

Neurobiological aspects of theory and practice of psychotherapy

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Psychological processes of learning may lead to biological changes in brain synapses, as was shown by Eric Kandel, the Nobel laureate for 2000. Factors connected with learning (for instance, psychotherapeutic procedures) can modify the expression of genes occurring in brain cells. Current neurobiological research make it possible to explain some theoretical concepts and mechanisms of action of psychotherapy on the ground of basic medical sciences. Experimental and clinical studies point to a prominent role for early untoward life experiences in brain development and vulnerability for psychiatric disturbances. Neuroimaging studies demonstrated the existence of unconscious processes in both cognitive and emotional functions. In several studies, changes in brain function or in the biology of the whole organism were measured, under the influence of psychotherapy. It was found that in such illnesses as depression or obsessive-compulsive disorder, similar changes in brain function, as measured with neuroimaging methods, were observed either after pharmacotherapy or psychotherapy. Attempts have been also made to interpret psychotherapeutic mechanisms in the light of current concepts of memory processes, functioning of brain circuits or neurobiological theories of character and temperament.

Key words: psychotherapy, neurobiological mechanisms

Nobel Prize in year 2000 for Eric Kandel

Nobel Prize in physiology and medicine at the end of 20th century was awarded to Eric Kandel who has been a psychiatrist by education, doing research in the field of neurobiology. This event gives a credit to his scientific achievements but also makes a symbolic summary of psychiatric theories of the past century. The prize was awarded for Kandel's studies on biological-molecular mechanisms of memory and learning which are the processes reflecting brain plasticity. The studies have implicated a possibility of "biological" modification of brain synapses as a result of "psychological" processes of memory and learning. This makes a very strong case pointing to a dynamic nature of interaction between genetic predisposition and environmental factors. Undoubtedly, such findings may serve as a bridge between biological and psychological sciences underlying psychiatric knowledge.

In the 1998 issue of *The American Journal of Psychiatry*, the official organ of the American Psychiatric Association, the paper written by Kandel appeared, which

may be regarded as a manifest of this scientist [1]. The author has proposed a broader incorporation of modern neurobiological findings for shaping the psychiatrist's thinking and psychiatric education at the dawn of 21st century. According to Kandel, there is a necessity of grasping by the future psychiatrist much more information on brain structure and function, especially on memory functioning, neuroimaging of mental functions and their pathology, and molecular genetics of psychiatric disorders. Only such an approach can rectify a unique position of psychiatry among medical branches, which gives a possibility of better understanding of an interaction between psychosocial and biological factors determining human behaviour. In particular, this may enable the explanation of the mechanism of action of psychotherapy on the ground of neurobiology.

A new paradigm in psychiatry?

The advances in neurobiology, especially remarkable in the last decade of the 20th century, the so-called also "decade of the brain" may mean an inevitable decline of thinking in the vein of the Cartesian dualism. This way of thinking in psychiatry has been reflected by the opposing illnesses of apparently "endogenous" versus "psychogenic" origin, pharmacotherapy vs. psychotherapy, as well as the indications for treatment: psychotherapy for the disturbances of psychogenic origin, pharmacotherapy for the disturbances of "biological" origin. In a not so very distant past, the absurd questions were also asked, such as: what is better - biological or humanistic psychiatry? However, the concept that all mental processes derive from the activity of the brain has never been questioned in recent decades either by researchers or by clinicians. Nevertheless, many problems still exist and they may prove extremely difficult to solve, such as, for example, an interpretation in neurological terms for the phenomenon of consciousness or subjective experiences.

Certainly, one of the main events at the turn of century has been the human genome project. This spectacular technological and scientific success brought about a number of comments elaborating its possible implications for mental functions and psychiatric disturbances. Most of them have been highly deterministic in nature. For example, it has been thought that knowing in detail the genome of each individual, will be sufficient to predict what personality, and what diseases, both psychiatric and somatic, this individual will have. However, only one function of the gene is taken into account here, which is a function of template used for replication of DNA, and this is invariable. On the other hand, when a gene is performing its transcriptional function connected with its ability of protein synthesis, this function is regulated throughout the life by the signals from the environment. Such signals may among others involve drug administration, stressful experiences and, as Kandel showed, procedures connected with learning (e.g. psychotherapy).

Molecular genetics studies of personality and of psychiatric illnesses performed in the last decade of the 20th century brought about a disappointment for those who anticipated a quick discovery of a "gene" for schizophrenia, depression or bipolar illness. It was shown that in the development of these psychological and psychopatho-

logical phenomena, an interaction of multiple genes occurs and many genes have to be induced by the appropriate environmental factors.

Thus, beyond doubt, genetic factors are important for determining a basic program of structure and function of the nervous system in each individual. However, the development and fine tuning of the nervous system is determined in various stages of life by a number of biological and psychosocial factors, including those connected with social learning and behaviour. These factors may significantly modify the expression of genes located in the brain cells. Thus, changes in gene expression resulting from learning and environmental experiences lead to changes in synaptic connections. Both number and character of environmental stimuli exert an effect on emotional and cognitive development throughout life. It is also known that the processes of neuronal plasticity involve the modification of enormous number of synaptic connections and undergo integration within the associative cortex of the brain [2]. These processes contribute to the development of personality as well as to increased vulnerability for psychiatric disorders. Realisation of these facts by a psychiatrist can enable a better understanding of the issue of interaction of biological and psychosocial factors both in the pathogenesis of psychiatric disorders and in the mechanisms of their treatment.

Psychotherapy and basic medical sciences

Remarkable progress in the treatment of psychiatric disorders observed in recent decades can be mostly regarded as a derivative of “psychopharmacological revolution”. One feature of this process has been an introduction of new psychopharmacological agents that are more efficacious, have broader therapeutic spectrum and are more patient-friendly in terms of somatic and subjective tolerance. This multidirectional progress touched also such basic treatment modality in psychiatry as psychotherapy. Novel and specific psychotherapeutic techniques were introduced. Also, numerous studies were performed verifying their efficacy, comparing the effects of various kinds of psychotherapy, as well as psychotherapy versus pharmacotherapy, or combination of psychotherapy and pharmacotherapy compared with the efficacy of each of these methods alone. Despite the reluctance expressed by some representatives of psychotherapy, regarding this field more as an “art”, this is the only way to introduce psychotherapy as the therapeutic method into the “evidence-based medicine”. For two decades now, the efficacy of many psychotherapeutic methods (mainly behavioural and cognitive) in the treatment of various psychiatric disturbances (among others depressive and anxiety disorders) has been demonstrated by means of methodologically rigorous studies [3].

The results of new research make it possible to verify some theoretical concepts connected with psychotherapy on a neurobiological ground and also to explain the mechanisms of therapeutic action of some psychotherapeutic procedures. This may have a special value when applied to psychodynamic psychotherapy because some advocates of the latter tend to use a highly esoteric terminology that cannot be translated into the vocabulary of basic sciences. In the 1990s, and in its second part in particular, some breakthrough studies on these issues appeared in scientific literature.

Early life experiences and psychiatric disturbances

Psychoanalytic theory highlights a prominent role for early untoward life experiences in adult functioning and in the vulnerability for psychiatric disturbances. The most conspicuous one is a postulated association between response to parental loss and an increased risk for depression during adulthood. These speculations have already been confirmed on clinical ground. A quarter of century ago, Brown et al. [4] found in a population of London women a relationship between a loss of mother before 11 years of age and the increased risk for depression. Kendler et al [5] in early 1990s studying female twins revealed an association between the kind of psychiatric disturbances in adulthood and the kind of situation of loss before 17 years of age. Increased risk for depression and for generalised anxiety disorder was associated with long-lasting separation from either parent. On the other hand, increased risk for panic disorder was connected with death of one of the parents or permanent separation from the mother. A recent study of Israeli researchers is a methodologically most sophisticated one [6]. The authors used a case-control design, matching each psychiatric patient studied with a healthy person of similar age and gender. The study included 79 patient-control pairs for major depression, 79 pairs for bipolar affective illness and 76 pairs for schizophrenia. Early parental loss was defined as a death of parent or physical separation from a parent when the subject studied was 17 years of age or younger. Loss of parent during childhood increased significantly (3.8-fold) the likelihood of developing depression during adult life. Interestingly, the effect of loss due to permanent separation was more striking than loss due to death, as was loss before the age of 9 years (11-fold increase of depression risk). The likelihood of developing schizophrenia after parental loss in childhood was similar as for depression (3.8-fold) and increased to 4.3-fold when the situation of loss occurred before the age of 9 years. The risk for bipolar affective illness was increased 2.6 fold in case of early parental loss what may suggest a relatively larger contribution of genetic predisposition compared with depression or schizophrenia.

In recent years, numerous pre-clinical (animal) studies have been performed, investigating the effects of early adverse experiences on brain structure and function. They have demonstrated that early stress can alter the development of the “stress” (hypothalamic-pituitary-adrenal) axis, with concomitant abnormal secretion of corticotrophin releasing hormone, biogenic amines and other neurotransmitters. Stress has also been shown to promote structural and functional alteration in brain regions (e.g. hippocampus) similar to those seen in adults with depression. The results of studies also suggest that the long-term impact of early stress can be moderated both by genetic predisposition and by environmental factors (e.g. a quality of subsequent care-giving) [7].

Neuroimaging of unconscious processes

Increasing sophistication of neuroimaging methods enables a better recognition of what is going on in the brain during the mental processes. One may ask a question whether a possibility exists to image also the “unconscious” processes. The notion of unconsciousness has long been a milestone of theory and practice of some psy-

chotherapeutic schools. Recent neuroscience studies using neuroimaging methods conclusively demonstrated the existence of the unconscious processes, both cognitive and emotional ones.

The study of French neuroscientists, published in *Nature* in 1998 [8] is quoted as an evidence for a possibility of neuroimaging unconscious cognitive processes. They used a method of “masked priming”, where a prime numerical between 1 and 9 was presented (as a digit or as a word) for a very short duration (43ms). The prime was masked by two nonsense letter strings, and followed by another numeral, the target. Subjects were asked to press a response key with one hand if the target was larger than 5, and with the other hand if the target was smaller than 5. In some trials the prime was congruent with the target (both numbers fell on the same side of 5), and in other trials it was incongruent (one number being larger than 5 and the other being smaller). The researchers demonstrated that although the prime digit was presented so shortly, that was impossible “to see” it, nevertheless such unconscious exposition influenced a subsequent information processing linked to the prime information. Cognitive analysis of relationship between the prime and the target digits (apparently without gaining access to consciousness) had a measurable influence on brain activity, reflected by means of behavioural, electrophysiological and neuroimaging methods. On a behavioural level, subjects responded slower by pressing the key in incongruent trials than in congruent ones. Event-related potentials recorded during the task showed a generation of a readiness potential, preparing to a lateralized motor response appropriate to the prime. In the study of brain activity by means of functional magnetic resonance imaging (fMRI), a haemodynamic signal of cerebral blood flow was measured in motor areas of location congruent with a possible influence of unconscious perception.

Some other studies were performed in recent years pointing to a possibility of neuroimaging of unconscious emotional processes. Whalen et al. [9] employed for this aim the methodology of “masked faces”. Pictures of human faces bearing fearful or happy expressions were presented to subjects studied for 33 ms, following by a “mask” of 167 ms presentations of neutral facial expressions, and the intensity of fMRI signal in amygdala was measured. Although subjects reported seeing only neutral faces the fMRI signal in the amygdala was significantly higher during viewing of masked fearful faces than during the viewing of masked happy faces. Morris et al. [10], using positron emission tomography (PET) neuroimaging demonstrated that information processing connected with unconscious perception of behaviourally relevant visual events is performed by a route coming from midbrain colliculus (an element of visual pathway) to the right amygdala. This is in parallel to a cortical route necessary for conscious identification.

Biological mechanisms of action of psychotherapy

Studies of biological mechanisms of action of psychotherapy attempt to investigate possible changes in brain activity or in the biology of whole organism, occurring in the course of psychotherapeutic procedures. These changes can be measured by means of neuroimaging or biochemical methods or they may be interpreted in the context of

current neuropsychological or neurophysiological concepts.

An interpretation of psychodynamic psychotherapy employs a contemporary knowledge of memory and learning where the most important is the distinction between the two memory systems: explicit (declarative) memory and implicit (non-declarative) memory. These systems are different both in character and in the involvement of brain structures. Explicit memory refers to conscious recollection of facts and events and depends mainly on hippocampal-cortical circuits. Implicit memory refers to a heterogeneous collection of memory abilities, among others to procedural memory e.g. of motor procedures (with significant role of basal ganglia) or to the memory of emotional relations (dependent on amygdala). In the case of implicit memory, experience alters behaviour non-consciously. Learning occurring during psychotherapy involves both kinds of memory but especially, implicit memory. According to the interpretation of psychodynamic psychotherapy using the “memory” model, early attachment relationships are internalised and encoded as implicit memory. In the process of the therapeutic relationship and the attainment of insight, it is possible to restructure unconscious information, to make it available for conscious reflection and, in some cases, to enter explicit memory [11].

Liggin and Kay [12] made an attempt to explain the action of different forms of psychotherapy in terms of interventions on brain homeostasis at different levels of structural and functional organisation. For example, behavioural psychotherapy focusing on dysfunction in simple forms of learning and memory (operant and associative conditioning) and related motor behaviour affects mainly such brain structures as the basal ganglia, amygdala and hippocampus. Putative brain areas involved in cognitive psychotherapy which focuses on the modification of specific, abnormal patterns of information processing (cognitive constructs) include the neocortex, specifically the prefrontal cortex, and its secondary impact on subcortical structures. Psychodynamic psychotherapy has as a central focus on interpersonal representation (a set of expectations about self, others, and their relationship) which may involve complex neurocircuitry incorporating lateralized cerebral hemispheres and subcortical areas.

Gabbard [13] tries to define the complementary targets of psychotherapy and pharmacotherapy, based on a psychobiological model of temperament and character, constructed by Cloninger et al. [14]. According to this model, there are four dimensions of temperament – novelty seeking, harm avoidance, reward dependence and persistence, which are to great extent heritable (independently of one another) and linked to the status of such brain neurotransmitters as dopamine, noradrenaline or serotonin. Character variables include self-directness, co-operativeness and self-transcendence and are mainly shaped by environmental factors (e.g. family influences, social learning etc.). The author suggests that in the process of treatment planning, especially for combined treatment (psychotherapy and medication), temperamental features should be regarded as a target for the pharmacotherapy while character variables may respond favourably to psychotherapeutic interventions.

Recent EEG and neuroimaging studies, where brain changes measured with these methods were compared under psychotherapy or pharmacotherapy, brought interesting results. Thase et al. [15] demonstrated that the biological changes in sleep architecture

produced by effective cognitive behavioural therapy are similar to those produced by antidepressant medication. Brody et al. [16] performed neuroimaging studies using PET method in patients with depression receiving antidepressant treatment with paroxetine or treated with interpersonal psychotherapy (IPP). The IPP focuses mainly on the improvement of interpersonal relations (social networks), disturbed by depression, trying also to reduce depressive symptoms. Before starting treatment, depressive patients had a higher metabolism than control subjects did in the prefrontal cortex, caudate and thalamus and lower metabolism in the temporal lobe. After treatment, paroxetine-treated patients had a greater decrease in depressive symptoms than did subjects treated with IPP. However, both kinds of treatment resulted in normalisation of metabolism in similar brain regions (i.e. decrease in the prefrontal cortex and increase in the temporal lobe). The only difference was between normalisation in bilateral prefrontal cortex in paroxetine-treated patients and right prefrontal cortex normalisation after IPP. Martin et al. [17] using the method of single photon emission computed tomography (SPECT) compared brain changes in depressive patients following treatment with IPP or antidepressant venlafaxine. In both treatment groups, an increased right basal ganglia blood flow was observed. Additionally, patients treated with IPP had right posterior cingulate activation and patients receiving venlafaxine – right posterior temporal lobe activation. These initial findings may suggest a common final pathway for brain changes after various methods of antidepressant treatment, either pharmacological or psychotherapeutic. However, it cannot be excluded that treatments will have different effects based on the nature of pre-treatment brain changes; a detailed assessment of such changes may allow qualification of individual patients to be treated with specific biological or psychotherapeutic methods.

A similarity of cerebral effects of either pharmacotherapy or psychotherapy was also observed by Baxter et al. [18]. They performed a PET study in patients with obsessive-compulsive disorder treated with fluoxetine or behaviour therapy. In both groups of patients a similar decrease in cerebral metabolic rates in the head of the right caudate nucleus was demonstrated.

In the 1990s, several papers appeared measuring biochemical changes after various psychotherapeutic procedures. Joffe et al. [19] estimated thyroid hormone level in depressed patients treated with cognitive therapy. Patients who responded to cognitive therapy showed significant decreases in their level of thyroxine, while the non-responders showed increases of this hormone. Shear et al. [20] studied patients with panic disorder before and after successful cognitive therapy. They demonstrated that patients, in whom, before starting therapy, infusion of lactate caused a panic attack, became “resistant” to such precipitation after treatment. A number of reports were also published suggesting a possibility of an effect of psychotherapeutic procedures on immunological functions. Majority of such studies were performed in cancer patients showing that psychotherapy and supportive relationships can increase a survival rate and favourably influence immune parameters [21, 22]. Interesting novel hypotheses were also put forward concerning biological mechanisms of the psychotherapeutic effects of placebo. According to Stefano et al. [23], the placebo effect may be connected with the activation of physiological response that is the opposite of the stress

response (so called “relaxation response”). This process involves a significant role of endogenous opioids and nitric oxide system.

In summary, it is likely that in the 21st century, a progressive integration of biological and humanistic sciences will take place, based on the exponentially increasing knowledge of how the brain works. In the field of psychiatry, a significant contribution to this process can be the better explanation of theory and practice of psychotherapy on the ground of neurobiology.

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