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Schizophrenia seen in the perspective of ICD and ICF.

Most important points:

1. The most important patho-physiological processes - as far as known- at the level of neurons and networks in schizophrenia are summarised.
2. The conclusion is made, that a well-functioning NMDA-glutamate-system is essential to the functioning of the dopamine- and serotonin systems.
3. The symptoms of schizophrenia may explained from the poorly functioning dopamine-, serotonin- and NMDA-glutamate systems as disturbances of functions, abilities and activities like defined in ICD and ICF.
4. The poorly functioning of the NMDA-glutamate system seems to be the cause of the poorly functioning of all other processes; this on its turn seems mainly to be caused by an absent or low production of the NR1 protein, which is an essential component of the NMDA-glutamate receptor.
5. A hypothesis about this absent or reduced production is formulated: a virus could very well interfere with the production of this protein. The Herpes Simplex Virus is a good candidate here for. This hypothesis is elaborated on in the next section (5b).

Key-words: Schizophrenia, dopamine, serotonin, glutamate, dysbindin, neuregulin, mRNA, Herpes Simplex.

Introduction.

Schizophrenia is a disorder which has at least two of the positive symptoms: delusions, hallucinations, incoherent speech, serious chaotic or catatonic behaviour, and the presence of one or more negative symptoms: apathy, lack of speech, passivity, or reduced affect. Investigations to find the pathophysiology of schizophrenia by investigators who target on a biological cause, are aimed at the misfunctioning of neurons, which cooperate in networks. Aim of this paper is to look at the symptoms of schizophrenia in terms of the ICD and ICF[1 2], (see as well article 3 on this website) These symptoms we try to link to pathophysiological processes. Based thereon we look for possible causes of schizophrenia. In the next page (5b) we elaborate more on the basic processes. The study in this page deals with the processes in neurons and networks thereof. Some factors which are mentioned as cause of schizophrenia, but which have no direct relationship with biological functions in terms of ICD and ICF, like heredity, virus infections etc are mentioned, but are no part of the central literature study, which focusses on the processes in neuron and networks.

Method.

This article is primarily a study of literature, based on recent publications with the words schizophrenia, combined with de name of a neurotransmitter or other word in relation with the functioning of neurons and neuronal networks, like discussed in the papers 2a and 2b. Only review papers found with Google and PubMed are cited, unless there was a ground to elaborate more on a specific topic[a]. All together gives it a review of what has been written

[a] Footnotes are in this paper indicated with a letter, and literature when quoted with a cipher.

during the recent years about the pathophysiology of schizophrenia, at the neurobiological level. The findings from literature are presented and discussed; more detailed results from literature are presented in appendices. The results are discussed and translated in terms of the ICF. Finally it is tried to establish a hypothesis about the direction in which the neuronal pathophysiology in schizophrenia should be sought. In the next paper (5b) there will be elaborated more on this base.

Results:

In literature the pathophysiology of schizophrenia is usually connected with abnormalities in neurotransmitters and the receptors which belong to these. We will follow this approach, and discuss dopamine, serotonin and glutamate with the biological processes which are connected to these. As there are connections between these there might be some overlap. Thereafter the possible causes of schizophrenia are discussed, and a hypothesis is formulated about this.

Dopamine. Dopamine is an important neurotransmitter in the brain of mammals and man[3]. This substance is considered to be an element of schizophrenia as from the 60th of the past century. Dopamine is a monoamine neurotransmitter[b]. It is produced in the dopaminergic neurons in the ventral tegmental area of the substantia nigra, in the midbrain and in the arcuate nucleus of the hypothalamus, and in glia tissue[4]. The substance is produced from phenylalanine, a substance which is a component of normal heathy food. This phenylalanine is transformed into tyrosine, which next is transformed in L-DOPA. This latter substance is transformed by an enzyme “aromatic L-amino acid decarboxylase (AADC)”[c] into dopamine. Neurons which utilise dopamine are especially found in the hypothalamus, olphactorical nerve, substantia nigra, midbrain and ventral tegmental are, the grey matter around the central channel and in the retina. Dopamine plays a central role in ‘reward’[d], in the inhibition of the production of prolactin, further in sleep, mood, attention, behaviour, control of nausea , vomiting and in conduction of pain. Further it is involved in the control of motion, emotion and cognition[5].

In schizophrenia there is a high activity of dopamine in the central nervous system[6], especially in the striatum, but in other parts like the frontal lobe there is a diminished activity[7] [8]. It became clear in the meantime that in schizophrenia there is not just an isolated hyperactivity of dopamine, but that as well aberrations in other neurotransmitters (glutamate, GABA, serotonin, acetylcholine and endocannaboids) play a role, and there is an inflammatory reaction[9] [10]. Novak[11] adds that CaMKII, a substance which release via kinases calcium from the endoplasmatic reticulum regulates both the dopamine and the serotonin system, and this substance is increases present inpatients with schizophrenia. Other diseases in which dopamine is involved are addiction or Parkinson’s disease, but these are not further discussed here.

Presently there are 5 dopamine receptors known, which we know as D_1, D_2, D_3, D_4 and D_5. It proves to be that there are two main groups of dopamine receptors: at first a group (D_1 and D_5) called the D_1-like group, which stimulates adeylcyclase (AC), and a group which does not do so (D_2, D_3 and D_4), as well called the D_2-like group, but these latter group does something

[b] See as well the paragraph dealing with this in paper 2a about the neuron.

[c] We will see this enzyme again when we deal with serotonin.

[d] The word reward is often used to indicate a pleasant feeling which one may have e.g. after a happening or after the administration of a substance.

in the formation of cyclic aminomonophosphatase (cAMP). The genes for the D_1 and D_5 receptors share a structure with a great number of other genes of receptors which work via a G-protein; the genes for the other dopamine receptors have this not. All work via G-proteins. D_1 receptors are mainly found in the frontal lobe and D_2 receptors in the striatum[12]. The effect of triggering of the diverse receptors is summarised in table 1 below:

Table 1. Summary of the effects of triggering of the diverse receptors by dopamine + means a stimulating effect and – means a inhibitory effect. The figure between hooks indicates the clarification in the text under the table.

	D_1	D_2	D_3	D_4	D_5
Adenylcyclase; stimulation hereof results in the release of energy from ATP and ADP, inhibition in the contrary and to tiredness. (1)	+	-	-	-	+
Release of Ca^{++} from the endoplasmic reticule.(2)	+	+	-	-	+
Effect on Ca^{++} channel (+ is opening - is closing) (2)	-	+	+	+	-
Opening K^+ channels (3)	sometimes	+	+	+	sometimes
Release of Arachidonic Acid (AA) (4)	-	+	+	+	-
ATP-ase (Na^+ /K^+ balance and therefore sensitivity to depolarisation) (3)	-	+	+	+	-
Growth of spines on cells (plasticity)		+	+	+	

(1) There is no reason known why dopamine in the synaptic cleft would chose a specific type of dopamine receptor, this means that the ratio of the number of available D1/D5 receptors towards the number of D2/D3/D4 receptors determines the ultimate effect of triggering with dopamine: energy available to maintain and repair the potential difference across the cell membrane , ant thus the transmission of signals of not.

(2) A high level of CA^{++} intracellularly increases the irritability of the cell.

(3) The flow of K^+ out of the cell increases the difference in the potential between inside and outside the cell. This on its turn makes it more difficult for the neuron to have dopamine released from the cell. Triggering of the $D_{2/3/4}$ receptors has therefore a stabilising effect.

(4) AA, an essential fatty acid, ha two physiological roles in the body. It has a role in the immune system, and there is an interaction with the transcription of chemical signals to and from the karyon of the cell. Which is the meaning thereof for the transmission of signals is not yet clear. It is obvious that a shortage thereof will disturb the transmission of signals.

Anti-psychotics have in common that these block the D_2 receptors[13] [14]. Recent investigations showed that dopamine is involved as well in the regulation of many cellular responses, e.g. the fine tuning of the expression of behaviour and other functions. This has to do with alternating coupling of G-proteins or other mechanisms aside of coupling to G-proteins, in which ion channels, or proteins like β-arrestine are involved. There prove also to be substances which appear like dopamine, and therefore mimic the effects of dopamine[15]. Dopamine is also important in the homeostasis of connections within the central nervous system, and thus to the balance between some neuronal networks[16]. The strength with which certain genes may express themselves in influenced by dopamine. The active-being of the dopamine receptors is coupled back to the responsible gen, which becomes less active when a receptor gets active. The activity hereof is stimulated by creatine, more creatine means that the gen can perform better [17]. The presence-or-not of dopamine activity is also important for the production of other neurotransmitters. Dopamine and serotonin influence each other [18]. The distribution of dopamine receptors in the cerebrum is not equally[19] and according one of the hypotheses would this explain the symptoms of schizophrenia. In the article 2a is has been made clear that dopamine is involved in many processes in the neuron. This passage

from article 2a is repeated in the block below. Finally we remark, that dopamine has a central role in addiction. This has been documented thoroughly by Korpi et Al[20].

Dopamin receptors are found all over the nervous system, but D_1-like receptors are more concentrated in the prefrontal cortex and the D_2-like receptors in the striatum. These receptors are in the nervous system involved in voluntary movement, reward, regulation of sleep, feeding, affection, attention, cognitive functions, smell , vision, regulation of hormones, regulation of the sympatic system and of erection. In the peripheral nerve system these receptors influence the immune apparatus, and the function of heart and blood vessels, kidneys and bowels. The signals may be via G-proteins of via primary stimulation of ion channels. The effects of dopamine are described in detail in literature; the most important are summarised in the table 2 in the article 2a together with that of other receptors. Finally we should know that dopamine receptors influence both glutamate and GABA receptors and reversely the receptors for these substances that of dopamine receptors.

Dopamine is very much present in the dACC network, which is involved in decision making and in filtering relevant issues[21]. The dACC network is build up from connections between the dorsal anterior cortex of the cingula and a number of subcortical structures like the Nucleus Accumbens. Stahl[22] described in 2018 that in networks in which there is a liason between the dorsal striatum, the ventral striatum, the substantia nigra and the ventral tegmental area via dopaminergic connections, psychotic symptoms like hallucinations and delusions may occur. But he connected this finding to disturbances in the networks of the glutamate and the serotonin systems, which occur simultaneously.

In summary we find in schizophrenia an increased activity of dopamine in the striatum and a decreased in the frontal lobe, whilst in the striatum we find mainly D_2 receptors and in the frontal lobe D_1 receptors. Whether the increased activity od dopamine is cause or result of the condition is not yet sure at all. The negative symptoms and the disturbances in cognition have a relation to the frontal lobe, therefore to the fronto-parietal network; the positive symptoms mainly to the striatum and the networks there. There is a relation between some factors which are involved in the neurotransmission. From a great number of anti-psychotics which are being used the way these work is due to interaction with the way dopamine works, especially by blocking receptors or hampering reutilisation. Certain of the positive symptoms of schizophrenia may be explained by an increased irritability of the neuron due to an increased activity of dopamine. However the sometimes opposite effects of triggering either the $D_{1/5}$ group or the $D_{2/3/4}$ group, combine with the absence of a relation between the diverse subgroups of receptors and the prevalence of disorders like schizophrenia, make it difficult to understand the symptoms really. It seems likely that the fatigue which we see after a psychotic attack has to do with over-excitation of the $D_{2/3/4}$ receptors. Psychotic fear could be due to over-excitation of the neuron, resulting in increased activity of (nor)adrenalin.

Serotonin. 14 different receptors for serotonin have been identified; 13 of these work through G-protein mediated processes, the other one through ligand induced ion channels [23]. The different receptors are usually labelled with a number and a letter; therefore there is 5HT1A,5HT1B, 5HT2A, et cetera. The serotonin receptor consists out of a protein which lurches several times through the membrane of the cell. At the protein there are several places where ligands may bind. These cause somewhere else on the protein a reaction, either by activation of an enzymatic process, or by dissection of complexes of amino acids, or by the production or release of G-proteins. These processes have different effects: triggering of the receptor firstly has effects on the Ca^{++} level intracellularly [24]: the sensitivity

for depolarisation is increased by it. The G-proteins and ligands cause in the second place the ion channels to open, and thus depolarisation. And thirdly other process inside the neuron are influenced via enzyme-cascades, in which respect mostly an activation of kinase is mentioned. Triggering of a receptor may thus cause activation of AC, and some other enzymatic processes in the cell. Finally the receptor has an important place in the functioning of micro-tubules inside the neuron, so there is a relation with intracellular transmission of signals.
The serotonin receptors are especially present in the cortical pyramid areas; these influence the release of glutamate here, and in the ventral tegmental areas where these influence the release of dopamine. However these are also present in the cells in the brainstem, from where these neurons connect with really every place in the brain[25].
The 5HT1A receptor is important in the release of serotonin itself and in mood and emotional regulation. Triggering this receptor decreases the negative symptoms of schizophrenia, like apathy and emotional flatness. The 5HT2a receptor is one of the most studied on with respect to schizophrenia. This receptor is abundantly present in the prefrontal cortex, and there it modulates the activity of dopamine and glutamate. Over-triggering of this receptor results in hallucinations, delusions and cognitive disturbances[26] . The two receptors have in the respect of stress an opposite effect. Triggering of the 5HT1A receptor makes that the person can handle more stress; triggering of the 5HT2A receptor induces the person to react on stress, increases the capacity of the nervous system to change, to make new connections etcetera [27]. Receptors like 5HT3 and 5HT4 in the bowels are important in handling the side effects of antipsychotics.
Serotonin is also found outside the central nervous system; only 1-2 % of the total amount of serotonin in the body is within the central nervous system. The main part is found in the bowel and the blood platelets;. Recent investigation demonstrates that serotonin is important in the exchange of signals via the vagal nerve and the CNS; however this investigations are still in the first stages[28].
Serotonin itself is a neurotransmitter which is made from tryptophane. This happens both in the bowel and in the CNS, especially in the median and dorsal nuclei of the raphe. Tryptophane in an amino acid, and comes with the food. The substance passes the Blood-Brain-Barrie (BBB). However the serotonin which is made from itt cannot pass the BBB; therefore there is ‘brain serotonin” and “bowel serotonin” [29]. In the production of this substance from tryptophane there is an enzym important, the same which we saw in the production of dopamine, “aromatic L-amino acid decarboxylase (AADC)”. This enzyme increase the production of both dopamine and serotonin. The production of this enzyme is regulated via the NMDA-Glutamate receptor; when this receptor is not active this increases the production of the enzyme[30].

In summary we may say that Inside the central nerve system serotonin is involved in the regulation of appetite, mood, fear, awareness and observation, aggression and pain. It has also a role in cognition[31]. Its role in schizophrenia is not specific; the concentration of serotonin is increased in schizophrenia, but the elevation cannot be coupled to specific symptoms. Details about this are given in literature. Stahl[32] mentions that serotonin works especially by the release of glutamate. Whether is is cause or result from the condition is also for serotonin not clear. The substance is important for mood, cognition and emotional balance. In schizophrenia there is to much of the substance, and this affects certain receptors, and the substance is as well involved in the regulation of the levels of dopamine and of glutamate. Over-triggering of the 5HT2A receptor results in hallucinations, delusions and cognitive disturbances. Triggering of the 5HT1A receptor influences mood, fear and emotion. Some anti-psychotics influence the serotonergic system. Based on the effects of

serotonin we may understand certain symptoms of schizophrenia. The transmission of signals is being facilitated by hyperactivity of serotonin and that fits with many positive symptoms of schizophrenia. However there are as well many parts of the brain which are innervated by serotonin which seem to function normally in schizophrenia, and that does not correspond with a disturbance of the metabolism of serotonin as a primary cause of the condition.

Glutamate. Glutamate is the most important neurotransmitter in the central nervous system. Nearly all neurons in the brain are influenced by the amino acid glutamate[33], but the receptors for it are especially found in the prefrontal cortex, the striatum and the thalamus. The substance can be made by the body itself, but in common circumstances most of it comes with the nutrition as glutamine. Glutamine is converted into glutamate by the enzyme glutaminase. This happens in the central nervous system in the astrocytes. Glutamine can pass the Blood-Brain-Barrier, glutamate cannot. There is as well glutamate in the body (e.g. heart, pancreas) but that is synthesised there. For our aim we do not go further into this process. The astrocutes regulate the level of glutamate in the liquor[34]. Glutamate may by an enzymatic process been converted into Gamma Amino Buteric Acid (GABA) [35] .
Glutamate is an amino acid with a high concentration inside the brain. However it should remain wihin certain limits , otherwise neurons will dy. Glutamate is excreted into the synaptic cleft and triggers there the glutamate receptor. What is left over in the cleft will be absorbed by the astrocytes and partly brokendoown and partly made ready to be used again[36].

Receptors for glutamate: there are both metabotropic and ionotropic receptors. The metabotropic act through G-proteins and intracellular cascades, the ionotropic through depolarisation. The metabotropic regulate especially the release of glutamate. These might be involved in schizophrenia as well[37]. It concerns especially (the lack of) a modulating effect of the NMDA-receptor, and concerns both positive and negative symptoms and cognition[38]. There are three subtypes ionotropic receptors: the N-Methyl-D-Aspartate (NMDA) group, the AMPA group and the Kainate group. Each of these receptor has a single gen. In schizophrenia no aberrations have been found in these genes. De NMDA receptor desensitises slower than the other two. Especially the NMDA subgroup seems to be related to schizophrenia; it has been found that the function of the NMDA receptor lacks or disfunctions [39] [40]. Some people think that this might have a relation to the function of serine, a co-enzyme which is necessary to enable the NMDA receptor to work [41]. The same author also stipulates that the NR2 protein is needed to enable the NR1 protein, together with which it forms the NMDA receptor, to function well. About this more hereunder.
Blocking the NMDA receptor causes schizophrenia-like symptoms. Decreased functioning of the NMDA-receptor is therefore seen as an important factor in schizophrenia, while in some areas in the brain the level of glutamate is elevated [42] [43]. This may have a neurotoxic effect like mentioned above and is is seen to be one of the factors which contribute to the atrophy of the cortex in patients with chronic schizophrenia[44]. The number of NMDA receptors is decreased in certain brain areas in this condition, especially in the dorsal anterior cortex of the cingula, but as well in the striatum and the prefrontal cortex. This goes together with a low level of GABA in these areas[45]. Efforts to influence the quantity and activity of NMDA receptors are still in an early stage of development, and as far as these effort have an effect , this affects negative symptoms, and in this it is thought that GABA might play a role [46]. It seems that the GABA receptors do not function well in schizophrenia[47], and this could be the result of poorly functioning NMDA receptors as well. Further it proves that the level of PSD is low in glutamatergic receptors[48]; whether this is a result of problems in the glutamate receptor of is a separate factor is not clear. And finally it is suggested that there is a relation

between inflammation and a poorly functioning NMDA receptor [49] [50] [51]; in this microglia is involved[52].
While the findings that there is an increased synthesis and release of dopamine in schizophrenia consistently is being found, this is less clear with respect to glutamate. However it is clear that disfunctioning of glutamate mainly via the NMDA receptor leads to the symptoms of schizophrenia, while decrease of glutamate in the frontal cortex and hippocampus leads to negative and cognitive symptoms[53].
Another biological factor being mentioned is adenosine[54]. Adenosine acts via controlling the dopamine pathway; a shortage of adenosine results in a loss of control. Administration of adenosine in patients with schizophrenia results in a reduction of the activity of the D_2 receptor in this patients, and thus to a reduction of symptoms, The glutamate system as well may be influenced by adenosine, in strengthens the activity of the NMDAS receptor. A shortage of adenosine is the result of genetic factors. However this shortage cannot be demonstrated in all patients with schizophrenia.
The AMPA/Kainate receptors are also thought to have a relation with schizophrenia. These reduce the inhibiting effect of GABA in th hippocampus. Kainate receptors are important in the regulation of the release of transmitters, and in the post synaptic effects of glutamate[55]. This makes these important in the regulation of the sensitivity of the brain to triggers and the conduction of pain. Kainate receptors seem as well to have a relation to Epilepsia. An aberration in the mGlu-6 subunit may possibly have a relationship with schizophrenia.

In summary we can conclude, like we have seen the paragraphs about dopamine and serotonin, the NMDA receptor is important in regulating the levels of dopamine and serotonin via the enzyme “aromatic L-amino acid decarboxylase (AADC)”. This enzyme increases the production of both dopamine and serotonin. The production of this enzyme is regulated through the NMDA-glutamate receptor; when this receptor is not active this increase the production of the enzyme [56], and this results in high levels of dopamine and serotonin. The symptoms of schizophrenia therefore are mainly due to the high dopamine and serotonin levels, but the cause of this lies in the shortage in well-functioning NMDA receptors. Like mentioned before disfunctioning of the NMDA receptor is seen by a great number of authors as the cause of schizophrenia[57] [58]. Like mentioned before glutamate is a component of a regulating circle with dopamine and RSG24. A low number functioning NMDA receptors causes a high level of dopamine and serotonin, resulting in the symptoms of schizophrenia. Regrettably it is not yet clear why this receptor does not function well or is present in a reduced amount. None of the substances which influence the function of the NMDA receptor (dysbindin, neuregulin etc) show aberrations which are specific for schizophrenia. These substances are also not known to change the NR1 or NR2 protein of the NMDA receptor thus disabling the receptor. These have an influence on the transport thereof, e.g. neurofibromin in the transport of the NR2 protein in the neuron (see hereunder). Some of these substances influence the number of NMDA receptors. It seems therefore not likely that these aberrations are “the” cause of schizophrenia. Possibly an aberration in one or more of these substances may influence the clinical presentation. It is possible that these substances in people who have no schizophrenia influence their personality. There are still other genetic defects which in association with schizophrenia often occur, of which the mode of action is not known, but which might shape the clinical picture. But the schizophrenia-problem cannot be solved with these, therefore we need to know how the functionally reduced number of NMDA receptors develops.

The NMDA receptor studied in more detail. As in literature the NMDA receptor is the focus we will further elaborate on this. The NMDA receptor consists out of two NR-1 proteins and two NR-2 proteins, fixed together by glycine[59]. Both pairs of proteins should be there, in order to enable the glutamate to fix on the receptor. Herein the NR-1 sub-unit is essential in order that the receptor may function. A small variation in the structure of the NR-1 protein suffices to make that the receptor does not function; a small variation in the structure of the NR-2 sub-unit should not immediately result in disease, but contributes also not to a good functioning. The receptor cannot function without glycine. In schizophrenia the amount of NR-1 protein is decreased and the PSD-95 protein which belongs to it is aberrant. In the GRIN-1 gen which leads to the NR-1 protein no abnormalities are found[60 61]. In patients with schizophrenia a low level of the mRNA which codes for the NR-1 protein has been found[62].

The NMDA channel allows the passage of both Ca^{++} and other ions (Na^{+} , K^{+}), (from intra- to extracellular); Ca^{++} seems to be the most important from a clinical perspective. All ionotropic glutamate receptors are activated by L-glutamate. The sensitivity of the receptor is determined by the condition of the intra- and extracellular tails. This is firstly determined by the structure of the RNA which produced this, but as well by the concentration of e.g. Ca^{++} in the cell. The presence of other substances, e.g. cysteine, zinc and extracellular polyamines, influences the activity of the receptor also. The NMDA- receptors seem to be more sensitive to let Ca^{++} pass than other glutamate receptors. Mg^{++}ions block the channel, just like extracellular polyamines in especially the AMPA/Kainate receptor.
There are a number of intracellular proteins which may fix to the intracellular loops of the NMDA receptors. This is important in the activation of the receptor, e.g. by phosphorylation, but also in the activation of other intracellular signalling routes. Herein both G-proteins and other enzymes (e.g. calmodulin) are involved; while as well the PSD-95 protein (=Post Synaptical Density protein) is mentioned as being essential for the receptor in order to be able to function, and this is decreased in patients with schizophrenia[63].
Triggering of the NMDA-receptor has an effect on the functioning of the transmission of signals via the actine skeleton and on the development and functioning of dendritic spines; this is discussed in the article about the neuron (2a). When this receptor is not triggered these systems do not function well. About the effects on karyon and perikaryon of triggering of the NMDA-receptor is no documentation available. It is however clear that triggering the NMDA-receptor leads to the transport of substances via the cytoskeleton; these have to be dealt with in the perikaryon. At the start of the transport in the axon hillock are again NMDA receptors involved.
Glutamate receptors are not only important in the central nervous system, but have as well a role in the regulation of the production of insulin or release thereof in the pancreas and in the resorption of bone[64]. As this falls beyond the scope of this study, we leave that.

Factors which may Influence of the glutamate receptor.
If we should know the physiology and pathophysiology in schizophrenia of glutamate and the NMDA receptor, we might be able to find clues for treatment[65]. In the literature which already has been mentioned a number of substances are mentioned which have in special an influence on the NMDA-receptor: dysbindin, neuregulin, DAAO and some other. This was also extensively elaborated on in article 2a and will therefore not be repeated here, but is named in appendix I. Summarising we may say:

- Dysbindin is decreased in many patients with schizophrenia, and this results to less active NMDA-receptors[66], but this cannot be seen as the only factor contributing to the clinical picture. However there is a close relation with the occurrence of negative symptoms [67].

- Neuregulin is also decreased present in many patients with schizophrenia, and this low level let the symptoms increase. It is obvious that the substance has an important role, together with the ERB receptor, in the transmission of signals, especially in the interneurons[68]. Luvsannyam[69] et al reported in 2022 that they could not find a clear relationship between the changes in the structure of neuregulin and the pathophysiology of schizophrenia. The fact that the clinical picture varies a lot in this group of patients excludes this shortage as sole primary cause of the disorder, there has to be more. However it is clear that the substance plays an important role in the clinical presentation of the disorder [70]. It has been suggested that the substance is important in the transport within the neuron of the NMDA-receptor, of of components thereof. A shortage of neuregulin could contribute this way to a shortage of functioning NMDA-receptors[71].
- DAAO influences the NMDA receptors via D serine. In schizophrenia there is to much DAAO, and therefore a decreased level of D serine. It is possible to relieve the symptoms of schizophrenia with D serine[72], especially the positive ones, however not to eliminate these. Recent investigations shows that inhibition of DAAO has a favourable effect on the NMDA-receptors .[73] [74]
- RSG24 is a part of a control loop in which the NMDA receptor is involved regulating the amount of - amongst others- dopamine[75]. There are decreased levels in schizophrenia [76, 77].
- Interneurons with GABA are decreased present in the frontal lobe in patients with schizophrenia. The meaning hereof is not yet clear. A study from 2025 [78] suggests that GABA is important to regulate the balance between glutamate and dopamine. This balance should be disturbed in schizophrenia.
- Neurofibromin is involved in the action of kinases which are necessary for the transport of substances within the neuron, e.g. the transport of GRIN2B to the synaps. This means that neurofibromin is involved in components of the NMDA-receptor. Shortage of neurofibromin results thus in en shortage of NMDA-receptors. Further the substance is involved in the supply of energy in the synaps and the substance binds to caveolin-1, a substance which is important in the construction of membranes inside and around the cel[79]. The prevalence of schizophrenia is higher than average in persons with a deficiency of neurofibromin[80] [81].

Seeing all influencing factors together it is clear that the NMDA-receptor has a central place in the disorder. Tandon et al[82] consider schizophrenia therefore to be a syndrome, in which several factors which influence the NMDA-receptor separately, play a role. The problems as a result of a decreased amount of mRNA for the production of the NR-1 protein, a component of the receptor, should not be overlooked aside from the problems with dysbindin, neuregulin etc. We will see this later. There could be more contributing factors; from genetic investigations it became cleat that there are many aberrations in genes found in patients with schizophrenia (appendix II).

Networks.

Nowadays the problem of schizophrenia is often delt with from the perspective that the functioning of some networks is disturbed. This means that one goes one level less deep that when discussing the abovementioned factors which are aimed at the cellular level. Petterson-Yeo et al (2010)[83] think that the disorder is due to the lack of a number of connections between several brain areas, especially in the frontal lobe. Schmidt et al (2015)[84] support this idea, just like Luvsannyam et al[85] . The question why this networks do not function well is mostly not answered. The symptoms of schizophrenia like mentioned before can be seen as disturbances in the central nervous system of functions and/or

activities[e] . We see than delusions as a disturbance of thinking, hallucinations as a disturbance of perception, incoherent speech as disturbance of functions related to language, severe chaotic behaviour as disturbance of global psychosocial functions and catatonic behaviour as a disturbance of psychomotoric functions, apathy as a disturbance of temperament and personality, lacking speech as a disturbance of functions related to language, passivity as a disturbance of functions related to energy and temper, flatness of affect as a disturbance in functions relate to mood. All these functions have their own specific network, whilst sometimes parts of these networks coincide. (See also the article 2[b] on this website, where the networks fitting in here are described). Looijestijn et Al[86] indicate that different symptoms of schizophrenia are linked to a number of factors, which may be described on different levels: on the microscopic level where neuronal networks are disturbed, on mesoscopic level where global brain conditions can be found and on macroscopic level in relation with social network structures[f]. Ribolsy et Al[87] determined that there are structural defects in the corpus callosum in patients with schizophrenia, which makes the two brain halves to function asymmetrically. Schmidt et Al [88] (see before) found that there are aberrant connections in the frontal cortex; they suppose that this is the result of aberrations in the glutamate system. Zhu et AL[89] in contrary found no or little structural differences between healthy persons and patients with schizophrenia in the connexions in the prefrontal area and the two brain halves. In schizophrenia there is thus a number of not well functioning networks, and the focus thereby is on the connections between the prefrontal cortex, the striatum, the substantia nigra, the nucleus accumbens and the ventral tegmental area. However with this all nothing is said about the cause of this disturbances, but it is clear which neuronal networks are involved in the disease. Not all networks are always equally involved. Several different combinations ae possible, and that explains the multiform clinical picture. Not al these networks have been pictured completely in all details, further investigations are going on.

Causes. The cause of the disturbance of the networks is not yet known. In literature several etiological factors are mentioned which seem to play a role. The opinion that the condition is psychogenic (the dominant mother) is completely left. The potential factors possibly related to the cause we summarise as follows:

- Genetic factors seem to play a role for sure[90]. Defects on the places on the chromosomes which at the end synthesize the receptors for dopamine, serotonin and/or glutamate have however not been demonstrated[91]. Other defects in the genes have been found which possibly have a relation with the disease[92,93 ,94,95]. These are in more detail described in appendix II. In literature there ae many indications that the disease is due to a problem in the NMDA-glutamate receptor [96 97 98 99 100] and the overactivity in the dopamine and serotonin system is secondary to this[101]. We see as well the thought that not one single defect in the genes should be responsible for schizophrenia, but that several gen defects together contribute to the disease[102,103]. At the other side it is strange that a great number of gen defects acting together should be responsible for the disorder, that would make the disorder more rare than what we see now. It seen more likely that one or two single defects are essential to the development of the clinical picture, while other defects- when present-

[e] Functions and activities in terms of the ICF (See the article 3 on this website)

[f] It is attractive to try to connect this concept with the systematics of the ICF; as far as known to me this has not yet happened; the microscopic level could possibly be linked to functions (in terms of the ICF), the mesoscopic level to activities and the macroscopic level to participation. But the central; problem remains the disturbance of functions, and thus the networks on the microscopic level. More about the ICF in article 3 on this website.

colour the presentation thereof, this would explain the multiform picture of schizophrenia. Which these essential genetic defects is or are is not yet clear.

- Influences of the season. It became clear that children who later would get schizophrenia, are more often born during winter or early spring than might be expected on the base of the population birth figures[104]. Others doubt whether this is so[105]. It has been investigated whether, if this is taken for true, there might be a relation with a disease during pregnancy[106], but although probably some influences of the season may play a role, it s not definite clear which infection this should be.
- Problems during the first trimester of the pregnancy. There seems to be a relation with malnutrition during the first trimester of the pregnancy, being the period in which the neural tube develops to brain, and schizophrenia[107]. The mechanism through which this should go is not yet known.
- Infection: There has been sought for a correlation with influenza-like symptoms during pregnancy. This could not been demonstrated[108]. Also the mechanism through which influenza could lead to schizophrenia is not clear; it has been thought that influencing the immune apparatus could be it, but this is merely speculation. Najar et al (2013)[109] presented a case-study with a girl who got psychoses due to an auto-immune inflammatory process. Al-Diwani et al (2017)[110] think that Schizophrenia is an auto-immune problem and Anderson et al (2023)[111] support this. Based on their findings we may conclude that immunological processes are involved in schizophrenia, which we do not see in healthy persons. This processes have to be a part of the total process which results in the disorder. Also the fact that the utilisation of antibiotics like penicillin or its derivates, which act by the breakdown of peptidoglycanes, thus activating the immune apparatus[112], may induce psychoses or reinforce these supports this. This could as well be caused by the disturbance of the flora in the bowels which can be caused by antibiotics, and which may activate the microglia[113]. This option is under investigation, there are not ye firm conclusions. There has been thought of a disturbance of he metabolism of short chain fatty acids[114].or of triggering the vagal nerve or a combination of the two.
- Other factors like living on the countryside and the social economical class have been searched, but were not conclusive[115]. It is however clear that amongst migrants there is a higher incidence of schizophrenia than amongst the autochthonic population[116]. A satisfying explanation therefore is not available.
- Also an aberrant architecture in the cortex has been described in patients with schizophrenia[117] [118]. Whether this is a result of the disorder or possibly has the same cause like schizophrenia, or is a cause thereof is not clear. Autophagia is mentioned as one of the mechanisms through which this could take place. [119]

Symptoms and the glutamate receptor.

Studying the symptoms of schizophrenia we may differentiate between primary, secondary and tertiary symptoms[120]:

- Primary symptoms are those which directly are due to the disturbance of the biological process at the neurophysiological and functional level [121] [122]. Not only the electrical impulses via the membrane of the cell are important, but as well the chemical signals running vias the actine skeleton (see as well article 2a about the neuron). When the transport of chemical signals does not go on the way which it should, this results in the transmission of faulty messages.
- Secondary symptoms are those, which are caused by the reaction of the patient on the wrong messages, and
- Tertiary symptoms are those which are caused by (the perception of the patient of) the reaction of the environment at the disease.

Only a part of the symptoms can therefore be linked directly to the disturbed function of the glutamate receptor, the others will be secondary or tertiary. This means therefore, that if ever we will be able to overcome the primary defect, support will remain necessary because of the secondary and tertiary problems, especially in persons who have been ill for a longer period.

Table 2 summarises the symptoms which can be called primary in relation to a poorly functioning NMDA-glutamate receptor, in relation to functions and activities and participation seen from the ICF.

Table 2. Effects of a shortage in well-functioning NMDA-glutamate receptors	
Via an increased level of Ca^{++}	This will result in easy depolarising. Spontaneous depolarisation may result in the transmission of "faulty messages", and thus to delusions and hallucinations (level of functions) but in the motoric part of the nervous system as well to stereotypical movement or freezing (level of activities)
Via defects in the formation of and shortage in dendritic spines and poor organisation of those	This results in "wrong" contacts, and to a disturbed functioning of neuronal networks. This may cause delusions and hallucinations as well(level of functions) and chaotic behaviour (level of activities)
Via disturbed transmission of signals via the actin skeleton	The results of these signals at the (peri)karyon are not yet fully clear, but that there should be disturbance is. The effects thereof on the labelling of substances in the Golgi apparatus is obvious. This as well may result in delusions hallucinations (level of functions) and chaos (level of both functions and activities)
Via increased irritability in the axon hillock	This result in the sending of a great number of signals via the axon. This again results in chaos and possibly catatonia (level of both functions and activities)

Summarising we see that there are to much signals, and signals arriving at a destination where these were not aimed for, and possibly of a nature not intended. Also the origin of the signals may not be recognised, This results primarily in delusions, hallucinations ang severe chatic or catatonic behaviour (mainly level of functions). The incoherent speech and the negative symptoms: apathy loss of speech, passivity, lack of affect (level of activities) may be seen as secondary, the patient tries to let as little as possible impulses through his brain. These symptoms may also be primary through e.g. a disturbed neuregulin of dysbindin activity (and then it is at the level of functions). The patient lives now in a world in which he cannot interpret the signals from others well, and this results tertiary in disturbances in the social life (level of activities and participation) Therefore we may well understand how a shortage of well-functioning NMDA receptors may result in the clinical picture of schizophrenia.

The glutamate receptor itself is not changed in patients with schizophrenia. The central problem is the shortage in functioning receptors. This may be caused by aberrant proteins in the glutamate receptor and / or by a changed secondary signalling system[123,124]. In table 3 below we summarise what we know about the process in which the receptor is synthesised.

Table 3 Summary about what is known about the synthesis of the NMDA-glutamate receptor.

Component	Findings
Chromosome/DNA	GRIN1 and GRIN2 no aberrations found
mRNA coding for NMDA receptor (NR1 protein)	Decreased amount found
Ribosome/endoplasmic reticule	No aberrations known
Golgi apparatus	No aberrations known
Cytoskeleton postsynaptic	Normal; possibly disturbed transport from receptor to dendrite by genetic defects, but not the same in every patient
NMDA receptor	Decreased amount of further normal receptors
Postsynaptic processes	Some aberrations, depending from genetic defect, but not the same in every patient
Actine skeleton presynaptic	Aberrant transport via this depending from genetic defect, but not the same in every patient

It became clear that there is a diminished quantity of NR-1 protein and a decreased quantity of NR-2a and NR-2c protein in schizophrenia[125]. The NR-1 protein is an essential component of the NMDA receptor. It seems therefore that a decreased production of mRNA is present, leading to a deceased number of receptors. The other factors which are mentioned contribute to the clinical picture, both in severity and in presentation.

What may lead to a reduced production of mRNA? mRNA is produced on the DNA when the double string opens. One could therefore imagine that this mechanism fails. It could be disturbed in several ways (table 4,):

Table 4: Ways to disturb the opening of the DNA double string, other otherwise the production of mRNA can be impaired.

1. Due to lack of substances which are the end result of an endogenous cascade or part of an intracellular feedback mechanism, an d this shortage impairs the opening of the helix. This might be by substances which impair the opening the helix itself or by lack of signalling substances to stimulate opening of the helix.	There is in literature no mention of such a mechanism in the mRNA for NR1; we skip it therefore
2. Substances fix to the DNA, impairing the formation of new mRNA.	This is a promising possibility; we will elaborate further on it.
3. The absence of a G-protein or other substance, as a result of a cascade due to triggering from outside the cell, causing the opening of the helix.	This mechanism is certainly there, e.g. in the synthesis of adrenalin under the influence of glutamate. About such a possible mechanism in the synthesis of the glutamate receptor no literature was found
4. (Lack of) spontaneously periodically opening of the helix e.g. because of temperature, irradiation or acidity, etc.	This mechanism is certainly there and might well be the source of the small amount of NMDA receptors which are still found in patients with schizophrenia.

This brings us to this hypothesis:
The most likely cause of the decreased production of mRNA is that there is a factor which impairs the feedback mechanism which in healthy people makes that the utilised NMDA-receptors are replaced.

- This factor might be a pure genetic defect. This genetic defect should result in that the DNA does not release the mRNA which has been formed on it. However in such a mechanism we cannot understand why schizophrenia debuts usually around adolescence and sometime much later. One would expect a pure genetic defect to result in symptoms from birth.
- This factor might have a viral origin. The virus should than compete with the mRNA for the places in the ribosome where the receptor-proteins are formed. Due to the lack of an adequate feedback signal it will look as if enough receptor protein has been formed, and the DNA will stop the production of the RNA.
- One could as well imagine that a virus produces substances which interfere with components of the feedback mechanism, either on the DNA or on the mRNA or on the ribosome.
- One could also imagine that a virus fixes to the DNA, impairing thus the production of mRNA. Alternative is that a virus produces substances, or makes the body to produce substances which fix to the DNA, thus inactivating it.

Whatever it may be, there remain questions in a viral cause.

- Why start in adolescence, and why often much later? A number of patients with schizophrenia tell that they had in their early youth some episodes during which they had another experience of the world than other people, though there was no clear psychosis. One might think that there was a cause like an intercurrent infection which activated the (supposed) virus a little and this resulted in preclinical symptoms. If this should be true, the viral infection should have taken place early, but influenced by puberty / adolescence (hormones, stress) this virus could become active. From literature it is clear that the administration of oestrogens reduces the symptoms[126]. The existing differences in the levels of neuro-active steroids between patients with schizophrenia and the healthy population[127] correspond herewith. In this situation we think of the following: after an infection took place the intracellular defence mechanism of the neuron is in healthy people able to neutralise or kill an invading virus. Hereby one should think about the action of dsRNA[128 129], or as well about the activity of autophagosomes; the latter will not be able to function well when the membranes thereof are not well built. A third defence mechanism is that of the action of microglia, which produce antibodies against invaders and phagocytise these eventually. In people with a genetic defect which impairs this intracellular defence mechanism – both via dsRNA or via autophagosomes or microglia - this defence does not go well, and this makes in genetically predisposed people the intracellular defence mechanism to fail. The changing level of hormones in puberty influences this, and in genetically predisposed people this is sufficient to make the intracellular defence mechanism to fail.
- When and how happens the infection usually? During the first trimester of the pregnancy the developing nervous system is very vulnerable, and the blood-brain-barrier does not yet function well. If added to this there is a situation of an insufficient blood supply to the foetus, whatever might cause it, than a micro-organism could easily enter and hide in places where in other situations it could not, as usually in healthy situations the general defence of the body will clear the virus before it enters

the nervous system. In people who have a genetic defect, but who were not infected during the pregnancy where they came from, could in a later moment infection of the central nervous system take place; this will not happen often as the blood-brain-barrier defends them. The pregnant woman from whom the child will be born who later gets the diagnosis schizophrenia, will probably experience the infection with the virus and have flu-like symptoms. Infections usually have more possibilities during a poor nutritional status and in a socially weaker environment.

- In pregnancies with twins it happens often that one of the two suffers more during the pregnancy. This might explain why not always both members of twins are getting infected.

If this hypothesis is correct which virus could be involved? We do not know as yet. What we know is that it should be a RNA virus, with a component which resembles the GRIN1 or GRIN2 place on the chromosome, otherwise it could not compete with the mRNA. But it should also share some properties with the HIV-1 virus; the HIV-1 virus influences the synthesis of NMDA-receptors. The Herpes Simplex Virus is a good candidate here.

Conclusion:

It is possible to explain the clinical picture of Schizophrenia from the absent action of the NMDA-glutamate receptor. A disturbed NMDA-receptor function leads to an increased level of dopamine and serotonin, and that results in a disturbance of neuronal networks. The cause of the shortage in well-functioning NMDA-receptors is not yet clear. The hypothesis like described above would include most elements of which it is known that these influence it. Prove for the hypothesis is not yet there. If the hypothesis should be correct this opens new perspectives for the treatment of the disorder.

Appendix 1. Substances which influence the NMDA receptor.

- *Dysbindin.* This substance regulates the transport of glutamate in the vesicles in the axon.[130,131]. The transport of the NMDA receptor to the postsynaptic membrane is as well regulated through dysbindin[132 133 134 135]. Dysbindin influences also the conduction of signals via the actin skeleton[136]. And also it became clear that dysbindin influences the immune response[137]. Disbindin further is involved in the regulation of the GABA-ergic transmission in the interneurons[138]. If there is only a small amount of dysbindin, there will also be a low level of GABA, and that results in a decreased inhibition of (especially dopaminergic) transmission. In schizophrenia there is often (but not always) a low level of the mRNA which codes for dysbindin[139 140], and thus there is a low level of dysbindin. A poor function of dysbindin results in a decreased quantity of NMDA receptors and possibly so to schizophrenia[141]. The basic levels of glutamate and dopamine in the frontal cortex is thus increased[142]. However no one of the cited authors thinks that a shortage of dysbindin is the sole cause of schizophrenia, apparently there is more. The poor functioning of dysbindin coincides in fact always with negative symptoms, like loss of affect, lack of speech and apathy[143]. All things together literature indicates that the lack of dysbindin in patients with schizophrenia contribute largely to the clinical picture but the shortage thereof is not the sole cause of the disorder.
- *Neuregulin.* Neuregulin stimulates ErbB-receptors, especially ErbB4, and influences neuronal differentiation, migration and synaptic plasticity[144]. There exist different isoforms of neuregulin-1, andthese differ in expression in the different brain areas. In people who suffer from schizophrenia there is often a significant presence of a genetic defect on the place on the DNA which codes for neuregulin[145 146]. However between groups which show ethnical differences there exists also a difference in the presence of the amount of neuregulin, not coinciding with the incidence of schizophrenia[147]. Three ways are described along which the interaction of this substance with the NMDA receptor could happen. The first takes a starting point in the influence on the receptor by kinases, may be or not via a specific intracellular receptor (ERB4) for this substance[148 149 150 151 152], the second through influencing the 'downstream signalling events' via PSD-95[153], which indeed is involved in the transport of substances via the actin skeleton. And thirdly: abnormalities in neuregulin-1 influence the GABA and the NMDA-receptor function[154]. The amount of NMDA-receptors functionally available is being controlled by the ERB4 receptor[155]. Neuregulin influences as well the synaptic plasticity[156], and the activity of the substance is influenced by sex hormones[157]. A poor function of neuregulin reduces thus the number of available NMDA-receptors. This will certainly increase the symptoms of schizophrenia[158]. However the big variation in the clinical picture[159] in people with schizophrenia excludes as well this defect as the sole primary cause, though there is an important role for this substance. It did become clear that the level of neuregulin in untreated patients with schizophrenia is lower that after treatment; this suggests that the absence of neuregulin plays a role in the development of the clinical picture[160], or possibly is the result of the decreased number of NMDA-receptors.
- *DAAO* (D-amino acid oxidase) and DAOA (D=amino acid oxidase activator). These are two emzymes which both are thought possibly to have a relation with schizophrenia. The relation of DAAO seems stronger than that of DAOA[161]. DAAO oxidises the substance D-serin, which on its turn activates the NMDA-receptor[162]. Administration of D-serin in the treatment of schizophrenia reduces the severity of symptoms, but does not eliminate these[163 164]. The presence of an increased level of DAAO results via an increased breakdown of D serin in a less active but not structurally changed NMDA receptor. There are both less and functionally poor quality NMDA receptors in schizophrenia and DAAO has

a role herein[165 166 167]. Recent investigations demonstrate the inhibition of DAAO has a favourable effect on the NMDA receptors.[168 169]

- *RSG4.* In 2001 it became clear that a substance called Regulator of G-protein Signalling 4 (RSG4) significantly often is decreased or absent in the prefrontal motoric and visual cortex in patients with schizophrenia[170,171]. RSG4 modulates the intracellular transmission of signals for a great number of G-protein coupled receptors[172]. There exists a special relationship between RSG4 and the functioning of adrenergic receptors. Low RSG4 means a high excitability of the adrenergic system[173]. The substance seems to be a component in a regulating circle[174]. A low activity of NMDA-receptors usually leads via a low RSG4 to a high activity of dopamine and serotonin receptors, which on its turn leads to increasing the activity of NMDA, and so on. Abnormal or lacking RSG4 interrupts this feedback mechanism. The substance is present in the cerebral cortex and in the thalamus an basal ganglia. RSG4 influences the transmission of signals, is involved in the differentiation of neurons, is regulated by dopamine and shows an interaction with ERB3 (A NRG1 receptor) The low level of RSG4 however is not specific to schizophrenia, it occurs also in Alzheimers disease. The substance could however be a component of a pathophysiological mechanism in schizophrenia. A low amount of NMDA receptors could via a decreased RSG4 lead to an increased activity of dopamine an serotonin like we see in schizophrenia.
- *GABA.* It is reported that a poor function of certain interneurons which use GABA as a neurotransmitter could inhibit the function of the NMDA receptor[175 176]. Certain interneurons in the frontal cortex should be involved. How this is precisely is not yet clear. A study from 2016[177] suggests even that there is no place at all for GABA in the pathophysiology of schizophrenia. In a study from 2025[178] there is argued that GABA is important to regulate the balance between glutamate and dopamine, and thus has a role in schizophrenia; this balance should be disturbed.
- *Neurofibromin.* This is a protein which is involved in the control of the growth of certain cells in the supporting cells of the neuron. A shortage of this substance results often in the development of certain tumours, called neurofibromas. But it causes as well aberrations in the skin, in the skeleton, tumours in the optic nerve, pheochromocytomas motoric problems, defects in memory problems in learning and other cognitive deficits[179]. The biological mechanism hereby is that neurofibromin is involved in the action of kinases which are needed in the transport of substances in the neuron, amongst which the transport of GRIN2B to the synaps. This means tat neurofibromin is involved in the transport of components of the NMDA receptor. A shortage of neurofibromin means therefore as well a shortage of NMDA-receptors. The substance is as well involved in the supply of energy in the synapse and the substance binds to caveolin-1, a substance that is important in the construction of membranes inside and around the cell[180]. The prevalence of schizophrenia is higher than average in persons with a deficiency of neurofibromin[181 182]; this corresponds with a shortage of NMDA receptors. Neurofibromin could therefor on two ways contribute to the disorder schizophrenia: in the first place by disturbing the NMDA-receptor, and secondly by being present inside the skull as a space occupying process (fibroma).

Appendix II Genetic factors.

There are clear indications that there is a genetic component in schizophrenia. In members of the families of patients with schizophrenia the prevalence of schizophrenia is higher than in the general population. Therefore there has intensively been sought and up to 128 places on chromosomes have been investigated, however none of these gave a definite conclusion. The table hereunder shows on which things there has been thought.

Author	year	findings
Levinson et al[183]	1998	No specific relation found
Levinson et al [184]	1998	Probably multiple genes involved
Sakurai et al[185]	2000	The GRIN1 gen probably not involved in the etiology of schizophrenia.
Schwab et al[186]	2000	On chromosome 10 and 6 there seem tob e locations which could fit with schizophrenia
Mowry et al[187]	2000	There seems to be a relation between chromosome chromosome 10q and possibly as well 2q and 4 q
Shibata et al[188]	2001	No relation between schizophrenia and aberration in the gen of GRIN1.
Gurling et al[189]	2001	Many relations found strong on 1q33.2, 5q33.2 8p22.1-22 and 11q21, and less strong on 4q13-31 and 11q23.3-24
Miyamoto et al[190]	2003	No relations found
Harrison et al[191]	2005	Relations with the genes for neuregulin, dysbindin, COMT, DISC1, RGS4, GRM3, and G72
Owen et al[192]	2005	Supposes a relation with the glutamatergic synapse.
Hanson et al[193]	2005	Considers genetic predisposed inflammations
Craddock et al[194]	2006	Signals overlap with bipolar, especially for the genes for DAOA, dysbindin, COMT, BDNF, DISC1 and NRG1.
Werner et al [195]	2006	The reduced activity of the NMDA receptor is caused by (genetical determined) hypo-activity of neuregulin 1.
Stahl [196]	2007	Not a single gen but a combination of genes for DBNF, dysbindin, neuregulin , DAOA en RSG4
O'Donovan et al[197]	2008	Little if any relation with aberrations in genes
Sanders et al[198]	2008	No relation to aberrations in the genes for RGS4, DISC1, DTNBP1, STX7, TAAR6, PPP3CC, NRG1, DRD2, HTR2A, DAOA, AKT1, CHRNA7, COMT, and ARVCF
Holmans et al[199]	2009	The chromosomes 8p21 8q24.1 9q34 and 12q24.1 strongly suspicious less strong but present: 10p12 and 22q11.1
Europe PNC funders[200]	2009	Significant co-occurrence with a gen on chromosome 6 and on chromosome 11 and a possible relation with a gene on gen op chromosome 18
Papiol et al[201]	2011	No relation found
Hosák et al[202]	2012	No specific relation found
Bergen et al[203]	2012	Not clear
Fanous et al[204]	2012	Genetic factors can be linked to negative symptoms and confusion . Not mentioned which.
Levinson et al [205]	2012	No specific relation found
Hass et al [206]	2013	6 correlations found localised on the genes NR2F6 USHBP1 and BABAM1 and 4 others in thre other regions (Chromosome 1, 2 and 10)
Bergen et al[207]	2014	No single gen resulting in schizophrenia
Europe PNC funders [208]	2014	128 associations found, many in relationship to glutamatergic transmission or immune apparatus.
Xu et al [209]	2014	No relation can be demenstrated.
Arnedo et al [210]	2014	A heterogenic group of genes, nothing specific..
Bigdeli et al [211]	2016	No specific relationship, probably is schizophrenia not one but a group disorders.
Prasad et al [212]	2017	No relationship with disorders on chromosome 6.

Rujescu et al [213]	2019	In schizophrenia there are delations found (1q21.1; 2p16.3; 15q11.2; 15q13.3), which are as well present in other neurobiological disorders.
Priya et al [214]	2019	NOTCH4 (rs2071827) and GRIN1 (G100C) show a significant association.
Karimian et al[215]	2020	There was only an association with the NrCam gene
Ishii et al [216]	2025	In this paper no specific genes are mentioned

In conclusion we must state that no clear relationships could be demonstrated via genetic research. The gene for apo A-IV lies on chromosome 11[g] and that was mentioned in some of these studies. It is striking that in none of these studies chromosome 7 is mentioned, while there the gen for caveolin-1 lies, which together with apo A-II seems to be important in the pathophysiology of schizophrenia like we see this (see article 5b). Possibly this has to do with the low frequency of defects in this gen in schizophrenia.

In a number of the articles like mentioned here there is a suggestion of a relationship with neuregulin, dysbindin or DAOA. All three these substances have to do with the intracellular transmission of messages. Dysbindin is thought to have a relation to negative symptoms, but that is not yet clear. At the same time we must conclude that there are many persons who have no schizophrenia but have genetic aberrations on the field of these substances. These can therefore be excluded as the sole cause of schizophrenia.

[g] For clarification why this gene and that for caveolin-1 are important see article 5b.

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