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Self-Frustration of Expectations in Major Depressive Disorder: The Syncytiopathy Hypothesis of Depression Revisited

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Abstract

This paper is a further elaboration of my model of the pathophysiology of major depressive disorder focusing on imbalances of glial-neuronal interactions in tripartite synapses and the glial network (syncytium). Basically, it is proposed that the connexin proteins building gap junctions in the glial syncytium are underexpressed or dysfunctional in major depression, called syncytiopathy. As a compensatory effect the astrocytic receptors in tripartite synapses are overexpressed. This leads to protracted synaptic information processing because of a relative lack of neurotransmitter substances for the occupancy of astrocytic receptors. Based on a new biophysical formal description of astrocytic receptors as expectation variables it can be shown that the protracted processing of sensory information frustrate the full comprehension of the expected event, since it cannot be grasped in time. Moreover, expectation frustration may stress the glial syncytium aggravating memory impairment. This cyclic process of dysbalanced synaptic information processing is characterized as self-frustration of expectations explanatory for the main cognitive dysfunctions in major depression as slowing down processing speed, deficits in attention and working memory. The main result of the study is that patients with major depression cannot fully acknowledge the existence of an intended event.

Keywords

Major Depression, Glial Syncytiopathy, Protracted Information Processing, Self-Frustration of Expectations, Cognitive Impairment

1. Introduction and Hypothesis

The basic symptoms of major depressive disorder are depressed mood and loss

of interest or pleasure [1]. However, the complex pathogenesis of this severe affective disorder is still not clear. Various factors such as biogenic amine deficiency, genetic, environmental, immunologic and endocrine factors, as well as neurogenesis have been considered as mechanisms that provide explanations for the pathophysiology of depression [2] [3].

In 2010 I proposed the "syncytiopathy hypothesis of depression" [4]. It has been hypothesized "that disorders in the astrocytic syncytium (network) may represent a main component of the pathophysiology of depression, called syncytiopathy. If the expression of connexin proteins (building gap junctions in the astrocytic syncytium) is downregulated, a compensatory upregulation of astrocytic receptors may occur leading to an overproduction of these. Such an excess of astrocytic receptors exerts an imbalance of synaptic neurotransmission, because of a relative lack of neurotransmitters for the occupancy of astrocytic receptors so that neurotransmission is protracted. This delay of information processing may be responsible for the main symptoms of depression [4].

Significantly, the biophysical interpretation of these imbalances of synaptic information processing [5] opens a new perspective of depressive behavior as follows: If the astrocytic receptors coding the expected sensations from the environment outnumber the number of neurotransmitters that code the environmental sensations, then the overexpression of astrocytic receptors connotes over expectation in the sense of unrealizable expectations. The unrealizability of expectations is caused by the prolonged processing of sensory information that frustrates the full comprehension of the expected event, since it cannot be grasped in time. Moreover, expectation frustration affects memory. This cyclic mechanism of imbalanced synaptic information processing may exert the self-frustration of expectation responsible for cognitive dysfunctions in major depressive disorder.

The study starts with a model of a balanced tripartite synapse and the astroglial syncytium. Then the operation loops between the memory-based model of reality and the expected external reality running in tripartite synapses and their networks are outlined. Next, from a formal description of the logic of balance between expectation variables and sensation values a system state of over-expectation is deduced. On this background the novel pathophysiological model of self-frustration of expectations in major depression is discussed.

2. Model of a Balanced Tripartite Synapse

A tripartite synapse is composed of the presynapse and the postsynapse as the neuronal components and the astrocyte with its network (syncytium) as the glial component [6]. **Figure 1** outlines a model of a balanced tripartite synapse [7] [8]. Neurotransmitters (NT) occupy astrocytic receptors (acr) and postsynaptic receptors (por) released from the presynapse (double-headed arrows designate activation and reuptake). The activation of acr by NT activates calcium ions (Ca^{2+}) that interact with the glial syncytium (depicted as lattice). Activated Ca^{2+}

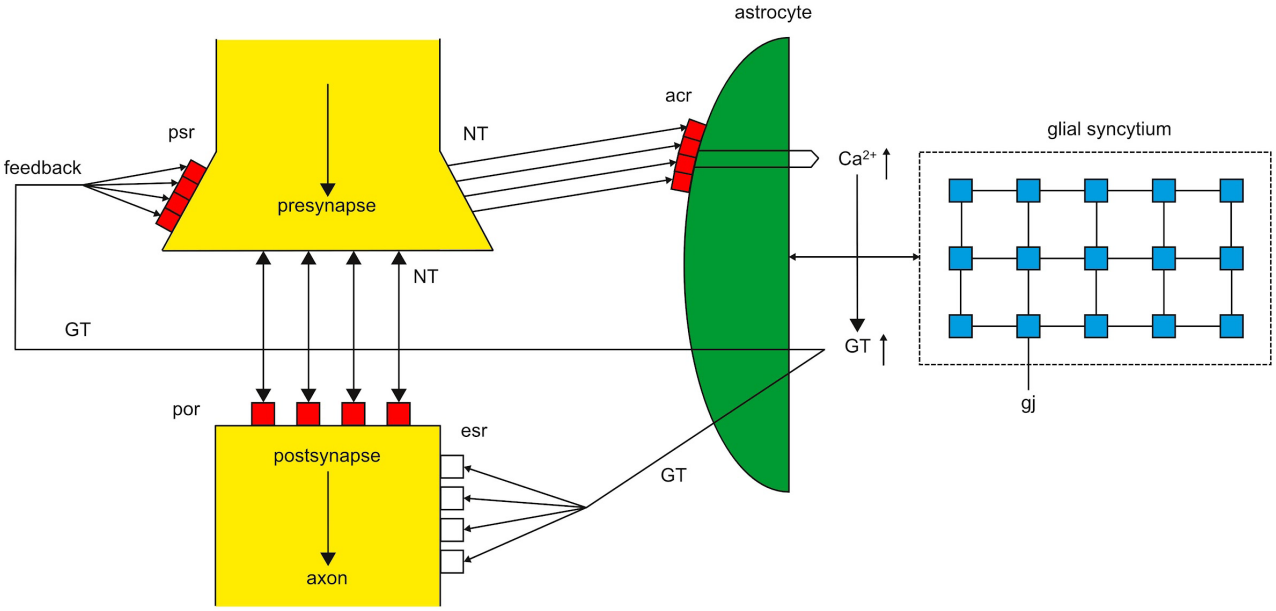

Figure 1. Schematic diagram of a balanced tripartite synapse and the glial syncytium. Neurotransmitter substances (NT) released from the presynapse activate postsynaptic receptors (por) and astrocytic receptors (acr) leading to an increased calcium production ($Ca^{2+}\uparrow$) in the astrocyte and the glial synctium (lattice). Ca^{2+} activate the production of gliotransmitters (GT) that occupy extrasynaptic receptors (esr) and feed back to the presynaptic receptors (psr).

causes the production of gliotransmitters (GT) that occupy extrasynaptic receptors (esr) and in parallel exert a feedback to presynaptic receptors (psr). The balance of receptors and transmitter substances enables a normal synaptic information processing.

3. Outline of an Astroglial Syncytium

The biological structure suggested focuses on gap junctions between astrocytes, the main glial cell type together with oligodendrocytes and microglia. Gap junctions provide a structural link through which single cells are coupled to form a functional network, called syncytium, with communication dynamics that cannot be effected by individual cells. Gap junctions of an astroglial syncytium are composed of connexin proteins forming gap junction channels by various hemichannels [9]. While astrocytes are interconnected with their neighbors via gap junctions, the interactions of astrocytes with neurons occur mainly in tripartite synapses [6].

Figure 2 shows a diagram of an astroglial syncytium. Six astrocytes (Ac_1, …, Ac_6) are completely interconnected via fifteen gap junctions (gj). Each astrocyte contacts neuronal synapses (not shown) forming tripartite synapses. The simple diagram refers to the basic components and their interconnections in the astroglial syncytium. Frequently activated gap junctions (downward arrows) generate a plaque. An example of a plaque formation is given between the Ac_3-Ac_4-Ac_5-Ac_3-loop. This loop becomes embodied in a gap junction plaque that consists of a hierarchical loop structure (cycles) [10].

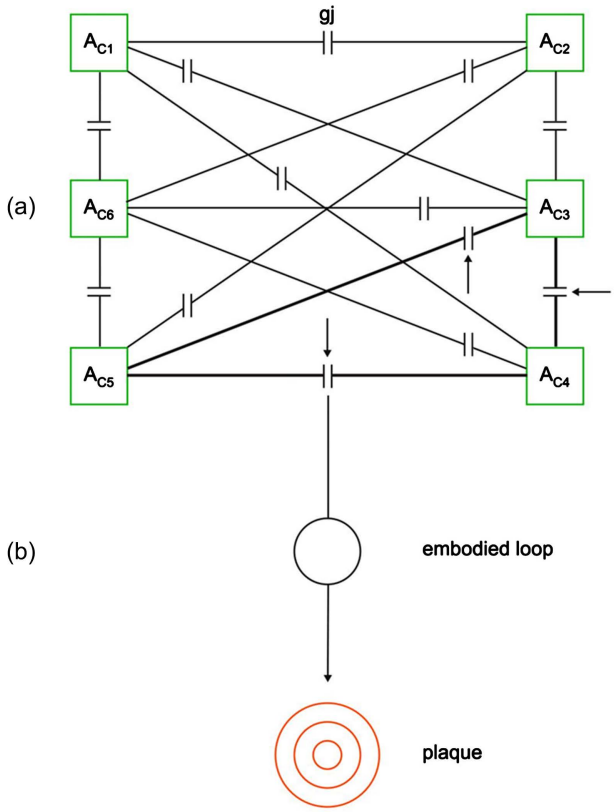

Figure 2. Outline of an astroglial syncytium (see text). (a) astroglial syncytium; (b) plaque formation.

4. Memory and the Realization of Expectations in Glial-Neuronal Interactions

Based on my model of glial-neuronal interactions [7] [8] [10] [11] the role of gap junctions in memory formation can be interpreted in the following: gap junctions register already generated cyclic pathways in the astroglial syncytium. Depending on feedback from the neuronal network to the glial syncytium based on feasible expectations with regard to environmental information, gap junctions could strengthen their structure embodying a memory mechanism. In this case we have a double memory function of gap junctions: a local embodiment of memories and a pathway memory determined by gap junctions [10]. This double memory function of gap junction plaques may work as expectations expressed in the receptor pattern of astrocytes experienced in synaptic neuroglial interactions and realized in the neuronal networks via sensory-motor activation in the environment [5] [12] [13].

If the amount of neurotransmitters exactly corresponds to the amount of expressed astrocytic receptors, a balance between the glial and neuronal network is generated and gliotransmitters released occupy presynaptic receptors that exert a feedback mechanism. The comparison between expected internal and measured external signals provides updated feedback to the glial syncytium that modifies the information flow through the neuronal network [5].

5. Logic of Balance between Expectation Variables and Sensation Values

The formalism of the logic of balance was introduced by the German-American philosopher Gotthard Guenther [14]. The proposition is that the operations of a living system are balanced if the number of variables (n) and the number of values (m) is equal. If the values outnumber the variables (m > n), then the system is overbalanced. Inversely, if the variables outnumber the values (n > m), then the system is underbalanced.

Figure 3 shows the formalism of balance between glial receptors (acr) as expectation variables (n) and neurotransmitters (NT) representing sensation values (m). The balanced system states are designated as pairs of equal numbers in squares (diagonal). The overbalanced states are listed below the diagonal, and the underbalanced states above. Here the expectation variables outnumber the sensation values representing a system state of over-expectation (embodied by overexpressed astrocytic receptors).

6. Downregulation of Expression of Astroglial Connexins Causes Memory Impairment in Depression

Figure 4 depicts a diagram of an incomplete astroglial syncytium that may cause memory impairment in depression. A complete astroglial syncytium is outlined (a). If the expression of connexins is downregulated (downward arrows), then the structure of the network is incomplete, since the number of gap junctions is reduced (dotted squares). Such a "leaky" network may be responsible for memory impairment in depression (b).

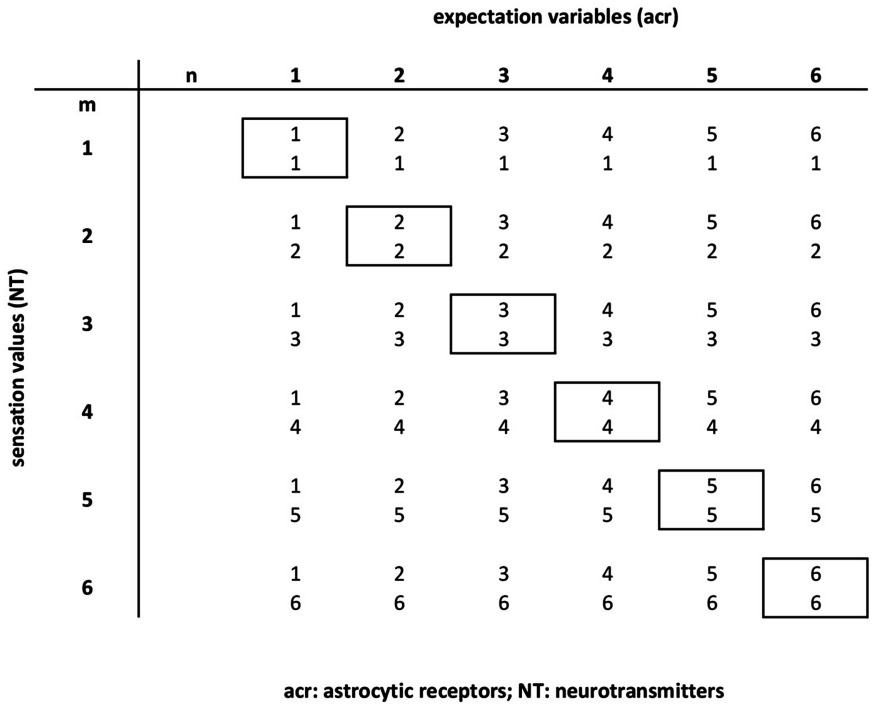

Figure 3. Logic of balance between expectation variables and sensation values (see text).

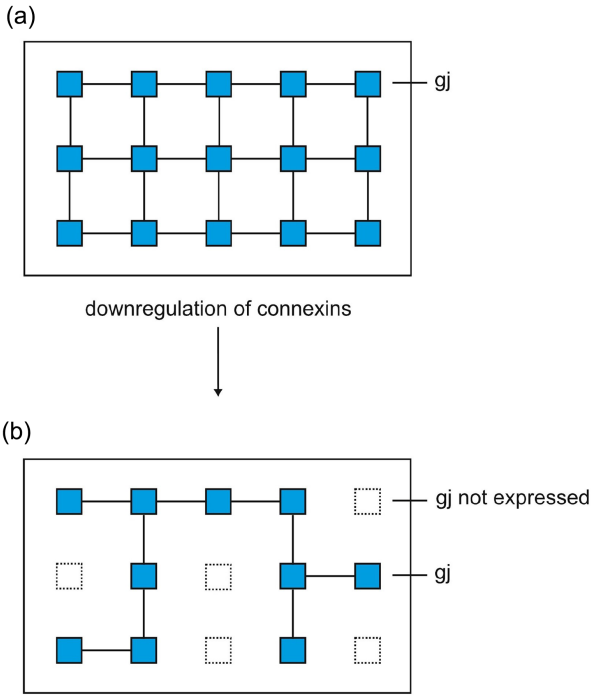

Figure 4. Schematic diagram of an incomplete astrocytic syncytium responsible for memory impairment in depression. The complete structure of the gap junction (gj) network (syncytium) is outlined in (a). In the case of downregulation of connexin expression, the structure of the syncytium becomes incomplete, since the expression of the connexins or the gap junctions is reduced (dotted squares). Such a "leaky" network embodies a syncytiopathy responsible for memory impairment in depression (b) [4], Incomplete "leaky" syncytium.

Of note, this was the first hypothesis that the downregulation of connexins in the astroglial syncytium is responsible for the pathophysiology, especially for memory impairment of major depressive disorder [4] [15]. Since then this hypothesis has been supported by various experimental investigations. Nagy and colleagues [16] found a widespread astrocytic connexin gene repression in depressed suicides, possibly mediated through epigenetic mechanisms. Similarly, aberrant expression of astrocytic connexins Cx30 and Cx43 in the medial prefrontal cortex and hippocampus significantly affects brain region-specific neuronal activity responsible for depressive-like behavior in mice [17]. Moreover, deletion of glial connexins and loss of gap junction communication result in a loss of short-term spatial memory [18]. Basically, disrupting astroglial coupling impairs spatial learning and memory [19].

7. Downregulation of Glial Connexins May Cause an Upregulation of Astrocytic Receptors Responsible for the Pathophysiology of Depression

Figure 5 depicts the basic effects on synaptic information transmission if the expression of connexins in the astroglial syncytium is downregulated, and compensated by the upregulation of astrocytic receptors (acr) as follows: overexpressed

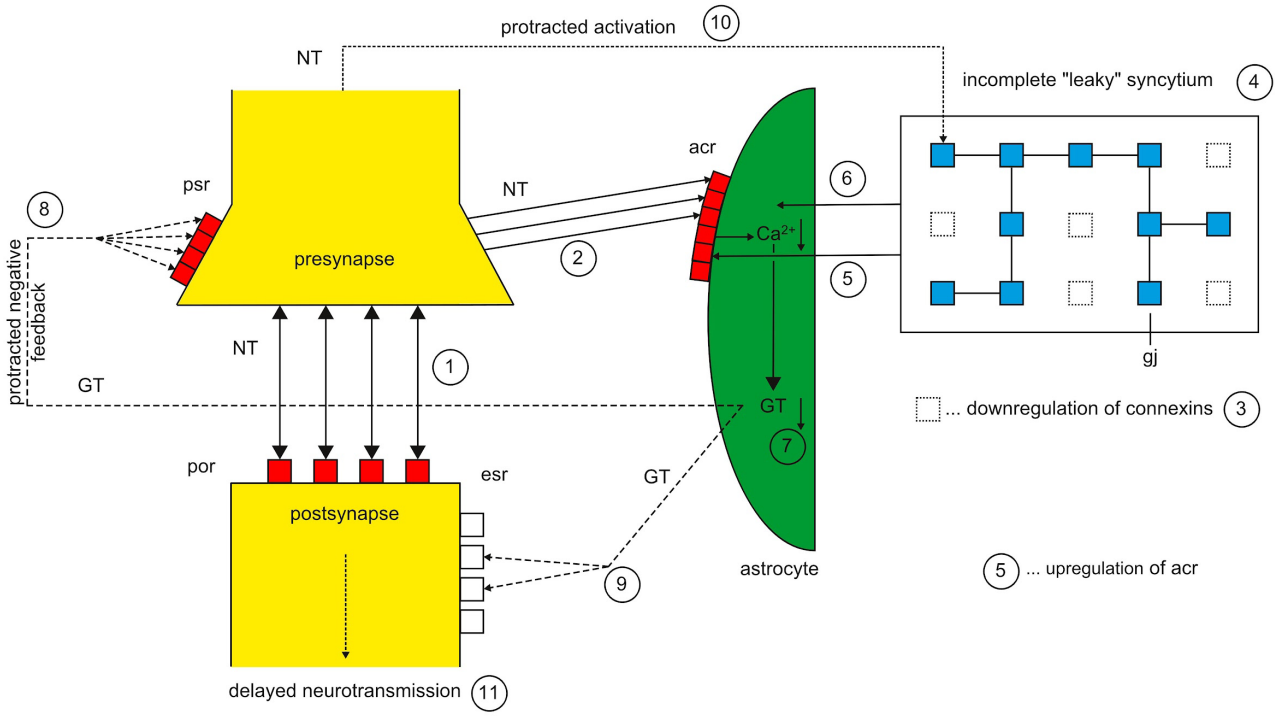

Figure 5. Downregulation of glial connexins may cause an upregulation of astrocytic receptors responsible for the pathophysiology of depression. Neurotransmitters (NT) are released from the presynapse occupying both the postsynaptic receptors (por) (1) and the astrocytic receptors (acr) (2). In parallel, the downregulation of connexins (3) forms an incomplete "leaky" astroglial syncytium (4) that is compensated by the upregulation of the expression of acr (5). This leads to a relative lack of NT so that synaptic information transmission is imbalanced. Since the astroglial syncytium is incomplete, the activation of calcium (Ca^{2+}) waves is diminished (6) causing an underproduction of gliotransmitters (GT) (7). In addition, the overproduction of acr may delay the production of GT (dotted line), and therefore the negative feedback mechanism on the presynaptic receptors (psr) is protracted (8). The same holds for the depolarization of the postsynaptic neuron (9). Because of the relative lack of NT, the activation of gap junctions (gj) may also be protracted (10). In such a tripartite synapse neurotransmission is significantly delayed (11).

astrocytic receptors cannot be activated by neurotransmitters (NT) in real time. This leads to diminished calcium Ca^{2+} concentration and production of gliotransmitters (GT) in the astrocyte causing protracted negative feedback on presynaptic receptors (psr) and extrasynaptic receptors (esr), so that information processing is delayed. Similarly, the synaptic activation of the astroglial syncytium is protracted and the propagation of calcium waves (Ca^{2+}) is slowed down (see **Figure 5**). This could explain symptoms of retardation of thinking, concentration, and motor behavior [4].

Basically, most of the typical receptors for neurotransmitters have been identified on the astrocytic membrane. Individual astroglial cells express as many as five different receptor systems linked to Ca^{2+} mobilization [20]. Dependant on the pattern of astrocytic receptors, synaptic information processing may be qualitatively modified [7].

There is some evidence that receptors on astrocytes are upregulated. In animal models of chronic stress adenosine A_{2A} receptors are upregulated. This A_{2A} receptor overexpression may explain the depressive signs found in aging, chronic stress, and Alzheimer's disease [21]. Similarly, the expression of A_{2A} receptors

was upregulated in the cortex of rats in which early febrile seizures induced depressive-like behavior [22]. Importantly, inhibition of adenosine A_{2A} receptors by pharmacological and gene knockout methods exerts an anti-depressive-like effect [23].

8. Self-Frustration of Expectations in Major Depression

Figure 6 shows the elementary cycle of self-frustration in major depression. As discussed above, in the pathophysiological model proposed memory impairment is caused by the downregulation of the expression of connexins or connexin deficits. It is further suggested that the downregulation of connexins may be compensated by the upregulation of astroglial receptors. Since astrocytic receptors coding the expected sensations from the environment outnumber the amount of neurotransmitters that code the environmental sensations, the overexpression of astrocytic receptors connotes overexpectations. This leads to a protracted processing of sensory information that frustrates the full comprehension of the expected event, since it cannot be grasped in time. In addition, expectation frustration stresses the syncytium aggravating memory impairment. Here we deal with a cyclic pathophysiological mechanism of major depression that causes self-frustration of expectations. Significantly this mechanism is explanatory for cognitive dysfunctions in depression, as slowing down processing speed, deficits in attentions and working memory [24].

In a psychological perspective it is suggested that patients with major depression suffer from dysfunctional expectations which are maintained despite experiences contrary to the expectations. Two mechanisms may be responsible for the maintenance of expectations: The experience in the expectation-violating situation may be considered an exception or the credibility of the information is called into question. Basically, the self-concept associated with future expectations may also play a key role in expectation maintenance [25]. Here we speak of the narcissistic personality structure of persons inclined to depression [26].

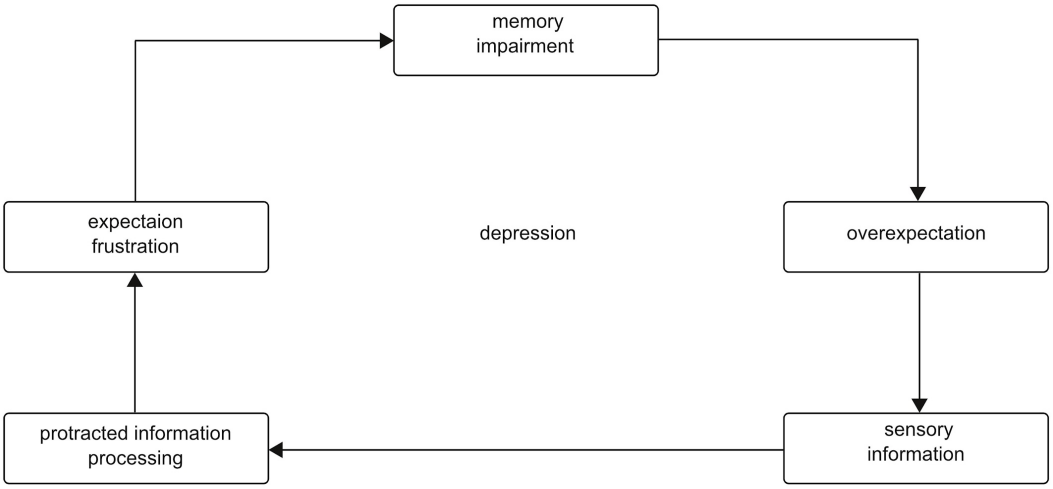

Figure 6. Elementary cycle of self-frustration of expectations in major depression

Decisively, the model of self-frustration of expectations in major depression is based on imbalances in tripartite synapses and the glial networks along with the pathophysiological mechanism of connexin underexpression with a compensatory astrocytic receptors overexpression [4]. Fundamentally, the interpretation of astrocytic receptors as expectation variables is based on the quantum physical model of the Cognitive Action Theory of W. Baer [27]. The original syncytiopathy hypothesis of major depression is meanwhile experimentally supported what the underexpression or deficits of connexins concerns, but the overexpression of astrocytic receptors awaits experimental support, especially in humans.

9. Concluding Remarks

My work on depression research focuses on synaptic imbalances in tripartite synapses and the glial network (syncytium). The present study represents a further elaboration of the syncytiopathy hypothesis of depression [4]. Based on a new biophysical interpretation of astrocytic receptors as expectation variables it can be shown that the prolonged sensory information processing frustrates the full comprehension of sensory events, since they cannot be grasped in real time. Crucially, this mechanism of self-frustration of expectations is explanatory for cognitive deficits in major depression as slowing down processing speed, deficits in attentions and working memory. Admittedly, in depression astrocytes undergo morphological alterations (astrocyte atrophy) in various brain regions [28] [29]. However, experimental findings depend on the stage or course of illness [30]. The main message of the present study is that patients with major depression are unable to fully acknowledge the existence of an intended event.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders. 5th Edition, APA, Washington DC. https://doi.org/10.1176/appi.books.9780890425596

[2] Jesulola, E., Micalos, P. and Baguley, I.J. (2018) Understanding the Pathophysiology of Depression: From Monoamines to the Neurogenesis Hypothesis Model-Are We There Yet? *Behavioral Brain Research*, **341**, 79-90. https://doi.org/10.1016/j.bbr.2017.12.025

[3] Kamran, M., Bibi, F., Rehman, A. and Morris, D.W. (2022) Major Depressive Disorder: Existing Hypotheses about Pathophysiological Mechanisms and New Genetic

Finding. *Genes*, **13**, Article No. 646. https://doi.org/10.3390/genes13040646

[4] Mitterauer, B.J. (2010) The Syncytiopathy Hypothesis of Depression: Downregulation of Glial Connexins May Protract Synaptic Information Processing and Cause Memory Impairment. *Medical Hypotheses*, **74**, 497-502. https://doi.org/10.1016/j.mehy.2009.09.058

[5] Mitterauer, B. and Baer, W. (2020) Disorders of Human Consciousness in the Tri-Partite Synapses. *Medical Hypotheses*, **136**, Article ID: 109523. https://doi.org/10.1016/j.mehy.2019.109523

[6] Araque, A., Parpura, V., Sanzgiri, R.P. and Haydon, P.G. (1999) Tripartite Synapses: Glia, the Unacknowledged Partner. *Trends in Neuroscience*, **22**, 208-215. https://doi.org/10.1016/S0166-2236(98)01349-6

[7] Mitterauer, B.J. (2012) Qualitative Information Processing in Tripartite Synapses: A Hypothetical Model. *Cognitive Computation*, **4**, 181-194. https://doi.org/10.1007/s12559-011-9115-2

[8] Mitterauer, B.J. (2013) The Proemial Synapse: Consciousness-Generating Glial-Neuronal Units. In: Pereira, A. and Lehmann, D., Eds., *The Unity of Mind, Brain and World*, Cambridge University Press, Cambridge, 233-264. https://doi.org/10.1017/CBO9781139207065.009

[9] Ransom, B.R. and Giaume, C. (2013) Gap Junctions, Hemichannels. In: Ketterman, H. and Ransom, B.R., Eds., *Neuroglia*, Oxford University Press, New York, 292-305. https://doi.org/10.1093/med/9780199794591.003.0024

[10] Mitterauer, B.J. (2015) Tripartite Synapses and the Glial Network. *Quantum Biosystems*, **6**, 1-9.

[11] Mitterauer, B.J. (2007) Where and How Could Intentional Programs Be Generated in the Brain? A Hypothetical Model Based on Glial-Neuronal Interactions. *BioSystems*, **88**, 101-112. https://doi.org/10.1016/j.biosystems.2006.04.003

[12] Mitterauer, B. (2001) Clocked Perception System. *Journal of Intelligent Systems*, **11**, 269-297. https://doi.org/10.1515/JISYS.2001.11.4.269

[13] Mitterauer, B. (2004) Computer System, Particularly for Simulation of Human Perception via Sense Organs. US-Patent Nr. 2004; 6,697,789B2.

[14] Guenther, G. (1963) Das Bewußtsein der Maschinen. Agis Verlag, Baden-Baden.

[15] Xia, C., Wang, Z., Yamakuni, T. and Chen, N. (2018) A Novel Mechanism of Depression: Role for Connexins. *European Neuropharmacology*, **28**, 483-498. https://doi.org/10.1016/j.euroneuro.2018.01.009

[16] Nagy, C., Torres-Platas, S., Mechawar, N. and Turecki, G. (2017) Repression of Astrocytic Connexins in Cortical and Subcortical Brain Regions and Prefrontal Enrichment of H3K9me3 in Depression and Suicide. *International Journal of Neuropsychopharmacology*, **20**, 50-57. https://doi.org/10.1093/ijnp/pyw071

[17] Hwang, D., Li, C., Zhang, W., Quin, J., *et al.* (2019) Dysfunction of Astrocytic Connexin 30 and 43 in the Medial Prefrontal Cortex and Hippocampus Mediates Depressive-Like Behaviors. *Behavioral Brain Research*, **372**, Article ID: 111950. https://doi.org/10.1016/j.bbr.2019.111950

[18] He, J., Li, X., Yang, L. and Zhao, X. (2020) Astroglial Connexins and Cognition: Memory Formation or Deterioration? *Bioscience Reports*, **40**, BSR20193510. https://doi.org/10.1042/BSR20193510

[19] Hösli, L., Binini, N., Ferrari, K., Thieren, L., *et al.* (2022) Decoupling Astrocytes in Adult Mice Impairs Synaptic Plasticity and Spatial Learning. *Cell Reports*, **38**, Article ID: 110484. https://doi.org/10.1016/j.celrep.2022.110484

[20] Kettermann, H. and Zorec, R. (2013) Release of Gliotransmitters and Transmitter Receptors in Astrocytes. In: Kettenmann, H. and Ransom, B.R., Eds. *Neuroglia*, Oxford University Press, New York, 197-211. https://doi.org/10.1093/med/9780199794591.003.0017

[21] Coelho, J., Alves, P., Canas, P., Valdas, J., *et al.* (2014) Overexpression of Adenosine A_{2A} Receptors in Rats: Effects on Depression, Locomotion and Anxiety. *Frontiers in Psychiatry*, **5**, Article No. 67. https://doi.org/10.3389/fpsyt.2014.00067

[22] Crespo, M., Leon-Navarro, D. and Martin, M. (2018) Early-Life Hyperthermic Seizures Upregulate Adenosine A_{2A} Receptors in the Cortex and Promote Depressive-Like Behavior in Adult Rats. *Epilepsy and Behavior*, **86**, 173-178. https://doi.org/10.1016/j.yebeh.2018.06.048

[23] Zhao, Y.F., Verkhratsky, A. and Illes, P. (2022) Astrocytes and Major Depression: The Purinergic Avenue. *Neuropharmacology*, **220**, Article ID: 109252. https://doi.org/10.1016/j.neuropharm.2022.109252

[24] Lam, R.W., Kennedy, S.H., McIntyre, R.S. and Khulbar, A. (2014) Cognitive Dysfunction in Major Depressive Disorder: Effect on Psychosocial Functioning and Implications for Treatment. *Canadian Journal of Psychiatry*, **59**, 649-654. https://doi.org/10.1177/070674371405901206

[25] Kube, T., Rief, W. and Glombiewski, J.A. (2017) On the Maintenance of Expectations in Major Depression—Investigating a Neglected Phenomenon. *Frontiers in Psychiatry*, **8**, Article No. 9. https://doi.org/10.3389/fpsyg.2017.00009

[26] Mitterauer, B.J. (2009) Narziss und Echo. Ein psychobiologisches Modell der Depression. Springer, New York. https://doi.org/10.1007/978-3-211-99140-4

[27] Baer, W. (2020) Conscious Action Theory. An Introduction to the Event-Oriented World View. Routledge, London. https://doi.org/10.4324/9781315618883

[28] Machado-Santos, A.R., Loureiro-Campos, E., Patricio, P., Aranjo, B., *et al.* (2022) Beyond New Neurons in the Adult Hippocampus: Imipramine Acts as a Pro-Astrogliogenic Factor and Rescues Cognitive Impairments Induced by Stress Exposure. *Cells*, **11**, Article No. 390. https://doi.org/10.3390/cells11030390

[29] Verkhratsky, A., Butt, A., Li, B., Illes, P., *et al.* (2023) Astrocytes in Human Central Nervous System Diseases: A Frontier for New Therapies. *Signal Transduction and Targeted Therapy*, **8**, Article No. 396. https://doi.org/10.1038/s41392-023-01628-9

[30] Hasler, G. (2010) Pathophysiology of Depression: Do We Have Any Solid Evidence of Interest for Clinicians? *World Psychiatry*, **9**, 155-161. https://doi.org/10.1002/j.2051-5545.2010.tb00298.x