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Morphological changes of the brain in mood disorders

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Summary

Brain morphological changes in affective disorders occur mainly in the fronto-limbic cortex, hippocampus and amygdala – the structures regulating emotional and cognitive functioning, as well as development of somatic symptoms in the course of disorders. The largest number of reports of structural changes in the cerebral cortex include the dorsolateral prefrontal cortex, the orbitofrontal cortex and the anterior cingulate cortex. The results of neuroimaging and sectional studies reveal changes in the volume of structures involved in the creation of neuronal circuits that affect development of mood disorders. Microscopic studies show changes in cell count, density, and morphology in these areas. Some of those changes are observed only in certain layers of the cerebral cortex. A valuable addition to this data are histochemical studies of neuronal survival markers, proinflammatory cytokines, trophic factors, and markers specific for particular cellular structures. The role of monoaminergic, GABA-ergic and glutamatergic neurotransmission is confirmed by the studies on concentration of neurotransmitters, their receptors and transporters. Some of the results correlate quantitatively with the type and severity of symptoms, duration of the disorder, as well as pharmacotherapy and nonpharmacological treatment.

Key words: mood disorders, post mortem studies, neuropathology

Introduction

Postmortem studies let us expand our knowledge of the pathogenesis of mental disorders, including cellular, molecular and neurochemical pathologies. They both confirm and supplement the results of neuroimaging and neurophysiological studies of the same brain regions. Postmortem changes in patients with mood disorders are related to the structures responsible for emotional disturbances, cognitive dysfunctions, and psychosomatic symptoms occurring in the course of the disorder [1].

Structural changes in mood disorders occur primarily in the association cortex (mainly in dorsolateral prefrontal cortex, orbitofrontal cortex and the anterior cingulate

cortex), hippocampus, amygdala; they are not found in the sensory cortex (e.g., in the visual or somatosensory cortex). Volumetric, metabolic and neurochemical changes found in neuroimaging and neurofunctional studies correspond with changes at the cellular level determined postmortem. The changes within the neurons and the glia, affecting specific types of cell and site-typical ones, supplement and broaden the hypotheses suggesting the presence of a relationship between psychiatric disorders and monoaminergic, glutaminergic and GABA-ergic neurotransmission [1].

In affective disorders, morphological changes in neuronal circuits regulating brain functions are affected by the disease process. These are changes, among others, in density and size of neurons in the dorsolateral prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex – areas forming the neuronal circuits responsible for higher cognitive functions and mental processes associated with limbic system. There is a decrease in neuronal density and size of nerve cells in the association cortex, but this type of lesions have not been reported in the sensory and motor cortex, which is consistent with neuroimaging and neurofunctional findings [1]. Some of the morphological abnormalities are similar to those observed in patients with schizophrenia, such as a decrease in the density of oligodendroglia in layer VI in Brodmann area 9 described in schizophrenia, depression and bipolar disorder [2].

The etiology of histopathological changes of the brain in patients with affective disorders is not well known. The role of genetic and neurodevelopmental factors, individual course of the disorder and exposure to psychotropic medication in the development of neuronal and glial tissue changes is suspected [1].

Macroscopic changes in unipolar depression

In patients with unipolar depression there is no change in the total brain volume, however, there is a decrease in the volume of the hippocampus, prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (and its ventrocranial part – subgenual cingulate cortex) [3], as well as in subcortical structures – the caudate nucleus, globus pallidus, putamen, and the left nucleus accumbens [4], suggesting the presence of atrophy or cellular loss in these structures [1]. There is also a reduction in the proportion of gray matter to white matter in the prefrontal cortex [3].

Magnetic resonance imaging studies have shown a reduction in the volume of the hippocampus in patients suffering from depressive episode and also in those with a history of depression in the past [1]. Hippocampal atrophy refers specifically to elderly patients with high number of relapses and resistance to treatment. A meta-analysis based on the MRI studies of 351 depressive patients and 279 healthy ones showed a reduction in hippocampal volume by 8% on the left and 10% on the right side, on average. The authors of the meta-analysis suggest that those lesions may result from apoptosis of the hippocampal cells or from neurogenesis inhibition, which are mediated by glucocorticoid neurotoxicity [5].

Children with depression have been shown to present a decrease in frontal lobe volume inversely related to the age and an increase in the ventricular volume [6]. The thickness of the the posterior cingulate cortex correlates with the severity of depression according to the Hamilton score and gradually decreases with age [7].

Results of functional neuroimaging studies indicate the relationship between the treatment used and the severity of the symptoms with the severity of morphological lesions. In vivo resting fMRI studies show a decrease in communication between the prefrontal cortex, superior temporal gyrus and the insular cortex, as well as an increase in the number of connections between the amygdala and the prefrontal cortex. Adolescents with depressive and anxiety disorders presented excessive activity in the amygdala and ventral prefrontal cortex [3], and an increased ratio of amygdala volume to hippocampal volume, which correlated with the severity of anxiety symptoms in the course of depression [8].

Macroscopic changes in bipolar disorder

Volumetric studies show that the total volume of the brain and intracranial spaces in bipolar disorder is not significantly different from that of healthy individuals, and the volume of most brain structures is preserved [9]. However, there were some abnormalities observed like a slight decrease in total brain volume, most prominent in the frontal area [10], widening of the right ventricular system [4], enlargement of the lateral ventricles [11], enlargement of the temporal horn and the absence of normal frontal asymmetry, as well as the hyperintense foci in the deep white matter [12].

Patients with bipolar disorder exhibit changes in the volume of the frontal and prefrontal cortex, striatum and the limbic structures (amygdala, hippocampus) [13]. There is an increase in the volume of the anterior cingulate cortex, insular cortex, globus pallidus (associated with the treatment of mood stabilizers), basal ganglia and the amygdala [10, 14], as well as the volume of the left nucleus accumbens [4]. The volume of the anterior cingulate cortex and the hippocampus is higher in patients treated with lithium than in untreated patients, which can be explained by neurotrophic and proneuroplastic properties of mood stabilizers [14].

The results of a recent large-scale MRI study in patients with bipolar disorder revealed thinning of the frontal, temporal and parietal cortex of both cerebral hemispheres, particularly in the left opercular part, left fusiform gyrus and left rostral medial frontal cortex. Severity of those changes were correlated with duration of illness. The decrease in the cortical surface correlated with past history of psychotic episodes [15].

Microscopic changes in unipolar depression

In patients with depression, mainly older, with recurrent and drug-resistant course of the disorder, there is a decrease in the volume of hippocampus [1, 10]. In the CA1 and CA4 fields and in the dentate gyrus, an increase in the amount of fragmented DNA was observed, indicating an increase in the intensity of apoptosis and necrosis. In the CA fields and the dentate gyrus (especially in the granular layer), cellular density was increased and a decrease in Nissl-stained neuronal cell size was observed [16]. Neurobiological mechanisms of stress response and the antidepressant treatment may influence neuronal plasticity in the hippocampal region [1].

In the dorsolateral prefrontal cortex, orbitofrontal cortex and the anterior cingulate cortex there is a decrease in the density and size of Nissl-stained neurons [1, 17], which is selectively present in particular cortical layers rather than in its entire cross section. It may result from disturbed dendritic morphology or abnormal synaptic connections [1].

In layers II to VI of the dorsolateral prefrontal cortex and the rostral orbitofrontal cortex, the decrease in neuronal density of large cell bodies for smaller neurons has been observed, suggesting that the decrease in the volume of brain structures in depressive disorders is associated with neuronal size changes rather than loss of total neuron count [1].

In layer II and upper part of layer III of the dorsolateral prefrontal cortex, there was a decrease in the density of non-pyramidal neurons detected using calbindin, an antibody against the calcium-binding protein coexisting with gamma-aminobutyric acid, which may suggest that depression is associated with reduced GABA concentration in the cerebral cortex [1].

The results of tension diffusion imaging indirectly indicate the presence of microscopic lesions. In adolescents with depression an impaired integrity of the white matter fibers have been shown – there was a reduction of fractional anisotropy in neuronal pathways emerging from the subgenual anterior cingulate cortex associated with the fronto-limbic pathways, as opposed to the increase in the white matter at the expense of the gray matter observed in healthy adolescents. It has not been clearly established whether the described changes contribute to the etiopathogenesis of depressive disorders, or rather result from them [3].

Exposure to stress causes dendritic remodeling: diminished density of the dendritic spines in the prefrontal cortex and in the hippocampus, an increase in the number of spines in the amygdala and the nucleus accumbens [18, 19], and it affects neuronal survival and synaptic plasticity, which are mediated by the brain-derived neurotrophic factor (BDNF) [20]. It has been shown that treatment with antidepressants and nonpharmacological methods (electroconvulsive therapy, deep brain stimulation, transcranial magnetic stimulation) accelerate neuronal maturation, dendritic growth and maturation of dendritic spines and improve survival of newly formed neurons [21].

In depressed patients, there is a decrease in the density and number of glial cells in the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex and the amygdala [1, 10, 22]. Changes of this type show specificity in relation to cortex layers: they are found in the layer VI of the supragenual anterior cingulate cortex, layers III and V of the dorsolateral prefrontal cortex, and layers III–VI of the caudal part of the orbitofrontal cortex [17]. In turn, in the CA fields and the stratum granulosum of the dentate gyrus of the hippocampus there is an increase in glial cells density, which may be secondary to reduced volume of surrounding neuropil, consisting of glial cells filaments, branches of dendrites and proximal axons. The observed glial tissue pathologies may be related to the abnormalities in monoaminergic and glutamatergic neurotransmission [1].

Microscopic changes in bipolar disorder

In bipolar affective disorder there are changes in neuronal density: decrease in pyramid (excitatory, glutamatergic) neuronal density in layers III and V, and decrease in non-pyramidal (inhibitory, GABA-ergic) neuronal density in the layer II of the dorsolateral prefrontal cortex and the anterior cingulate cortex [1]. A decrease in the density and size of non-pyramidal nerve cells in the hippocampal CA2 region [23] and neuronal disorganization in the layers II and III of the entorhinal cortex was also described [1]. Some researchers also described the reduction in neuronal cell size, similar to that observed in unipolar depression [1]. It is believed that the reduction in neuronal cell size in affective disorders and schizophrenia is due to dysfunction of glial cells supporting neurons [17].

As in patients with unipolar depression, there is a decrease in the number and density of glial cells in the dorsolateral prefrontal cortex, orbitofrontal cortex, and the anterior cingulate cortex. In the dorsolateral prefrontal cortex, increased density and size of glial cell nuclei was observed, and their shape was changed to less regular [1]. There are reactive, regressive and progressive changes of oligodendroglia and a decrease in its total amount in the prefrontal cortex, however, as opposed to schizophrenia, such changes do not occur in the caudate nucleus. In turn, in Brodmann area 46 there is an increased density of microglia [22]. This type of lesions has already been reported in young patients at an early stage of disorder. In the white matter among adolescents in their first manic episode, a decrease in both neuronal and glial tissue density and the hypertrophy of glial cells in the white matter were described [24].

The location of some structural changes in the glia is layer-specific. In the dorsolateral prefrontal cortex (Brodmann area 9), there was a decrease in the density of glial cells in both cerebral hemispheres, most prominent in layer V with accompanying neuronal size reduction, especially in layers V and VI [17] and in the calls of layer VI of Brodmann area 10 a reduction in the surface area of the nuclei and the amount of the oligodendroglial euchromatin was reported [22]. The glial pathologies the most likely result from an increased metabolic burden of the cells [1].

In contrast to schizophrenia, in bipolar disorder the changes in dendritic arborisation and abnormal synaptic densities have not been reported [12], but abnormal neuronal cytoskeleton organization does occur [25].

Histochemical investigations in unipolar depression

Proteomic studies of the frontal cortex and the anterior cingulate cortex show cytoskeletal organization abnormalities in depressed patients associated with changes in expression of glial fibrillary acidic protein (GFAP), tubulin isoforms and MAP protein [25]. In hippocampal CA1 and CA2 fields the immunoreactivity of astrocytes with GFAP and neuronospecific phosphoprotein B50 is decreased [1].

In teenage suicide victims there was an observed increase in mRNA expression and expression of TNF-alpha and IL-6 and IL1-beta protein in Brodmann area 10, which may suggest, that proinflammatory cytokines take part in the pathogenesis of

psychiatric disorders [26]. The concentration of isoforms of tumor necrosis factor: soluble (sTNFα) and transmembrane (tmTNFα) was also investigated. There was a 458% increase in tmTNFα in the dorsolateral prefrontal cortex (Brodmann area 46) responsible for mood regulation. No similar correlation was found for soluble isoform and no changes in TNFα isoform concentrations were observed in Brodmann area 24, responsible for cognitive functioning. Due to the absence of increased concentrations of other proinflammatory cytokines and their receptors and no increase in levels of neuronal integrity markers (synaptophysin, PSD95) in the investigated cortical areas, the authors suppose that the increased level of tmTNFα in DLPFC results from causes other than inflammatory ones [27].

Immunohistochemical studies of patients treated with antidepressants (regardless of diagnosis) showed an increase in BDNF expression, a stress response mediator regulating synaptic plasticity and neuritic growth, in the dentate gyrus and the hilus of the hippocampus [20], as well as mRNA and BDNF protein reduction in suicide victims with depression and other psychiatric diagnoses [1]. A decrease in expression of CREB, a transcription factor regulating, among others, BDNF mRNA transcription, in adolescents who died because of suicide was also found [3].

The connection between affective disorders and monoaminergic neurotransmission makes researchers analyze the density and affinity of receptors and their transporters in the brain regions crucial for the development of these disorders. In the postmortem studies serotonin transporter expression in the dorsolateral prefrontal cortex, ventral orbitofrontal cortex and the brain stem was decreased in suicide victims diagnosed with depression [28]. In the layer VI of the prefrontal cortex, the serotonin transporter deficiency is also reported [29]. Subtle structural changes in the brain stem monoaminergic nuclei, the main source of serotoninergic (dorsal raphe nucleus) and noradrenergic (locus ceruleus) projections into the cortex, as well as the increased number and density of tryptophan hydroxylase immunoreactive neurons in the dorsal raphe nucleus were reported in suicide victims with depression. Data on changes in the number of pigmented neurons in the rostral locus ceruleus are inconsistent, but CRH immunoreactivity is increased in the locus ceruleus and dorsal and medial raphe nucleus [28].

Stereological studies of specific types of hypothalamic neurons have demonstrated an increase in arginine vasopressin (AVP), oxytocin and corticotropin-releasing neurons in the paraventricular nucleus, and an increase in CRH mRNA and CRH-neurons coexisting with AVP neurons. These data are consistent with reports on hypothalamic--pituitary axis activation in some patients with depression [28].

Histochemical investigations in bipolar disorder

In patients with bipolar affective disorder reelin immunoreactivity was decreased in the hilus of the hippocampus, and the concentrations of the synaptic proteins were decreased in the CA4 field [1]. There was also an increase in the concentration of transmembrane TNFα isoform in Brodmann area 24 and 46 in patients with bipolar disorder, as opposed to those with depression who, as described above, have increased tmTNFα concentrations in area 46 but not in area 24 [27].

As in depression, in bipolar disorder the number of arginine vasopressin (AVP), oxytocin and corticotropin-releasing neurons in the paraventricular nucleus was increased [28]. The number and density of GABA-ergic neurons identified by parvalbumin [30] in the entorhinal cortex is reduced, and reactivity of calbindin, a marker of non-pyramidal neurons, in layer II of the anterior cingulate cortex and the dorsolateral prefrontal cortex is decreased [1]. Moreover, the elevated levels of glutamate and glutamine were found in the brains of patients evaluated by magnetic resonance spectroscopy imaging [10].

Conclusions

Postmortem studies of morphology, histochemistry and immunoreactivity of the brain tissue may provide an opportunity for a better understanding of the neurobiology of affective disorders by verifying existing hypotheses. The obtained results may also facilitate the creation of new drug targets and, in longer perspective, more effective treatment of patients with mood disorders.

References

1. Stockmeier CA, Rajkowska G. *Cellular abnormalities in depression: Evidence from postmortem brain tissue*. Dialogues Clin. Neurosci. 2004; 6(2): 185–197.
2. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. *Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: A study from the Stanley Neuropathology Consortium*. Schizophr. Res. 2004; 67(2–3): 269–275.
3. Miguel-Hidalgo JJ. *Brain structural and functional changes in adolescents with psychiatric disorders*. Int. J. Adolesc. Med. Health 2013; 25(3): 245–256.
4. Baumann B, Danos P, Krell D, Dieknamm S, Leschinger A, Stauch R et al. *Reduced volume of limbic system-affiliated basal ganglia in mood disorders: Preliminary data from a postmortem study*. J. Neuropsychiatry Clin. Neurosci. 1999; 11(1): 71–78.
5. Videbech P, Ravnkilde B. *Hippocampal volume and depression: A meta-analysis of MRI studies*. Am. J. Psychiatry 2004; 166(11): 1957–1966.
6. Steingard RJ, Renshaw PF, Yurgelun-Todd D, Appelmans KE, Lyoo IK, Shorrock KL et al. *Structural abnormalities in brain magnetic resonance images of depressed children*. J. Am. Acad. Child Adolesc. Psychiatry 1996; 35(3): 307–311.
7. Truong W, Minuzzi L, Soares CN, Frey BN, Evans AC, MacQueen GM et al. *Changes in cortical thickness across the lifespan in major depressive disorder*. Psychiatry Res. 2013; 214(3): 204–211.
8. MacMillan S, Szeszko PR, Moore GJ, Madden R, Lorch E, Ivey J et al. *Increased amygdala: Hippocampal volume ratios associated with severity of anxiety in pediatric major depression*. J. Child Adolesc. Psychopharmacol. 2003; 13(1): 65–73.
9. Reite M, Reite R, Collins D, Teale P, Rojas DC, Sandberg E. *Brain size and brain/intracranial volume ratio in major mental illnesses*. BMC Psychiatry 2010; 10: 79.
10. Maddock RJ, Buonocore MH. *MR Spectroscopic Studies of the Brain in Psychiatric Disorders*. Curr. Top. Behav. Neurosci. 2012; 11: 199–251.

11. Pearlson GD, Garbacz DJ, Breakey WR, Ahn HS, DePaulo JR. *Lateral ventricular enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder*. Psychiatry Res. 1983; 12(1): 1–9.
12. Santosh PJ. *Neuroimaging in child and adolescent psychiatric disorders*. Arch. Dis. Child. 2000; 82: 412–419.
13. Brennand KJ, Simone A, Tran N, Gage FH. *Modelling psychiatric disorders at the cellular and network levels*. Mol. Psychiatry 2012; 17(12): 1–15.
14. Bora E, Fornito A, Yucel M, Pantelis C. *Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder*. Biol. Psychiatry 2010; 67(11): 1097–1105.
15. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK et al. *Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from ENIGMA Bipolar Disorder Working Group*. Mol. Psychiatry 2018; 23(4): 932–942.
16. Stockmeier CA, Mahajan GJ, Konick LC, Overholser JC, Jurjus GJ, Meltzer HY et al. *Cellular changes in postmortem hippocampus in major depression*. Biol. Psychiatry 2004; 59(9): 640–650.
17. Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP. *Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorders*. Cereb. Cortex. 2002; 12(4): 386–394.
18. Kida S, Kato T. *Microendophenotypes of Psychiatric Disorders: Phenotypes of Psychiatric Disorders at the level of Molecular Dynamics, Synapses, Neurons and Neural Circuits*. Curr. Mol. Med. 2015; 15(2): 111–118.
19. Qiao H, Li MX, Xu C, Chen HB, AnSC, Ma XM. *Dendritic spines in depression: What we learned from animal models?* Neural Plast. 2016; 2016: 8056370.
20. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. *Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication*. Biol. Psychiatry 2001; 50(4): 260–265.
21. Schoenfeld TJ, Cameron HA. *Adult neurogenesis and mental illness*. Neuropsychopharmacology 2015; 40(1): 113–128.
22. Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V, Rachmanova V. *Electron microscopy of oligodendroglia in severe mental illness*. Brain Res. Bull. 2001; 55(5): 597–610.
23. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF, Stanley Neuropathology Consortium. *Molecular abnormalities of the hippocampus in severe psychiatric illness: Postmortem findings from the Stanley Neuropathology Consortium*. Mol. Psychiatry 2004; 9(6): 609–620.
24. Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A et al. *Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: A diffusion tensor image study*. Am. J. Psychiatry 2006; 163(2): 322–324.
25. Coumans JVF, Palanisamy SKA, McFarlane J, Moens PDJ. *Proteomic and Microscopic Strategies towards the Analysis of Cytoskeletal Networks in Major Neuropsychiatric Disorders*. Int. J. Mol. Sci. 2016; 17(4): E581.
26. Pandey GN, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC et al. *Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims*. J. Psychiatr. Res. 2012; 46(1): 57–63.
27. Dean B, Gibbons AS, Tawadros N, Brooks L, Everall IP, Scarr E. *Different changes in cortical tumor necrosis factor-α-related pathways in schizophrenia and mood disorders*. Mol. Psychiatry 2013; 18(7): 767–773.
28. Furczyk K, Schutova B, Michel TM, Thome J, Buttner A. *The neurobiology of suicide – A review of postmortem studies*. Journal of Molecular Psychiatry 2013; 1(2): 1–22.

29. Austin MC, Whitehead RE, Edgar CL, Janosky JE, Lewis DA. *Localised decrease in serotonin transporter-immunoreactive axons in the prefrontal cortex of depressed subjects commiting suicide*. Neuroscience 2002; 114(3): 807–815.
30. Pantazopoulos H, Lange N, Baldessarini RJ, Berretta S. *Parvalbumin neurons in entorhinal cortex of subjects diagnosed with bipolar disorder of schizophrenia*. Biol. Psychiatry 2007; 61(5): 640–652.

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