]. These cortical areas introduce a neocortical component to the organization of consciousness. The multimodal information flow to the parietal cortex is scanned and integrated predominantly in the parietal area of the right hemisphere into a functional image of the sensory data of body-attached self-consciousness. The insula provides the self-consciousness with affective qualities such as bodily safety, well-being, and also pain and disgust [39].

The parallel existence of the two sources of bodily consciousness, the brain stem limbic-striatal and HPA system on the one hand and the parietal cortex and insula on the other, implies that all factors that significantly influence the primary consciousness in depression are able to change both the

psycho-physiological homeostatic balance and, conjointly with it, the variable contents and colors of the bodily self-consciousness [35].

The verbal and volitional control of the self-consciousness requires for its development a third level of regulation. This is provided by the dorsolateral, orbital, and medial prefrontal cortical areas, which have important regulating two-way loops with the limbic system for modulating the affective impact deriving from lower brain centers. Disturbance of these connections has been assumed to be relevant in the neurophysiological etiology of depression [17, 42–45].

To understand the different components of clinical depressive symptoms, all these three levels need to be considered (1) the basic vital homeostatic functions, (2) the emotions and affects, and (3) the self-image and the working control of the affective and cognitive self.

The Serotonin System in Depression

The hypo-activity of the serotonin-mediated neural connections in depression has been a widely accepted, although not a unanimous observation [18, 21, 46]. Other transmitter systems, such as noradrenaline, dopamine, and the inhibitory and excitatory cortical modulators, also play a role in depression, and interaction between them can complicate the evaluation of their respective roles [18, 22]. Serotonin transmitter function, however, modulates rather than instigates the mood and affects when compared to the other transmitters. Downgrading of the serotonin system is connected with the inhibition of affects. Decreased modulation of anger and frustration, in particular, has been suggested to associate with lowered serotonin transmitter function [21, 42].

The highest density of serotonin networks in the brain is found in the brain stem raphe nuclei. Changes in serotonin availability may thus influence the variation in psycho-physiological homeostasis and affect sleep, appetite, mood, and the body-related background consciousness, and thereby also the somatic signs of depression. Serotonin pathways are, however, distributed in multiple brain structures in the limbic system, hypothalamus, and the cortical areas. Thus, the availability of serotonin has an influence on a wide variety of brain functions. Damasio [47, p. 78] has emphasized this in an elegant way: “Serotonin is a part of an exceedingly complicated mechanism, which operates at the level of molecules, synapses, local circuits, and systems, to which socio-cultural factors, past and present, intervene powerfully.”

As the role of serotonin transmission can have an impact on the symptoms of depression at several levels of brain organization, serotonin transmission can consequently also be expected to be involved in the biological effects of psychotherapy for depression.

Serotonin Function and Psychotherapy for Depression

From the beginning of the 1990s, there has slowly emerged a body of literature on changes in brain activity in relation to psychotherapy. In the majority of the studies, changes in blood flow or energy metabolism of the brain have been measured (for reviews [48–50]). Cognitive and interpersonal psychotherapy have been found to associate with the normalization of flow and energy metabolism in relatively close relation to the subjective symptoms of the patients, which have ranged from depressive states to obsessive–compulsive disorders and phobias. The alterations in brain activity during psychotherapy have partly been similar to the effects of antidepressive medication, but in an interesting way also partly different [48, 51].

Studies focusing on measures of serotonin function during psychotherapy have, until recently, been non-existent with the exception of case studies, which are to be reviewed in more detail in the

text that follows. This is predominantly explained by the pharmacological effect of antidepressants, which interfere with brain imaging of presynaptic serotonin transporter (SERT) activity, but not in the imaging of postsynaptic serotonin receptor function. Clinical depressive conditions are usually treated by antidepressants, especially by selective serotonin re-uptake inhibitors (SSRI). In the serotonin synapse, these drugs bind to the presynaptic binding sites of the SERT molecule. SSRI medication thus competes with the radioligands used for SERT imaging in the brain. Therefore, efforts to follow up the possible changes in SERT binding during psychotherapy can be expected to be successful only when drug-naïve patient samples can be obtained. This makes patient recruitment arduous and presupposes careful ethical consideration. Recently, however, methods have been developed also to estimate the SERT function during SSRI treatment [18].

Case Studies and a Naturalistic Clinical Sample

After the advent of single photon emission tomography (SPET) technology in the 1990s [52], we started looking for its clinical applications in psychiatry [53, 54]. The development of a relatively specific ligand, nor-β-CIT, for SERT imaging made it possible to particularly focus on the dynamics of SERT and differentiating it from the dopamine transporter (DAT) function in the brain [55]. We first came across of a case of a 25-year-old man with MD and personality disorder who was motivated to undergo dynamic psychotherapy once a week for 1 year, and another male subject with similar clinical symptoms, but not motivated for active treatment. Both were followed up after 1 year with clinical evaluation and a second SPET examination. After 1 year of treatment, the index subject showed an increase in midbrain SERT binding comparable to the values of six healthy age-matched controls, and he also improved clinically and was accepted to start education in a demanding novel field he had been looking to enter. The subject without active treatment had the same low SERT binding as at baseline and his clinical condition was also unchanged [56].

Later, we have been able to follow up two other patients. A young lady aged 21 years with MD was examined before the initiation of psychotherapy and followed up after 12 and 18 months of treatment, twice a week, with dynamic psychotherapy. During the 12-month treatment follow-up, her initially lowered SERT binding had increased to a level comparable with healthy age-matched controls, although her Hamilton depression scores remained unchanged. At the 18-month follow-up, however, clinical remission with a decline in Hamilton scores had also appeared, suggesting that SERT changes and the clinical ratings are not necessarily synchronized [57].

In another case, a lady aged 25 years whose symptom picture fulfilled the SCID criteria (DSM-IV-R) of a type II bipolar disorder (hypomania, moderate depression, and dysthymia), elevated SERT binding was recorded before treatment while she was having hypomanic symptoms. After 8 months of dynamic psychotherapy, SERT binding had declined to the level of a healthy age-matched control group. At that point, the patient decided to end the treatment [58].

The initial observations of SERT changes in relation to psychotherapy prompted us to collect a naturalistic series of 18 patients with MD. They were offered 6 months of psychotherapy, 3–4 times a month, using supportive techniques based on psychodynamic understanding of their symptoms. SERT measurements at baseline and after 6 months of psychotherapy revealed a slightly inverted U-shaped curvilinear correlation with changes in the Hamilton depression scores (Fig. 10.1) [59]. The majority of the subjects showed an increase in SERT binding jointly with a decrease in Hamilton scores. There were, however, cases with a deterioration in both SERT binding and Hamilton scores, as well as subjects displaying clinical improvement with a decrease in Hamilton scores, but no marked change in SERT binding.

We thus had indications that the lowered SERT binding in subjects with MD [60] is not a stable phenomenon. There were depressive subjects who showed an increase in SERT binding during

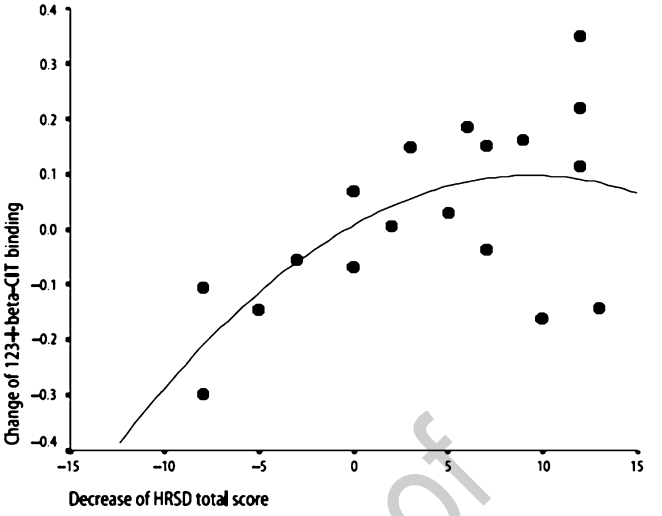

Fig. 10.1 Change in [^{123}I]-beta-CIT specific binding in the midbrain in relation to decrease in HRSD total score in depression ($r^2 = 0.403$; $p < 0.02$). A second degree polynomial was used in data fit (Reproduced by permission from Ref. [59])

196 psychotherapy to levels comparable with healthy controls, whereas clinical improvement without
197 SERT changes also seemed possible, as well as an increase in SERT binding without immediate
198 symptom relief.

199 A Study on the Effects of Dynamic Psychotherapy for Subjects 200 with Drug-Naïve First-Episode Depression

201 We next designed a study on first-episode drug-naïve subjects with depression with the intention of
202 offering 1 year of psychotherapy, twice a week, and comparing their clinical and SPET variables
203 before and after treatment.

204 The patients for the study were referred by health care centers, the student health care organiza-
205 tion, and occupational health care services for an examination to participate in the study. The inclu-
206 sion criteria were moderate or severe depression without psychotic symptoms (DSM IV diagnoses
207 296.22, 296.23, 296.32, 296.33). There was no time limit for the length of the preceding depression.
208 The patients were completely drug-naïve and had received no previous psychiatric treatment.
209 Psychotic symptoms, bipolar disorder, substance abuse, severe personality disorders, and somatic
210 illnesses were exclusion criteria.

211 Psychiatric diagnoses were based on clinical assessment and verified for all study subjects by a
212 trained independent psychiatrist using the Structured Clinical Interview for DSM-IV-R (SCID-1
213 [61]). The severity of symptoms was measured using the 17-item Hamilton Rating Scale for
214 Depression (HAM-D-17). Ratings were completed by a trained independent psychiatrist.

215 Clinical and laboratory examinations as well as MRI imaging were performed to exclude somatic
216 disorders and focal brain abnormalities.

217 All patients provided written informed consent, and the study was approved by the ethical com-
218 mittee of Kuopio University Hospital.

219 The therapists had received formal 3-year or longer postgraduate professional training in psycho-
220 dynamic psychotherapy. Their average length of experience as psychotherapists was 20 years. The
221 psychotherapy consisted of approximately 80 sessions per year, twice a week, in the outpatient clinic
222 of the Department of Psychiatry, Kuopio University Hospital.

The patients' motivation and aptitude for long-term psychodynamic psychotherapy without medication was assessed by an evaluation group consisting of a psychiatrist and a psychologist and/or a specially trained nurse. In the evaluation, meeting the patients received more information about the study.

The therapy process was independently evaluated by the patients and the therapists after 1, 3, 4, and 11 months of treatment. A set of questionnaires was designed for this purpose with the aim of comparing the evaluations of the therapy process by the patients and therapists. In order to assess the impact of the possible placebo effect of treatment expectancy prior to the initiation of psychotherapy, patients were randomly selected to either start the psychotherapy directly after the assessment or start the treatment after a 6-month waiting period.

The reliability of the SERT imaging method was evaluated by a 1-year follow-up of SERT binding in 11 healthy age-matched subjects. A control group with psychopharmacological treatment was not possible due its blocking effect on the ligand site of the SERT molecule.

Baseline Findings

So far, we have published the results from this study as follows: at baseline, i.e., before treatment, we observed lowered SERT levels in our patient sample compared to age-matched healthy controls [62]. Moreover, we have shown that there are baseline differences in SERT binding in the medial prefrontal areas, but not in the midbrain, between the carriers of short and long allelic variants of the SERT gene [63]. We also have compared the SERT binding at baseline between subjects with typical MD and those with atypical MD. Symptoms in the group of atypical depression (ATD) had a correlation with SERT binding, which was not found in patients with typical depression [64].

Follow-up of Patients with Double Depression

We compared patients fulfilling the criteria of double depression with patients with MD during the follow-up of 1 year of psychotherapy. No other significant differences were found, except that their DAT binding showed an inverse correlation to the duration of depressive and dysthymia symptoms, which was not present in patients with MD [65].

Differentiating Between the Typical and Atypical Subtypes of Major Depression

The effects of psychotherapy on SERT binding in this sample of drug-naïve patients have so far been investigated in a comparison between patients with typical and atypical MD [66].

Here, we review these results in more detail. In the sample obtained, we had ten subjects who fulfilled the DSM IV criteria for ATD and 12 subjects with a diagnosis of classical MD.

We found that SERT binding in the two groups differed significantly after 1 year of psychotherapy. Three subjects (two ATD and one MD), however, already showed symptom remission during the 6-month waiting period, so they were excluded from the final analysis. The remaining eight patients with ATD and 11 with MD were then compared.

The groups did not differ significantly in age, sex, or smoking status. Both groups had elevated Hamilton 21 scores for depression at baseline. Moreover, both groups showed a significant Hamilton score reduction during the 1 year of psychotherapy without significant between-group differences (Table 10.1).

t1.1 **Table 10.1** Serotonin transporter (SERT) binding after 1 year of dynamic psychotherapy in
t1.2 subjects with atypical ($n=8$) and typical major depression ($n=11$) (Adapted with permission of
t1.3 Elsevier from Ref. [66])

t1.4		Atypical depression	Major depression
t1.5	Age	28.2 (7.3)	27.1 (7.3)
t1.6	Female gender	75%	100.0%
t1.7	Smoking status	38%	27%
t1.8	*Hamilton 21 score*		
t1.9	Before treatment	19.13 (3.94)[1]	22.18 (7.45)[2]
t1.10	After treatment	12.50 (6.84)	10.64 (7.00)
t1.11	*Atypical score*		
t1.12	Before treatment	12.25 (6.45)[3]	5.18 (2.86)
t1.13	After treatment	7.63 (6.46)[4]	5.18 (4.85)
t1.14	*SERT midbrain binding*		
t1.15	Before treatment	1.12 (0.14)[5]	1.20 (0.13)
t1.16	After treatment	1.25 (0.17)[6]	1.14 (0.18)[7]

t1.17 [1]p-Value for the change in HAM 21 in atypical depression <0.02
t1.18 [2]p-Value for the change in HAM 21 in major depression <0.003
t1.19 [3]p-Value for the difference between the groups <0.005
t1.20 [4]p-Value for the change in atypical scores <0.02
t1.21 [5]p-Value for the difference between the groups <0.25
t1.22 [6]p-Value for the change in SERT binding in atypical depression <0.019
t1.23 [7]p-Value for the change in SERT binding in major depression <0.20

262 Scores measuring the amount of atypical features of depression were more than twofold higher in
263 the ATD group. These scores significantly declined after 1 year of therapy and nearly to the low level
264 of atypical features in the MD group, which also remained low after treatment (Table 10.1).
265 SERT binding at baseline was slightly, although not significantly higher in the MD group than in
266 ATD patients. In the ATD group, SERT binding rose significantly during therapy, whereas in the MD
267 patients there was a slight, non-significant decrease in the mean SERT binding (Table 10.1).
268 The changes in SERT binding during 1 year of psychotherapy were contrasted by the SERT data
269 of healthy age-matched controls ($n=11$), who were examined twice with a 1-year interval. Their
270 SERT levels were unaltered during this follow-up period (1.27 ± 0.11 and 1 year later 1.27 ± 0.14).
271 Thus, these two subgroups of patients with MD had similar clinical recovery rates, but a between-
272 group difference in their SERT response to psychotherapy, and even a suggestive tendency to respond
273 to treatment in opposite directions.
274 The remaining analysis of the data, including detailed evaluation of the outcome of the 1-year
275 psychotherapy period, is expected to be completed during the next few years.

276 Discussion

277 Our findings represent the first indications of changes in molecular neural transmission related to the
278 effects of psychotherapy. However, these observations need to be carefully evaluated for several
279 reasons, first and foremost because of the relatively small number of patients in the two groups
280 examined. The validity of the clinical differentiation between classical and atypical symptom pro-
281 files also has been regarded by some researchers as uncertain [67]. Furthermore, there was fluctua-
282 tion in the timing and synchronization of the clinical and SERT imaging examinations in some
283 patients, which may have increased the variance of our results.

Nevertheless, even considering the restrictions of the study, a conclusion seems founded that SERT function can be altered in individual patients during psychotherapy, and the decrease in SERT binding typical for MD is not necessarily irreversible. The quite stable SERT levels in healthy control subjects observed at two different examinations with a 1-year interval suggest that the SERT binding fluctuation observed in the patient sample was not due to variance caused by the imaging method. However, a slight contribution from the dopamine transporters to the rate of binding of the radioligand used cannot be completely ruled out.

Another strength of our study was that the subjects were drug-naïve, first-episode patients without experience of any previous treatment. Furthermore, the therapists had a similar training and a frame of working. They represented professionals engaged in the public sector. Although they were not randomly selected, they did not represent a group of therapists that would have been electively chosen for the project. The results obtained can thus be expected to be achieved in an average public sector outpatient environment where a psychodynamic model of working is applied.

No conclusions, however, can be drawn on the relative efficacy of psychodynamic and other psychotherapy forms. We only used healthy controls as a reference for the SERT changes observed, and not a clinical sample that would have been treated by another psychotherapeutic or medical method.

Although the small sample prevents far-reaching conclusions, the question may be raised whether the biological profile of classical MD differs from ATD, which is characterized by more interaction-tuned symptoms such as anxiety shown in rejection sensitivity [68]. This issue is not of minor importance, since it leads to the question of how to evaluate the changes in the clinical symptoms of depression occurring during treatment.

Both subgroups in our study showed significant clinical improvement, but only in the atypical subgroup was the symptom decrease connected with a corresponding increase in SERT binding as a sign of activation of serotonin transmission. Furthermore, in our previously reported case study on psychotherapy for a young depressive lady with atypical symptoms [57], the SERT increase took place earlier, while the symptoms of depression still remained high. Clinical symptom reduction was only seen 6 months after the second, follow-up SERT measurement. Thus, in this atypical case, SERT activation preceded clinical recovery, whereas in the subgroup of classical MD patients in our sample, no SERT changes were accompanied with the significant clinical improvement of these patients. There was probably even a slight tendency, although non-significant, for a decrease in SERT binding in these patients.

Parker et al. [68] have recently adduced evidence for the clinical validity of ATD on clinical grounds. The authors have concluded that the symptom of anxiety shown in rejection sensitivity may be more central in this clinical syndrome, and the homeostatic signs of overeating, oversleeping, and leaden paralysis probably represent more secondary features. Furthermore, Nemeroff et al. [51] have also provided evidence of differential pharmacotherapeutic and psychotherapy outcomes between subtypes of depression with and without a traumatic history. These findings support the hypothesis that there may be real differences between subgroups of depressive subjects that may also be reflected in their biological profile and therefore also in their biological responses to psychotherapy.

Although discussion of these differences can at present only remain tentative, it is important to recognize that in outcome studies on psychotherapy for depression, also when using biological markers, true inter-individual variability is to be expected. This being the case, the mean effects of treatment in a given patient sample may lead astray and bypass subgroup differences, whereas adequate consideration of subgroup differences is likely to assist in choosing a more individually tailored treatment and a more accurate evaluation of its effects.

Generalizations on the basis of our observations are not possible, except that the SERT level in depression seems to be variable and therefore also an indirect target for psychotherapy, especially in patients with anxiety and clinical sensitivity to interaction. Interestingly, however, our findings of

a SERT binding increase in a subgroup of depressive patients are supported by a recent positron emission tomography study. Karlsson et al. [69] observed an increase in serotonin 1A receptors after 6 months of dynamic psychotherapy, whereas a control group treated with SSRIs did not show serotonin receptor changes (see Chap. 11).

A decrease in both SERT levels and the number of active serotonin 1A postsynaptic receptors has been found to prevail in depression [60, 70]. From a physiological point of view, the pre- and postsynaptic sides of the serotonin synapse are interdependent. Postsynaptic serotonin receptor activity is plausibly dependent on the amount of serotonin available in the synapse. The relationship of the presynaptic SERT function, addressed in our study, with the postsynaptic serotonin receptor function is a multifaceted issue in which besides postsynaptic receptors, the role of somato-dendritic autoreceptors also needs to be considered [71]. Despite these complexities, the findings of Karlsson et al. [69] of an increase of postsynaptic serotonin 1A receptors during short-term dynamic psychotherapy also seem to point to biological effects of dynamic psychotherapy that extend their action, at least in some patients, to the molecular level of serotonin transmission.

Another factor that merits discussion with regard to the differential response to treatment in these two subgroups concerns the therapeutic technique [72]. All therapists had received similar training and they were supervised, at the start of the research project, to practice a similar approach when challenging the depressive symptoms. We created a protocol to follow up the treatment process by focusing on the evaluation of its course by both the patients and therapists. These results are not yet at our disposal, but they might shed some light on the question of whether there are differences in the treatment process between patients with different symptom profiles and whether process variables of the psychotherapy correlate with the treatment outcome [73].

One more finding in our study is of interest concerning the efficacy of psychotherapy for depression [63]. We obtained evidence that SERT availability in the medial prefrontal cortex is lower in patients carrying the short allelic variant of the SERT gene compared to long allele carriers. This difference was present only at the level of the medial prefrontal cortex, but not in the midbrain, where SERT density is highest. In an interesting way, this finding is in agreement with notions that the medial prefrontal area plays a central role in affect modulation, especially that of anger [42]. Variance in the functioning of the prefrontal-limbic loop of stress and affect modulation has been seen as central to the predisposition to adverse and eventually depressive symptoms [17]. Our findings of lower medial prefrontal SERT binding in short allele carriers also accord with the observations that short allelic variants of the SERT gene are connected with an increased predisposition to the adverse effects of life stress [74, 75]. Although this connection has been disputed [76], if it were to be proved correct, it may at least partly be based on the effects of the short allele especially in the medial prefrontal cortex.

Consequently, the lack of allelic differences in the midbrain SERT binding may indicate that the homeostatic functions of the midbrain and their disturbances in depression, such as fatigue and neurovegetative symptoms, may represent a more secondary phenomenon. This has also been suggested on clinical grounds by Parker et al. [68] and on genetic epidemiological grounds by Lux and Kendler [16].

Unfortunately, because not all patients gave their consent to genetic analysis, the subgroups of these allelic variants remained too small to allow meaningful correlation with the therapy outcome.

Conclusions and Summary

The symptoms of depression and the capacity to modulate them derive from several levels of brain organization that include the vital homeostatic functions of the brain stem, the limbic–hypothalamic complex, and the medial, dorsolateral prefrontal, parietal, and insular cortex.

Serotonin transmission is central to the midbrain regulation of homeostatic functions, but it also has an important role in other regions such as the limbic and prefrontal cortical structures of the brain.

Disturbances in serotonin function have been regarded as central in the disposition to depression, not least due to the opportunity they offer for antidepressive medical treatment. However, serotonin function as a target of the effects of psychotherapy has not previously been investigated.

Here, we have reviewed the neurophysiological and anatomical background necessary to understand the different components of clinical depressive symptoms. Thereafter, we have presented an overview of the first studies on the effects of dynamic psychotherapy on the SERT function in depressive patients.

These studies were initiated by three case reports from the late 1990s and early this millennium. We found an elevation of SERT availability after 1 year of dynamic psychotherapy in a male and a female patient. Moreover, we detected the normalization of an elevated SERT level in a patient with hypomanic symptoms of a type II bipolar disorder after 8 months of dynamic psychotherapy.

These findings first prompted us to collect a naturalistic series of depressive patients who were treated once a week with dynamic psychotherapy for 6 months while their SERT levels were also followed up. A slightly inverted U-form curvilinear correlation between their Hamilton score decrease and SERT elevation was noted, which further supported us to hypothesize that serotonin transmission may change in relation to dynamic psychotherapy.

Thereafter, we collected a series of first-episode drug-naïve patients with MD and compared their clinical outcome after 1 year of dynamic psychotherapy with their SERT levels before and after therapy. This study yielded the observation that patients with atypical symptoms, such as anxiety shown in rejection sensitivity, had a significant SERT increase after 1 year of psychotherapy, whereas patients with classical symptoms of MD showed no upgrading of SERT function. Both subgroups improved clinically in a significant and approximately similar way.

These findings warrant a conclusion that there is a subgroup of patients in the MD disorder spectrum, especially those showing signs of rejection sensitivity and other atypical symptoms, whose response to dynamic psychotherapy also is reflected in an increase in SERT binding. Patients with classical MD symptoms show a similar clinical improvement, but no changes in SERT binding. These findings call for a more detailed analysis of the significance of the improvement in clinical scores of depression and their complex correlation with the biology of depression, including the impact of genetic allelic variation of the SERT gene.

We close our review by suggesting that the inclusion of molecular markers of depressive symptoms and their genetic background reveals new dimensions for understanding the complexity of the treatment responses of depression. The application of new molecular information to outcome studies in psychotherapy can lead us slowly to the era of molecular psychotherapy and bring psychotherapy closer to other fields of psychiatry. This would be in good accordance with recently expressed visions of how to promote research in psychiatry today [77–79].

References

1. Kendler KS, Walters EE, Truett KR, Heeath AC, Neale MC, Martin NG, et al. Sources of individual differences in depressive symptoms: analysis of two samples of twins and their families. Am J Psychiatry. 1994;151:1605–1614.
2. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157:1552–1562.
3. Kendler KS, Aggen SH. Time, memory and the heritability of major depression. Psychol Med. 2001;31:923–928.
4. Kendler KS. Anna-Monika-prize paper. Major depression and the environment: a psychiatric genetic perspective. Pharmacopsychiatry. 1998;31:5–9.

5. Kendler KS. Explanatory models for psychiatric illness. Am J Psychiatry. 2008;165:695–702.
6. Fanous AH, Neale MC, Aggen SH, Kendler KS. A longitudinal study of personality and major depression in a population-based sample of male twins. Psychol Med. 2007;37:1163–1172.
7. Kendler KS, Campbell J. Interventionist causal models in psychiatry: repositioning the mind-body problem. Psychol Med. 2009;39:881–887.
8. Luyten P, Blatt SJ, Van Houdenhove B, Corveleyn J. Depression research and treatment: are we skating to where the puck is going to be? Clin Psychol Rev. 2006;26:985–999.
9. Carhart-Harris RL, Mayberg HS, Malizia AL, Nutt D. Mourning and melancholia revisited: correspondences between principles of Freudian metapsychology and empirical findings in neuropsychiatry. Ann Gen Psychiatry. 2008;7:9. Published online 24 July 2008.doi: 10.1186/1744–859X-7–9.
10. Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry. 2000;57(4):375–380.
11. Keller MC, Neale MC, Kendler KS. Association of different adverse life events with distinct patterns of depressive symptoms. Am J Psychiatry. 2007;164(10):1521–29.
12. Busch FN, Rudden M, Shapiro T. Psychodynamic treatment of depression: development of a psychodynamic model of depression. Arlington: American Psychiatric Publishing; 2004. p. 13–30. [AU1]
13. Morgan N, Taylor T. Psychodynamic psychotherapy and treatment of depression. Psychiatry. 2005;4(5):6–9.
14. Taylor D, Richardson P. The psychoanalytic/psychodynamic approach to depressive disorder. In: Gabbard GO, Beck SJ, Holmes J, editors. Oxford textbook of psychiatry. Oxford: Oxford University Press; 2005. p. 127–136.
15. Luutonen S. Anger and depression – theoretical and clinical considerations. Nord J Psychiatry. 2007;1(4):246–251.
16. Lux V, Kendler KS. Deconstructing major depression: a validation study of the DSM-IV symptomatic criteria. Psychol Med. 2010;40:1–12.
17. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. J Clin Invest. 2009;119:717–725.
18. Nemeroff CB, Owens MJ. The role of serotonin in the pathophysiology of depression: as important as ever. Clin Chem. 2009;55:1578–1579.
19. Wampold BE. The great psychotherapy debate. New Jersey: Lawrence Erlbaum; 2001.
20. Shelder J. The efficacy of psychodynamic psychotherapy. Am Psychol. 2010;65:98–109.
21. Meltzer HY. Role of serotonin in depression. Ann N Y Acad Sci. 1990;600:486–499.
22. Tiihonen J, Kuoppamäki M, Någren K, Bergmand J, Eronen E, Syvälahti E, et al. Serotonergic modulation of striatal D2 dopamine receptor binding in humans measured with positron emission tomography. Psychopharmacology. 1996;126:277–280.
23. Young EA, Aggen SH, Prescott CA, Kendler KS. Similarity in saliva cortisol measures in monozygotic twins and the influence of past major depression. Biol Psychiatry. 2000;48:70–74.
24. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry. 2002;159:728–737.
25. Tafet GE, Idoyaga-Vargas VP, Abulafia DP, Calandria JM, Roffman SS, Chiovetta A, et al. Correlation between cortisol level and serotonin uptake in patients with chronic stress and depression. Cogn Affect Behav Neurosci. 2001;1:388–393.
26. Hettema JM, An SS, van der Oord EJ, Neale MC, Kendler KS, Chen X. Association study between 1A receptor (HTR1A) gene and neuroticism, major depression, and anxiety disorders. Am J Med Genet B: Neuropsychiatr Genet. 2008;147B:661–666.
27. Castrén E. Is mood chemistry? Nat Rev Neurosci. 2005;6(3):241–6.
28. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science. 2008;320(5874):385–8.
29. Damasio A. Looking for Spinoza: joy, sorrow and the feeling brain. London: Vintage; 2003.
30. Panksepp J. Affective neuroscience. Oxford: Oxford University Press; 1998.
31. Freud FS. The ego and the Id. 1923. Standardth ed. London: Hogarth Press; 1963. p. 3–66.
32. Lehtonen J, Partanen J, Purhonen M, Valkonen-Korhonen M, Könönen M, Saarikoski S, et al. Nascent body ego. Metapsychological and neurophysiological aspects. Int J Psychoanal. 2006;87:1335–1353.
33. Solms A, Turnbull O. The brain and the inner world. London: Karnac; 2002.
34. Edelman G. Second nature. Brain science and human knowledge. New Haven: Yale University Press; 2006.
35. Watt D. Toward a neuroscience of empathy: integrating affective and cognitive perspectives. Neuro-Psychoanal. 2007;8:119–40.
36. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroenceph Clin Neurophysiol. 1949;1:455–473.
37. Magoun HW. The waking brain. Springfield: Charles C. Thomas; 1965.
38. LeDoux J. The emotional brain. New York: Simon and Schuster; 1996.

39. Craig AD. Pain as an interoceptive aspect of homeostasis. In: Kalso E, Estlander A-M, Klockars M, editors. Psyche, soma and pain, Acta Gyllenbergiana. Helsinki: The Signe and Ane Gyllenberg Foundation; 2003. p. 161–172.
40. Raij TT, Valkonen-Koronen M, Holi M, Therman S, Lehtonen J, Hari R. Reality of auditory verbal hallucinations. Brain. 2009;132:2994–3001.
41. Truex RC, Carpenter MB. Human neuroanatomy. 6th ed. Baltimore: Williams & Wilkins; 1969.
42. Dougherty DD, Rauch SL, Deckersbach T, Marci C, Loh R, Shin LM, et al. Ventromedial prefrontal cortex and amygdala dysfunction during an anger induction positron emission tomography study in patients with major depressive disorder with anger attacks. Arch Gen Psychiatry. 2004;61:795–804.
43. Frokjaer VG, Vinberg M, Erritzoe D, et al. High familial risk for mood disorder is associated with low dorsolateral prefrontal cortex serotonin transporter binding. Neuroimage. 2009;46:360–366.
44. Liotti M, Mayberg HS, Brannan SK, McGinnis S, Jerabek P, Fox PT. Differential limbic-cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biol Psychiatry. 2000;48:30–42.
45. Thomas EJ, Elliott R. Brain imaging correlates of cognitive impairment in depression. Front Hum Neurosci. 2009;3:1–9.
46. Cannon DM, Ichise M, Rollis D, et al. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry. 2007;62:870–877.
47. Damasio AR. Descartes' error. London: Macmillan; 1996.
48. Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL. Neuroimaging and the functional neuroanatomy of psychotherapy. Psychol Med. 2005;35(10):1385–98.
49. Linden DEJ. How psychotherapy changes the brain – the contribution of functional neuroimaging. Mol Psychiatry. 2006;11:528–38.
50. Beauregard M. Effect of mind on brain activity: evidence from neuroimaging studies of psychotherapy. Nord J Psychiatry. 2009;63:5–16.
51. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush JA, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci USA. 2003;100:14293–14296.
52. Kuikka JT, Tenhunen-Eskelinen M, Jurvelin J, Kiilianen H. Physical performance of the Siemens MultiSPECT 3 gamma camera. Nucl Med Commun. 1993;14:490–497.
53. Tiihonen J, Kuikka JT, Bergström KA, Karhu J, Viinamäki H, Lehtonen J, et al. Single-photon emission tomography imaging of monoamine transporters in impulsive violent behaviour. Eur J Nucl Med. 1997;24:1253–1260.
54. Tiihonen J, Kuikka J, Viinamäki H, Lehtonen J, Partanen J. Altered cerebral blood flow during hysterical paresthesia. Biol Psychiatry. 1995;37:134–135.
55. Hiltunen J, Akerman KK, Kuikka JT, et al. Iodine-123 labeled nor-beta-CIT as a potential tracer for serotonin transporter imaging in the human brain with single-photon emission tomography. Eur J Nucl Med. 1998;25:2728.
56. Viinamäki H, Kuikka J, Tiihonen J, Lehtonen J. Change in monoamine transporter density related to clinical recovery: a case–control study. Nord J Psychiatry. 1998;52:39–44.
57. Saarinen PI, Lehtonen J, Joensuu M, Tolmunen T, Ahola P, Vanninen R, et al. An outcome of psychodynamic psychotherapy: a case study of the change in serotonin transporter binding and the activation of the dream screen. Am J Psychother. 2005;59(1):61–73.
58. Tolmunen T, Joensuu M, Saarinen PI, Mussalo H, Ahola P, Vanninen R, et al. Elevated midbrain serotonin availability in mixed mania: a case report. BMC Psychiatry. 2004;4(13):27.
59. Laasonen-Balk T, Viinamäki H, Kuikka JT, Husso-Saastamoinen M, Lehtonen J, Tiihonen J. ^{123}I-β CIT binding and recovery from depression. A six month follow-up study. Eur Arch Psychiatr Clin Neurosci. 2004;254:152–155.
60. Malison RT, Price LH, Berman R, et al. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 betacarbomethoxy-3 beta-(4-iodophenyl) tropane and single photon emission computed tomography. Biol Psychiatry. 1998;44:1090–1098.
61. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
62. Joensuu M, Tolmunen T, Saarinen PI, Tiihonen J, Kuikka J, Ahola P, et al. Reduced midbrain serotonin transporter availability in drug naive patients with depression measured by SERT-specific [(123) I] nor-beta-CIT SPECT imaging. Psychiatry Res. 2007;154(2):125–131.
63. Joensuu M, Lehto SM, Tolmunen T, Saarinen PI, Valkonen-Korhonen M, Vanninen R, et al. 5-HTTLPR polymorphism and serotonin transporter binding in drug-naïve patients with major depression. Psychiatry Clin Neurosci. 2010;64:387–393.
64. Lehto SM, Tolmunen T, Joensuu M, et al. Midbrain binding of [123I]nor-beta-CIT in atypical depression. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1251–1255.

65. Lehto SM, Tolmunen T, Kuikka J, Valkonen-Korhonen M, Joensuu M, Saarinen PI, et al. Midbrain serotonin and striatum dopamine transporter binding in double depression: a one-year follow-up study. Neurosci Lett. 2008; 441:291–295.
66. Lehto SM, Tolmunen T, Joensuu M, Saarinen PI, Valkonen-Korhonen M, Vanninen R, et al. Changes in midbrain serotonin transporter availability in atypically depressed subjects after one year of psychotherapy. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):229–37.
67. Stewart JW, McGrath P, Rabkin J, QuitKin FM. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Clin Psychopharmacol. 1998;18:429–34.
68. Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadci-Pavlovic D. Atypical depression: a reappraisal. Am J Psychiatry. 2002;159:1470–1479.
69. Karlsson H, Hirvonen J, Kajander J, Markkula J, Rasi-Hakala H, Salminen JK, et al. Psychotherapy increases brain serotonin 5-HT1A receptors in patients with major depressive disorder. Psychol Med. 2010;40(3):523–8.
70. Drevets WC, Thase M, Moses-Kolko EL, Price J, Frank E, Kupfer DJ, et al. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol. 2007;34:865–877.
71. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. 1998;51:215–235.
72. Krupnick JL, Sotsky SM, Simmens S, Moyer J, Elkin I, Watkins J, et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol. 1996;64(3):532–539.
73. Ahola P, Valkonen-Korhonen M, Tolmunen T, Joensuu M, Lehto SM, Saarinen PI, et al. The perceptions of patients and their therapists of the process of psychodynamic psychotherapy for depression. Am J Psychother, in press. [AU2]
74. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301:386–389.
75. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry. 2005;62:529–5340.
76. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events and risk of depression: a meta-analysis. JAMA. 2009;301:2462–2471.
77. Kandel E. In search of memory: the emergence of a new science of mind. New York: WW Norton; 2006.
78. Akil H, Brenner S, Kandel E, Kendler KS, King M-C, Scolnick E, et al. The future of psychiatric research: genomes and neural circuits. Science. 2010;327:1580–1581.
79. Portin P, Lehtonen J, Alanen YO. Mental illness requires a multidisciplinary research plan. Science. 2010; 328:1229.

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