Psychobiological model of major depressive disorder

Author

Bernhard J. Mitterauer

Affiliation

Professor emeritus
University of Salzburg
Volitronics-Institute for Basic Research, Psychopathology and Brain Philosophy,. Gotthard Guenther Archives.

Correspondence
Autobahnweg 7,
A-5071 Wals (Salzburg), Austria
Email:
mitterauer.b@gmail.com

Abstract

A novel psychobiological model of major depression based on glial-neuronal interactions is proposed. Imbalance of information processing in tripartite synapses and the astroglial networks may be essentially caused by overexpression of astrocytic receptors and gap junctions in the astroglial network. Basic genetic and epigenetic predisposition as well as internal and/or external stress may be responsible for this dysregulation of information processing in depression. Both personality structure and the excess of astrocytic receptors and astroglia gap junctions cause a relative lack of neurotransmitter substances with protracted information processing. Since it has been hypothesized that intentional programs are generated in the astroglial network, the brain operates hyperintentionally in depression. Increased coupling of gap junctions leads to an expansion of the astroglial domain organization such that the astrocytic domains overlap with cognitive impairment as a consequence. The basic symptoms of depression can be deduced from the proposed model. Finally, an action oriented treatment based on antidepressant therapy is outlined.

Keywords*:* major depression, synaptic imbalance, astrocytic receptors, glial connexins, overexpression, treatment

1. Introduction

Depression is a worldwide psychobiological disorder. In the USA, the lifetime prevalence in the general population is estimated to 16,2% (1). Already in 1913 Kraepelin characterized depression as “to make it harder to think and act” (2). The basic symptoms are depressed mood and loss of interest or pleasure (3). Depression is thought to be a heterogenous disorder resulting from a dysfunction of several neurotransmitter or metabolic systems. Various theories try to explain the pathophysiology of depression based on studies investigating psychosocial stress and stress hormones, neurotransmitters, neurocircuitry, neurotrophic factors, and circadian rhythm (4). However, the etiopathogenesis of depression is still unknown. Although most hypotheses are “neurocentric”, there is growing evidence that the glial system, especially astrocytes, play a significant role in the pathophysiology of depression (5, 6).

The present study is written for a broad medical readership and does not refer to complex pathophysiological details and citations. The model proposed here is a further elaboration of my novel theory of the psycho-pathophysiology of depression (7, 8, 9, 10, 11). I outline the Hyperintentionality hypothesis of major depression (12) based on very recent findings in the glial networks. Implications for treatment and communication with patients suffering from depression are finally deduced. To begin with a balanced glial-neuronal synaptic unit, called tripartite synapse, and the glial network must be described.

2. Balance of information processing in tripartite synapses

The basic anatomical components of a tripartite synapse (13) are composed of the presynaptic neuron, the postsynaptic neuron, and the astrocyte embodying the glial cell with a synaptic cleft in between. The glial-neuronal interactions in chemical tripartite synapses occur via neurotransmitters, gliotransmitters and other substances (neuromodulators, neurotransporters, ions, etc.). Experimental neurophysiological research has demonstrated that the glial system exerts a modulatory function in its interactions with the neuronal system (14). Figure 1 shows schematic diagrams of balanced tripartite synapses focusing on the decisive effects of astrocytic receptors.

Figure 1(a) depicts a glutamatergic synapse and Figure 1(b) a GABA-ergic synapse. All neuronal synaptic, extrasynaptic and astrocytic receptors are equal in number such that the corresponding amount of activating transmitter substances is appropriate. The activation of astrocytic receptors (acr) causes the generation of transmitters within the astrocyte, called gliotransmitters (GT). Released GT occupy presynaptic receptors exerting a feedback mechanism. Dependent on the excitatory (a) or inhibitory (b) function of GT, a positive or negative feedback mechanism

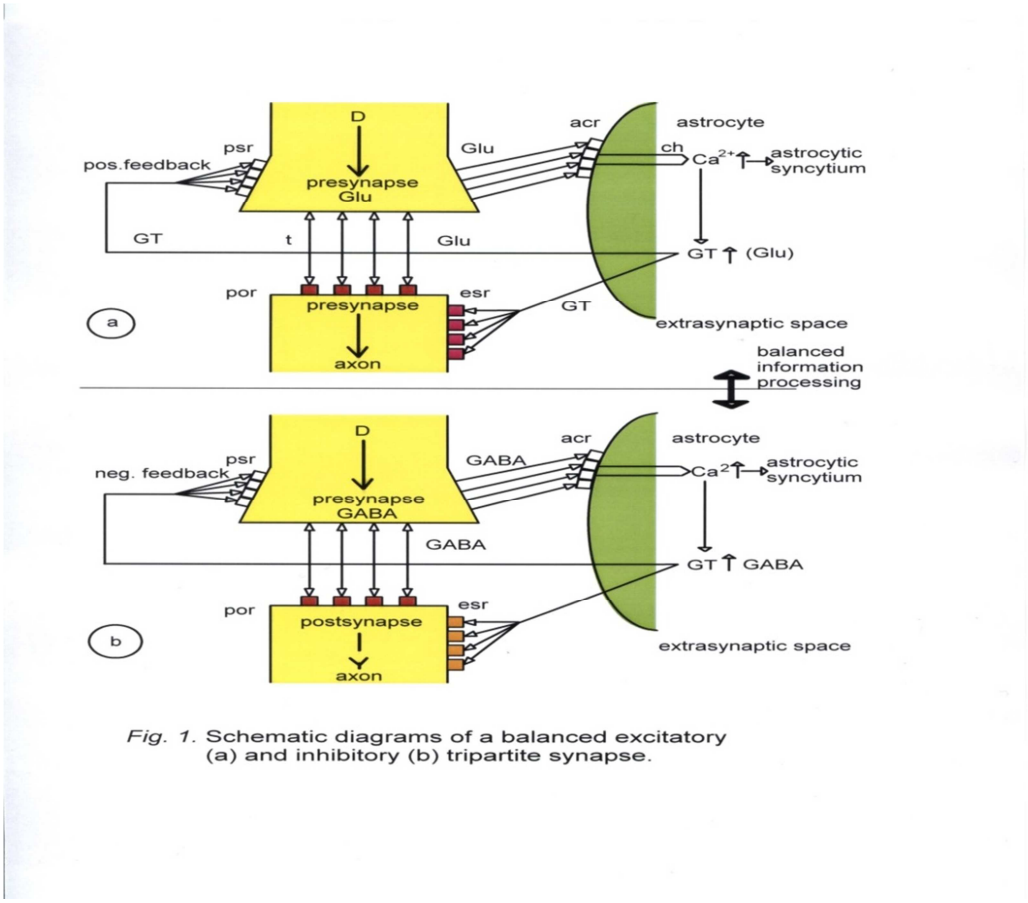

Fig. 1. Schematic diagrams of a balanced excitatory (a) and inhibitory (b) tripartite synapse.

Figure 1. Schematic diagrams of a balanced, an excitatory (a) and an inhibitory (b) tripartite synapse

a) A dendrite (D) activates the excitatory neurotransmitter glutamate (GLU) in the presynapse. GLU occupies postsynaptic receptors (por), reuptaken (↔) via transporters (t). In parallel, receptors on the astrocyte (acr) are occupied by an appropriate amount of GLU (→). This activates channels (ch), the production of Ca^{2+} -waves and gliotransmitters (GT) with the structure of GLU. GT occupy presynaptic receptors (psr) and extrasynaptic receptors (esr) on the postsynapse. The excitatory effect of GLU corresponds with a positive feedback mechanism on the presynapse and the depolarization by the occupancies of postsynaptic and extrasynaptic receptors. These mechanisms depict the excitatory effect of GLU in tripartite synapses.
b) In an inhibitory synapse GABA exerts inverse mechanisms. The synaptic effects of a and b enable a balanced information processing (↕) (11).

determines the production of neurotransmitters (NT) in the presynapse. Importantly, the interplay between these opposite synaptic functions enables the balance of information processing in tripartite synapses due to which a structuring of brain operations is possible (15, 11). In more detail, a dendrite (D) activates the excitatory neurotransmitter glutamate (GLU) in the presynapse. GLU occupies postsynaptic receptors (por), reuptaken (↔) via transporters (t). In parallel, receptors on

the astrocyte (acr) are occupied by an appropriate amount of GLU (→). This activates channels (ch), the production of Ca^{2+}
waves and GT with the structure of GLU. GT occupy presynaptic receptors (psr) and extrasynaptic receptors (esr) on the postsynapse. The excitatory effect of GLU corresponds with a positive feedback mechanism on the presynapse and the depolarization by the occupancies of por and esr (a). In an inhibitory synapse GABA exerts inverse mechanisms (b). The synaptic effects of (a) and (b) enable a balanced information processing.

3. Astroglial network

Gap junctions between (and even within) astrocytes, oligodendrocytes and microglia provide a structural link by which single cells are coupled to build a functional network, called syncytium, with communication dynamics that cannot be exerted by individual cells. Gap junctions of an astrocyte syncytium consist of connexins forming gap junction channels by hemichannels of different kinds (16). The astroglial syncytium consists of connexin 43 and connexin 30.

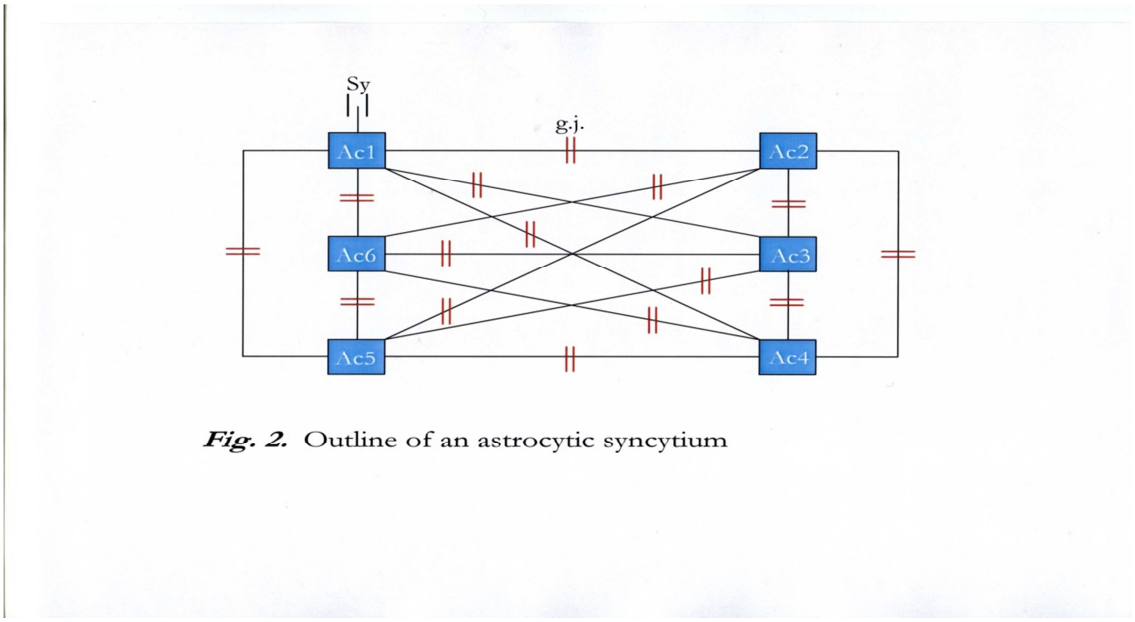

Fig. 2. Outline of an astrocytic syncytium

Figure 2. Outline of an astrocytic syncytium

Six astrocytes (Ac_1 … Ac_6) are completely interconnected via fifteen gap junctions (g.j.) according to the formula n:(n-1). Each astrocyte contacts a neuronal synapse (Sy, only one is shown) building a tripartite synapse in the sense of a glial-neuronal unit.

Figure 2 shows a diagrammatic scheme depicting an astrocytic syncytium. Six astrocytes (Ac_1 … Ac_6) are completely interconnected via 15 gap junctions (g.j.). Each astrocyte contacts a neuronal synapse (Sy, only one is shown), building a tripartite synapse. Importantly, astrocytes are organized into spatially non-overlapping domains that encompass both neurons and vasculature. An astrocyte domain defines a

contiguous cohort of synapses that interact exclusively with a single astrocyte (17). The capability of an astrocyte to couple with others is mainly determined by gliotransmitters expressed in hemichannels of the astroglial syncytium (18).

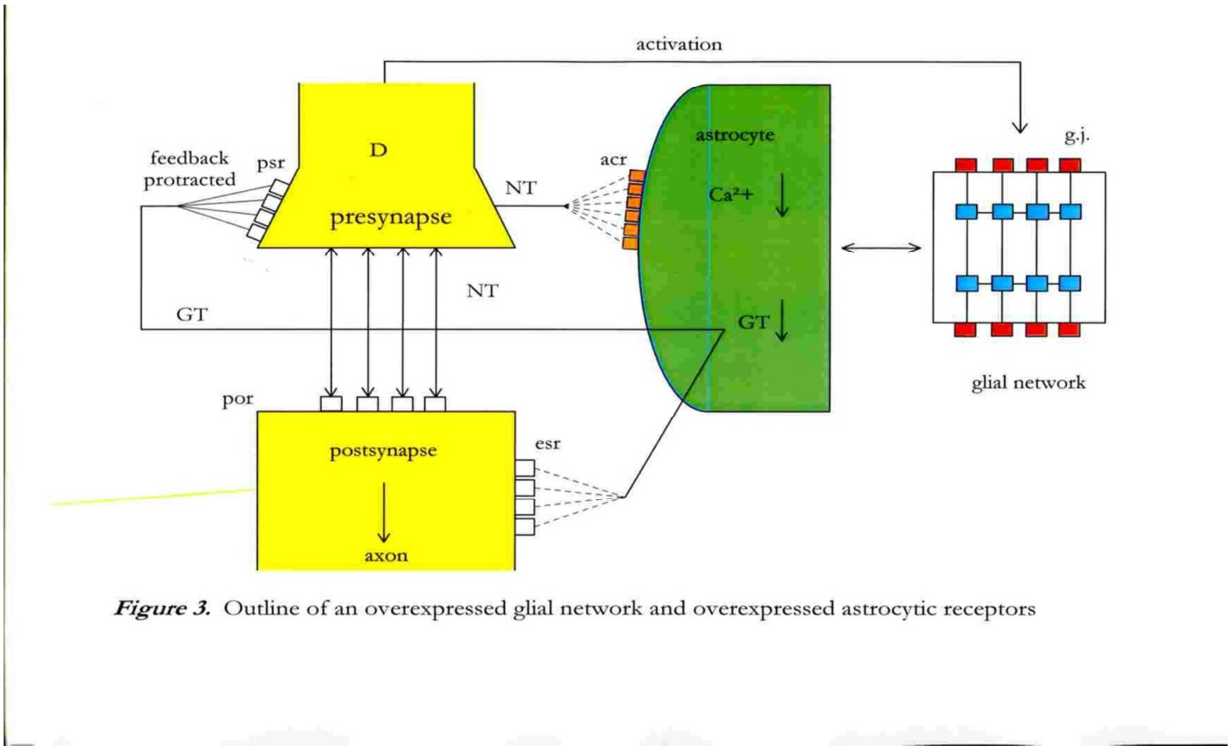

Figure 3. Outline of an overexpressed glial network and overexpressed astrocytic receptors

Figure 3. Outline of an overexpressed glial network and overexpressed astrocytic receptors.

Gap junctions in the glial network are overexpressed (red squares) activated by dendrites (D) of the presynapse. This causes an overexpression of astrocytic receptors (acr). Neurotransmitter substances (NT) are produced between pre- and postsynapse (double headed arrows) but the amount of NT is too small for occupying acr. The lack of NT for occupancy of acr causes a decreased Ca^{2+} production and a decrease of gliotransmitter (GT) expression. Since occupancy of presynaptic receptors (psr) and extrasynaptic receptors (esr) by GT is delayed (dashed lines), the negative feedback on psr is protracted. Synaptic information processing is prolonged.

4. Imbalanced tripartite synapse responsible for depression

Figure 3 outlines an unbalanced tripartite synapse, caused by an overexpression of g.j. (red squares) in the glial network as well as acr. A relative lack of NT cannot occupy acr (dashed lines) so that Ca^{2+} activation and GT production is decreased. This leads to a protracted feedback on psr (dashed lines). The activation of esr is also protracted (dashed lines). Whereas the overexpression of acr is presently found in neuropsychiatric disorders such as Alzheimer's disease (19) and Parkinson's disease (20), in depression overexpressed acr should be identified in

near future. Moreover, overexpression of g.j. has been identified in the glial network of animal models of neuropathic pain (19). Since antidepressants ameliorate neuropathic pain, the same pathopysiological mechanism may be at work both in neuropathic pain and in major depression (21).

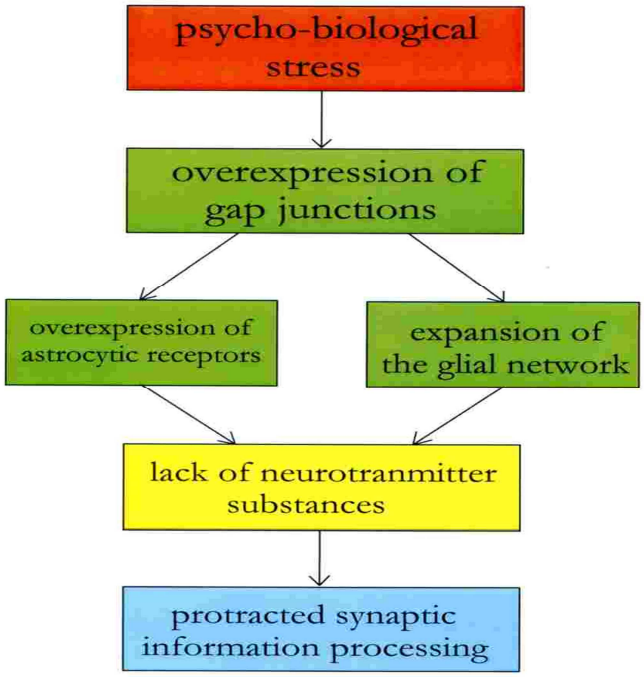

Figure 4. Pathophysiological model of major depression (see text)

5. Pathophysiological model of depression

Since pathophysiological findings in depression research are mostly controversial, a comprehensive theory is needed for a better understanding of the patients‘ subjective suffering, depressive behavior, treatment and empathic communication.

Figure 4 shows the basic components possibly underlying the pathophysiology of major depression. Based on genetic disposition and epigenetic factors a severe internal or external stress situation occurs. This may generate an overexpression of g.j. in the glial network. Moreover, an overexpression of g.j. causes a corresponding increase of coupling between astrocytes such that the astrocytic domain organization expanses. In parallel, acr may also be overexpressed. Both the expansion of the glia network and the overexpression of acr cannot be occupied by NT and a relative lack of NT in synaptic information processing arises, leading to a protracted synaptic information processing. The interactions of these basic mechanisms described generates a depressive mood and depressive behavior. This model of the pathophysiology of depression will now be discussed in more detail.

5.1. Psychobiological stress and hyperintentionality

Basically, pathophysiological findings with regard to the glial system mainly concern the astrogliopathology (5), the role of microglia in inflammation (22), and the glial network (syncytium) where g.j. dysfunctions are found (23). What the genetic susceptibility concerns, phenotype emerges as a final common outcome of diverse processes, called equifinality of disease susceptibility and stress.

I have hypothesized that intentional programs are generated in the astroglial network (24). If g.j. are overexpressed in depression, the patient is determined by a hyperintentional personality structure (8), where an epigenetic process expresses certain genes in a parent-origin-specific manner (25). Importantly, epigenetic modification of gene expression provides a mechanism for understanding the link between long-term effects of adverse life events and changes in gene expression that are associated with depression (26). It is frequently observed that parents of children susceptible to depression are convinced of having a genius daughter or son who will make „great things“ and innovations, which Bibring (27) called high aspirations of persons susceptible to depression. Basically, if a person with high aspirations is unable to realize an intentional program and is lacking a subjective explanation for this, a stress situation is generated. A feeling of impotence can activate a depressive episode caused by imbalances in tripartite synapses and dysregulations in the astroglial networks leading to impairments in action and cognition.

The question arises as to how non-feasible intentional programs activate genetic susceptibility to depression. Generally, genome-wide association and linkage results provide constraints on allele frequencies and effect sizes of susceptibility loci (28). Stress is caused by both environmental factors and factors within the nervous system. Patients with high genetic risk frequently experience depressive episodes without major environmental stressors (29). One can also say that in the case of non-feasible intentional programs the environmental situation is both stressful and inappropriate, since the patient himself generates this stress situation, unable to adapt his/her interactions to possibilities in the environment. If this inner stress persists, intentional programs

operate hyperintentionally, permanently striving to realize what cannot be realized. Such persons have a hyperintentional personality structure.

5.2. Overexpression of gap junctions and astrocytic receptors. Astroglial network expansion

In the brain the coupling of astrocytes through gap junction channels (GJC) contributes to ionic homeostasis maintenance and to various biochemical/metabolic processes (17). Hemichannels (HC) are involved in astrocyte release of gliotransmitters (GT), uptake of glucose and of flux of glutathione. In astrocytes two major connexins (Cx) have been identified, Cx43 and Cx30, both contributing to GJC. However, so far only Cx43 containing HCs have been shown to operate in astrocytes (30). Importantly, concomitant functional increases of Cx43 containing GJCs and HCs promote astrocyte coupling and enhance HC-mediated release of excitatory gliotransmitters, including glutamate and adenosine-triphosphate (ATP) that activate postsynaptic N-methyl-D-asparate (NMDA) receptors and purinergic receptors, respectively (19). Although these findings concern an animal model of neuropathic pain, there is some indication that major depression and neuropathic pain may have the same underlying pathophysiology (22). This issue is of interest, since the overexpression of GJCs and HCs may generate hyperintentional programs in the astroglial network, where intentional programming may represent a basic function in these networks (11, 25). Admittedly, the overexpression of GJCs in neuropathic pain generates physio-biological pain and is not a hyperintentional function comparable with psychosocial stress or a typical personality structure. However, the therapeutic effects of antidepressant drugs are not only based on their transmitter reuptake inhibition, but also on the inhibition of GJC-overexpression (19).

I hypothesize that the overexpression of GJC and HC also causes an overexpression of astrocytic receptors (acr). It is experimentally verified that astrocytes can express almost all receptors for transmitter systems (31, 32). In certain cases individual astroglial cells express as many as five different receptor systems linked to Ca^{2+} mobilization (33). Up to now, overexpression of acr in depression has not been thoroughly investigated, but my model is testable.

Importantly, the expansion of the astroglial network caused by increased coupling is as yet not discussed in depression research. However, this pathophysiological and structural mechanism affects the normal astrocyte domain organization. Physiologically, an astrocyte is interconnected by its processes (about 40 main processes), building a territory capable of information processing of neuronal information possibly corresponding to a quality of sensory activation (34). In the case of expansion of astrocyte domains by increased coupling between astrocytes, the originally non-overlapping territory loses its spatio-boundary-setting function so that the brain is impaired, especially what distinct cognitive conceptualization concerns, dependent on the brain location affected (e.g. prefrontal cortex). This could explain why patients suffering from severe depression have problems to clearly express what they would like to say.

5.3. Lack of neurotransmitter substances and protracted synaptic information processing

As shown in Figure 3, the overexpression of astrocytic receptors causes a relative lack of neurotransmitter substances. This deficiency of neurotransmitter substances in brains with depression leads to various hypotheses of the pathophysiology of major depression and is the main target of pharmacological treatment (35). In this context, it should be mentioned that brain diseases such as Parkinson's disease also show a lack of neurotransmitter in pertinent synapses, but this is not necessarily accompanied by depressive mood (36). Hence, depression may occur only if the glial system is also affected, as I am attempting to demonstrate.

Since protracted information processing in tripartite synapses is basically caused by an overexpression of acr and GJCs (Cx43), this pathophysiological mechanism can be interpreted as a hyperintentional system operating in brains with depression. Thus, one can speak of an Hyperintentional hypothesis of major depression (12). Non-feasible intentional programs and information processing that does not operate in real time regarding events in the environment, may be responsible for the basic symptoms of depressive behavior.

6. Depressive behavior

The protracted information processing exerts different effects in excitatory and inhibitory synapses. If excitation is prolonged, psychomotor agitation is generated. In the case of inhibition of synaptic information processing, psychomotor retardation occurs. These psychomotoric changes may be based on the patient's incapability to integrate actual information in time. Since this physiological dysregulation basically occurs in the hippocampus and related regions, a patient with depression is not emotionally affected by actual information or events in the environment in the sense of emotional retardation. In parallel, prolonged information processing in excitatory synapses in the prefrontal cortex may be responsible for reduced concentration and irritability. In the language of Kraepelin (2) we can say that protracted information processing makes it harder to think in depression.

There is convincing evidence that dysregulations of biorhythm in depression are mainly caused by genetic mechanisms. Mutations in clock genes may play a decisive role (37, 38, 39). But what makes it harder to act in depression? Normally, the modes of behavior (e.g. eating, sleeping, working, communicating, speaking, etc.) are distributed in different frequencies with a time constant of about the female menstrual cycle (40). This psychobiological behavior pattern may be generated in the reticular core of the brainstem (41, 42).

In major depression a severe displacement of the modes of behavior is observed. Most importantly, some modes cannot be produced, whereas others persist for a longer time space. Therefore, a patient suffering from depression is impaired by a „cannot do" and a „must do" (43). We have shown in case studies that all modes of behavior can be affected in depression (8). Since this displacement of modes of behavior often persists in a depressive episode or becomes chronic, the pathophysiology here proposed could be explanatory what the expansion of the astroglial network or the astrocytic domain organization concerns. As discussed above, the increased coupling of gap junctions generates an expansion of astrocytic domains so that the normally non-overlapping territories lose their structural and functional boundaries. The operations of distinct conceptualization of environmental information in real time are delayed and impaired. If the patient intends to find an

appropriate environment for realizing his/her intentions, this cognitive capability is severely reduced. In other words: cognitive and action behavior is made harder to realize in depression. Together, both protracted synaptic information processing and the expansion of astrocytic domains may basically be responsible for depressive behavior.

7. Treatment and communication

7.1. Biological treatment

With regard to the glial cell system the effects of antidepressant drugs can be experimentally shown (44). A most recent study based on excellent methodology may support my model of the pathophysiology of major depression. Quesseveur and coworkers (24) investigated the role of hippocampal astroglial connexin43 (Cx43) in emotionality and the effects of selective serotonin re-uptake inhibitors (SSRI) and stress. The main result was as follows: considering that phosphorylation is a prerequistie for acute function of connexins (45), the therapeutic effects of antidepressant drugs might implicate the functional inactivation of Cx43. However, this experimental finding is controversely discussed, since classic antidepressant drugs may also increase gap junction coupling (46). Although identified in an animal model of neuropathic pain, the group of Giaume demonstrated that both the antidepressant amitriptyline and the gap junction blocker methoquine inhibited Cx43-containing gap junctions (19). This drug combination may also exert therapeutic effects in my pathophysiological model of major depression. Moreover, a very promising therapeutic approach to chronic depression is ketamine that can produce rapid and robust antidepressant effects in patients with treatment-resistant major depression. I have hypothesized that in therapy-resistant depression a signficant excess of NMDA receptors (N-methyl-D-asparate) on astrocytes is causing a severe lack of glutamate which cannot be balanced by reuptake inhibitory drugs, and the blockade of the excess of NMDA receptors in astrocytes may rapidly balance synaptic information processing. Since ketamine could act on various neuronal and glial cell types, my hypothesis refers to pertinent experimental findings with supporting arguments (47).

7.2. Behavioral treatment and communication

The most common psychotherapeutic approach in depression is cognitive and behavioral therapy (48) with various modifications. As already discussed, the biological treatment with antidepressant drugs leads to a restitution of normal behavior but the hyperintentional personality structure of the patient mostly persists. Here we deal with a kind of keeping calm without real effects on the patient's intentions to actually experience feasible actions in the environment in the sense of a regained self-understanding. Note that the number of astrocytic receptors is only satisfied with neurotransmitters and not with intended experiences in the environment. Here, a behavioral treatment strategy can stepwise cope with non-feasible intentions. Such a behavioral treatment, called action therapy of depression (8, 49) enables the patient to stepwise observe events in the environment generated in real time by himself. This is an experience encouraging the patient to act event-related again. The main goal of action strategies is to reconstitute a balance between intentions and corresponding actions in the environment.

Originally, the action therapy of depression has been developed for clinical treatment of severe depressive episodes based on these therapeutic steps: self-explanation, self-experience, communicative self-experience, and creative self-programming (49). Generally, action therapeutic strategies should also be applied in medical practice. Since a patient suffering from depression is „obsessed“ by hyperintentions often not apparent or even negated by the patient, the patient should be encouraged to do something feasible. Despite his/her perfectionistic personality to act perfectly in an important and valuable manner, the patient must learn to accept anything realizable at the beginning of the treatment. Based on a mild improvement of depressed mood communicative actions must be encouraged. If several communication actions can be realized, the patient experiences a kind of self-liberation from his/her permanent intending too much. Of course, these therapeutic strategies should be applied empathically dependent on the state and course of depression.

In clinical and general medical practice we have frequently to do with patients with hidden depression. The rationale of communication should enable decisions that the patient accepts and realizes immediately by concrete action steps. Such experiences can stabilize the patient’s psychobiological state in various diagnostic procedures and burdening therapeutic interventions.

Acknowledgement: I am very indebted to Birgitta Kofler-Westergren for preparing the final version of this paper.

8. References

1. Albert PR, Benkelfat C, Descarries L. The neurobiology of depression-revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. Phil Trans R Soc B. 2012; 367: 2378-2381.
2. Kraepelin E. Psychiatrie, III. Band. Klinische Psychiatrie, II. Teil, Barth JA, Leipzig, 1913.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington DC, 2013.
4. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 2010; 9: 155-161.
5. Verkhratsky A, Rodriguez JJ, Steardo L. Astrogliopathology: a central element of neuropsychiatric diseases? Neuroscientist 2014; 20: 576-588.
6. Dallerac G, Rouach N. Astrocytes as new targets to improve cognitive function. Prog Neurobiol 2016; http://dx.doi.org/10.1016/j.pneurobio.2016.01.003.
7. Mitterauer B. Imbalance of glial-neuronal interaction in synapses: a possible mechanism of the pathophysiology of bipolar disorder. Neuroscientist 2004; 10: 199-206.
8. Mitterauer B. Narziss und Echo. Ein psychobiologisches Modell der Depression. Springer, Vienna 2009.
9. Mitterauer BJ. Synaptic imbalances in endogenous psychoses. BioSystems 2010; 100: 113-121.
10. Mitterauer BJ. Possible role of glia in the pathophysiology of major depression: a hypothetical model based on glial-neuronal interactions. Journal of Life Medicine 2014; 2: 1-9. www.vkingpub.com/journal/jlm/ ©AmericanV-King Scientific Publishing.
11. Mitterauer BJ. Balancing and imbalancing effects of astrocytic receptors in tripartite synapses. Common pathophysiological model of mental disorders and epilepsy. Medical Hypotheses 2015, http://dx.doi.org/10.1016/jmehy/2015.01.025.
12. Mitterauer BJ. Hyperintentionality hypothesis of major depression. Disordered emotional and cognitive self-observation in tripartite synapses on the glial networks. Int J Brain Disord Treat 2016; 2: 015.
13. Araque A, Parpura V, Sanzgiri RP, et al. Tripartite synapses: glia the unacknowledged partner. Trends Neurosci 1999; 22: 208-215.
14. Haydon PG, Carmignoto G. Astrocyte control of synaptic transmission and vascular coupling. Physiol Rev 2006; 89: 1009-1031.
15. Mitterauer B. An interdisciplinary approach towards a theory of consciousness. BioSystems 1998; 45: 99-121.
16. Ransom BR, Giaume C. Gap junctions, hemichannels. In: Kettenmann H, Ransom BR, Neuroglia. Oxford University Press, New York, 2013, 292-305.
17. Oberheim NA, Takano T, Han X, et al. Uniquely hominid features of adult human astrocytes. J Neurosci 2009; 29: 3276-3287.
18. Jeanson T, Duchene A, Richard D, et al. Potentiation of amitriptyline anti-hyperalgesic-like action by astroglial connexin 43 inhibition in neuropathic rats. Scientific Reports 2016; 6: 38766. http://doi:10.1038/srep38766.
19. Yu W, Mechavar N, Krantic S, et al. Upregulation of astrocytic α7 nicotinic receptors in Alzheimer's disease brain – possibly relevant to amyloid

pathology. Molecular Neurodegeneration 2012; 7 (Suppl 1): 07, http://www.molecularneurodegeneration.com/content/7/S1/07.
20. Ishida Y, Nagai A, Kobayashi S, Kim SU. Upregulation of protease-activated receptor-1 in astrocytes in Parkinson's disease: astrocyte-mediated neuroprotection through levels of glutathione preoxidase. J Neuropathol Exp Neurol 2006; 65: 66-77.
21. Han C, Pae C. Pain and depression: a neurobiological perspective of their relationship. Psychiatry Investig 2015; 12: 1-8.
22. Brites D, Fernandes A. Neuroinflammation in depression: microglia activation, extracellular microvesicles and micro RNA dysregulation. Front Cell Neurosci 2015; 9, 476, http://doi:10.3389/fncel.2015.00476.
23. Quesseveur G, Portal B, Basic JA, et al. Attenuated levels of hippocampal connexin 43 and its phosphorylation correlate with antidepressant- and anxiolytic-like activation in mice. Front Cell Neurosci 2015; http://doi.103389/fncel.2015.00490.
24. Mitterauer B. Where and how could intentional programs be generated in the brain? A hypothetical model based on glial-neuronal interactions. BioSystems 2007; 88: 101-112.
25. Bagot RC, Meaney MJ. Epigenetics and the biological basis of gene x environment interactions. Journal of the American Academy of Children and Adolescent Psychiatry 2010; 49: 752-771.
26. Dalton VS, Kolshus E, McLoughlin DM. Epigenetics and depression: return of the repressed. J Affect Disord 2014; 155: 1-12.
27. Bibring E. The mechanism of depression. In: Greenacre P, Affective disorders. Int Univ Press, New York 1953, 13-28.
28. Flint J, Kendler KS. The genetics of major depression. J Neurol 2014, http://dx.doi.org/10.1016/j.neuron.2014.01.027.
29. Kendler KS, Aggen SH, Neale MC. Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. JAMA Psychiatry 2013; 70: 599-607.
30. Giaume C, Leybaert L, Naus CC, Saez JC. Connexin and pannexin hemichannels in brain glial cells: properties, pharmacology, and roles. Front Pharmacol 2013; 4, 88.
31. Kettenmann H, Steinhäuser C. Receptors for neurotransmitters and hormones. In: Kettenmann H, Ransom BR, Neuroglia. Oxford University Press 2005, 131-145.
32. Verkhratsky A, Korchoff F. NMDA receptors in glia. Neuroscientist 2007; 13: 28-37.
33. McCarthy KD, Salm AK. Pharmacologically-distinct subsets of astroglia can be identified by their calcium response to neuroligands. Neurosci 1991; 2/3: 325-333.
34. Mitterauer BJ. Qualitative information processing in tripartite synapses: a hypothetical model. Cogn Comp 2012; 4: 181-194.
35. Caplan JD, Gobinat S, Abdallah CG, Barry BR. A neurobiological hypothesis of treatment-resistant depression-mechanisms for selective serotonin reuptake inhibitors non-efficay. Front Behav Neurosci 2014; 8: 189.
36. Barone P. Treatment of depressive symptoms in Parkinson's disease. Eur J Neurol 2011; 18, Suppl. 1: 11-15.
37. Desan PH, Oren DA, Malison R, Price LH, et al. Genetic polymorphism at the CLOCK gene locus and major

depression. Am J Med Genet 2000; 96: 418-421.
38. Johansson C, Willeit M, Smedh C, Ekholm J, et al. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. Neuropsychopharmacology 2003; 28: 734-739.
39. Zordan MA, Sandrelli F. Circadian clock dysfunction and psychiatric disease: could fruit flies have a say? Front Neurol 2015; 6: 80.
40. Iberall AS, McCulloch WS. The organizing principle of complex living systems. Transactions of the ASME 1969; 6: 290-294.
41. McCulloch WS. Commentary. In: Thayer L, Communication: theory and research, Thomas Publisher, Springfield 1966; 13-21.
42. Mitterauer BJ. Model of the reticular formation of the brainstem based on glial-neuronal interactions. Cogn Comp 2015; 7: 64-73.
43. Rothuber H, Mitterauer BJ. Comprehensive behavioral analysis of patients with major depressive disorder. Med Sci Monit 2011; 17: CR1-CR7.
44. Czeh B, DiBenedetto B. Antidepressants act directly on astrocytes: evidences and functional consequences. Eur Neuropsychopharmacol 2013; 23: 171-185.
45. Solan JL, Lampe PD. Connexin 43 phosphorylation: structural changes and biological effects. Biochem J 2009; 419: 261-272.
46. Sun JD, Liu Y, Yan YH, Li J, Chen NH. Gap junction dysfunction in the prefrontal cortex induces depressive-like behaviors in rats. Neuropsychopharmacol 2012; 37: 1305-1320.
47. Mitterauer BJ. Ketamine may block NMDA receptors in astrocytes causing a rapid antidepressant effect. Front Syn Neurosci 2012; http://doi:10.3389/fsyn.2012.00008.
48. Driessen H, Hollon SD. Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. Psychiatr Clin North Am 2010; 33: 537-555.
49. Mitterauer B. Hyperintentional self-observation in major depressive disorder. Combined biological and behavioral treatment. Journal of Global Issues and Solutions 2016; http://www.bwwsociety.org/journal/current/1607/Hyperintentional%20self-observation.BWW.htm.