



ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΝΕΥΡΟΑΠΟΚΑΤΑΣΤΑΣΗ

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Μεταπτυχιακή Διπλωματική Εργασία

**Γνωστικά Ελλείμματα στη Σχιζοφρένεια: Από- και ανα-διοργάνωση
του εγκεφάλου και Αποκατάσταση**

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Βιολόγος

Υπεβλήθη για την εκπλήρωση μέρους
των απαιτήσεων για την απόκτηση του
Μεταπτυχιακού Διπλώματος Ειδίκευσης
«ΝΕΥΡΟΑΠΟΚΑΤΑΣΤΑΣΗ»

Λάρισα, Οκτώβριος 2023



DEPARTMENT OF MEDICINE
SCHOOL OF HEALTH SCIENCES
UNIVERSITY OF THESSALY

POSTGRADUATE PROGRAM

NEUROREHABILITATION

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POSTGRADUATE THESIS

**Cognitive Impairment in Schizophrenia: Brain Reorganization and
Neurorehabilitation**

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Submitted for the partial completion of
requirements in order to obtain the
Master of Science Degree on
“NEUROREHABILITATION”

Larisa, October 2023

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου
δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη
δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω
παραθέσει της πηγές τους στο τμήμα της βιβλιογραφίας:

Υπογραφή: »

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- 1.
- 2.
- 3.

Αναπληρωματικό μέλος:

Cognitive Impairment in Schizophrenia: Brain Reorganization and Neurorehabilitation

To my brother, Konstantinos,
patiently carving our own path
and love

Acknowledgments

With this thesis, the cycle of my postgraduate studies is completed. By completing the requirements of these two years, I want to truly thank those people who were really by my side and showed their support in practice.

Firstly, I would like to thank Mr. Nasios Grigorios, Associate Professor at the University of the Speech Therapy Department at the University of Ioannina. The discussions we had always guided the course of my academic career. After many discussions, I decided that this master's degree would be the right one for me to develop in the field I am interested in, that of Neurobiology-Neuropsychology. I honestly thank him for his support and cooperation all these years.

Next, I would like to thank Mrs. Skokou Maria, Psychiatrist at the University of Patras. Her help and advice on the topic of the thesis were very useful in the course of writing. Her targeted observations and her immediacy played an important role.

I want to thank Dr. Siokas Vasileios, who gave me the opportunity to start a nice collaboration and discover my skill in academic writing by following his advice and instructions.

Also, I want to thank my parents, Chrysa, and Antonis, who are by my side and support my every professional step. They have been my support all these years and I thank them for everything they have offered me. I especially want to thank my brother, Konstantinos, who is by my side in his own unique way and encourages my every effort.

I thank my friends who support me with their love. Special thanks to my friends Dimitra and Eleni, who have been by my side for so many years and the dedication to our friendship always inspire me.

Finally, I could not mention the support and love of my partner, Stelios, who always encouraged me and gave me the motivation to continue chasing my goals and dreams.

Gialama Vaia

November 2023

Curriculum Vitae

I come from Larisa, and I am 27 years old. I studied for 5 years at the Department of Biological Appliances and Technologies at the University of Ioannina, acquiring an Integrated Master (October 2015- April 2021). In the 5th year, I was preparing my experimental thesis titled: "Risperidone: a new therapeutic approach in glioblastoma cell lines". After that, I worked for around 14 months (February 2021-July 2022) in a Medical Laboratory in Ioannina. In this job position, I practiced techniques and knowledge from my undergraduate studies, but I acquired experience in blood sampling, biochemical analysis, making appointment with clients and the execution of many tasks. In October 2021, I was accepted by the Neurorehabilitation Master Program, where I acquired knowledge about various clinical issues. In January 2022, I started a collaboration with Dr. Siokas Vasileios and the Neurogenetics Laboratory of the University of Thessaly, preparing an article for publishing.

In August 2022, I returned to Larissa aiming to complete the Master's Program. In December 2022, I was hired in a Medical Laboratory (Ioannis N. Papageorgiou) as a biologist, where I have been working till now (December 2022-now). In this job position, I oversee blood sampling, microscopic analysis and tests. Moreover, I handle Medical Software (Mediware) and I am training from June 2023 about ISO 15189 for ESYA certification.

Furthermore, I have just been accepted into the Erasmus+ program for an internship. I chose and be accepted to attend the University of Liege, Belgium at GIGA Institute and Athena Demertzi will be my supervisor. I am so excited to be accepted and be a member of this Laboratory.

Abstract

Schizophrenia is a psychiatric disorder that has a profound impact on the individual and society. The etiology and pathophysiology of the disease have not been fully elucidated due to its heterogeneity and complexity. Schizophrenia is a psychopathological syndrome characterized by positive, negative, and cognitive symptoms. Cognitive symptoms are related to deficits in thought, emotion, perception, and behavior. Moreover, the neurobiological background of the disease is not fully understood. However, there are hypotheses that could explain the etiology of schizophrenia. It appears to be a polygenic disorder where several genes play a role. The neurobiological background of the disorder is under investigation but there are some biological hypotheses that contribute to the pathophysiology. The NMDA hypothesis is the most known common theory describing the etiology of schizophrenia. Recently, glial cells, cells of the immune system, were associated with the pathophysiology of the disorder. Over the years, the administration of pharmaceutical treatments tried to improve the clinical symptoms of the patients. However, some of them persist without significantly improving the individual's daily and social life. Recent studies have shown that neurorehabilitation and cognitive training techniques offer not only clinical improvement of the individual but also modify the neurobiological background. Nowadays, cognitive therapies are widely known, such as Cognitive Remediation Therapy, RehaCOM, and Cognitive Behavioral Training applying new techniques and methods. Neuroimaging studies have shown that cognitive rehabilitation reorganizes the brain's structure, improving cognitive functions, individual's daily and social life.

Keywords: schizophrenia, neurobiology, neurorehabilitation, cognitive

Περίληψη

Η σχιζοφρένεια είναι μια ψυχιατρική διαταραχή που έχει σοβαρές επιπτώσεις τόσο στο άτομο όσο και στην κοινωνία. Η αιτιολογία και η παθοφυσιολογία της νόσου δεν έχουν διευκρινιστεί πλήρως λόγω της ετερογένειας και της πολυπλοκότητας της. Η σχιζοφρένεια είναι ένα ψυχοπαθολογικό σύνδρομο, καθώς χαρακτηρίζεται από θετικά, αρνητικά και γνωστικά συμπτώματα. Τα γνωστικά συμπτώματα σχετίζονται με ελλείμματα στη σκέψη, στο συναίσθημα, στην αντίληψη και στη συμπεριφορά. Επιπλέον, το νευροβιολογικό υπόβαθρο της νόσου δεν είναι πλήρως κατανοητό. Ωστόσο, υπάρχουν υποθέσεις που θα μπορούσαν να εξηγήσουν την αιτιολογία της ασθένειας βάσει αυτού. Η σχιζοφρένεια φαίνεται να είναι μια πολυγονιδιακή διαταραχή όπου διάφορα γονίδια επηρεάζουν την έκβαση της νόσου. Το γονίδιο της COMT είναι ένα από τα πιο καθοριστικά στην εξέλιξη της νόσου. Αν και το νευροβιολογικό υπόβαθρο της ασθένειας διερευνάται, υπάρχουν ορισμένες υποθέσεις που μπορούν να εξηγήσουν την παθοφυσιολογία. Η υπόθεση NMDA είναι η πιο κοινή θεωρία που περιγράφει την αιτιολογία της ασθένειας. Πρόσφατα, τα νευρογλοιακά κύτταρα του ανοσοποιητικού συστήματος συσχετίστηκαν με την παθοφυσιολογία της νόσου. Στην πορεία των χρόνων, Η χορήγηση φαρμακευτικών θεραπειών, αντιψυχωσικά φάρμακα 1^{ης} και 2^{ης} γενιάς, προσπάθησε να βελτιώσει τα κλινικά συμπτώματα των ασθενών. Ωστόσο, ορισμένα από τα συμπτώματα δεν υποχωρούσαν, και χωρίς να βελτιώνουν σημαντικά την καθημερινή ζωή του ατόμου. Πρόσφατες μελέτες έχουν δείξει ότι οι τεχνικές νευροαποκατάστασης και γνωστικής εξάσκησης προσφέρουν όχι μόνο κλινική βελτίωση του ατόμου αλλά τροποποιούν και το νευροβιολογικό υπόβαθρο. Στις μέρες μας οι γνωστικές θεραπείες είναι ευρέως γνωστές, όπως η Γνωσιακή Θεραπεία Αποκατάστασης, το RehaCOM, και η Γνωσιακή Συμπεριφορική Εκπαίδευση. Μελέτες νευροαπεικόνισης έχουν δείξει ότι η γνωστική αποκατάσταση αναδιοργανώνει τη δομή του εγκεφάλου, βελτιώνοντας τις γνωστικές λειτουργίες, την καθημερινή και κοινωνική ζωή του ατόμου.

Λέξεις-κλειδιά: σχιζοφρένεια, νευροβιολογία, νευροαποκατάσταση, γνωστικός

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1. Abbreviations

Abbreviations	
A	
AMPA	a-amino-3-hydroxy-5-methyl-4-isoxazoleprprionic acid
ARMS	At-risk-mental-state
B	
BVMT	Brief Visuospatial Memory Test
C	
CAT	Cognitive Adoption Training
CBT	Cognitive Behaviour Training
CET	Cognitive Enhancement Therapy
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
CPT	Continuous Performance Test
CRT	Cognitive Remediation
D	
dACC	Dorsal Anterior Cingulate Cortex
DISC	Disrupted-In-Schizophrenia
dLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
F	
FA	Fractional Anisotropy
FFA	Fusiform Face Area
FGAs	First-generation Antipsychotic
H	
HVLT	Hopkins Verbal Learning Test
I	

IFG	Inferior Frontal Gyrus
ILF	Inferior Longitudinal Fasciculus
IPL	Inferior Parietal Lobule
G	
GWAS	Genome-Wide Association Study
M	
MATRICES	Measurement and Treatment Research to Improve Cognition In Schizophrenia
Mg	Magnesium
Met	Methionine
MHC	Major Histocompatibility Complex
MPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
N	
NMDA	N-methyl-D-aspartic acid
P	
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PRS	Polymorphism Risk Score
R	
RECOS	Cognitive Remediation Program For Schizophrenia and other Related Disorders
RMET	Reading the Mind in the Eyes Test
S	
SCET	Cognition Enhancement Training
SCIT	Social Cognition and Interaction Training
SCST	Social Cognitive Skills Training
SGAs	Second-generation Antipsychotic
SLF	Superior Longitudinal Fasciculus
SNP	Single Nucleotide Polymorphism
SST	Social Skill Training

STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
SZ	Schizophrenia
T	
ToM	Theory of Mind
V	
Val	Valine
vIPFC	Ventrolateral prefrontal cortex
W	
WCST	Wisconsin Card Sorting Test
WM	Working Memory

Table 1: Table of abbreviations referred to in the text.

2. Introduction

Schizophrenia (SZ) is a psychiatric disorder that has a profound impact on the individual and the society. SZ has a prevalence of about 1 percent in all cultures and men and women are inflicted by the disease at a ratio of 1:4:1 with different distributions of age at onset.

Men typically present with the disease in their late teenage years or early 20s, whereas women get ill in their late 20s or early 30s (1). Males are affected by SZ more frequently and more severely than females (2). Moreover, individuals with SZ tend to have a reduced life expectancy, 15 years less than healthy ones (3). Indeed, patients have a higher risk for suicide. The onset of SZ occurs before the first psychotic episode and often it manifests itself in early adolescence. The period between the first sign of the disease and the onset of the first psychotic episode is called “prodrome” and may last up to 10 (4).

Schizophrenia is characterized by positive and negative symptoms. Positive symptoms are considered delusions and hallucinations and represent distortions of reality, for which the patients are not aware of, or else, do not have insight (4). Negative symptoms include states with loss of normal function, loss of behaviors, and motivation such as anhedonia (5,6), asociality, affective flattening, alogia, and diminished initiative and energy (4). Positive symptoms tend to relapse and remit, even though some patients experience residual long-term psychotic symptoms. On the other hand, negative symptoms tend to be chronic and are associated with long-term effects on social function. Diagnosis of SZ, by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), requires the presence of at least two of these symptoms -the one being necessarily delusions or hallucinations, or disorganized thought-, along with a decline in functioning, lasting at least six months, and ensuring that these symptoms cannot be better explained by another medical disease, substance use or another psychiatric disorder. Antipsychotic treatment is frequently effective for positive symptoms, however, for negative symptoms, efficacy is unclear, because of different pathophysiological mechanisms (6).

A core aspect of the symptomatology of schizophrenia is the cognitive impairment. Deficits in cognitive function are more severe than the other symptoms of SZ (7). Manifestation of cognitive deficits begins before the onset of the disease and years

before the clinical diagnosis (8,9) and persists across the entire course (10). These abnormalities are observed in different cognitive domains, such as working memory, language function, executive function episodic memory, verbal memory, processing speed, and attention (11,12). They are present in 62-98% of patients with SZ.

2.1.Genetic Background

Schizophrenia has been found to be a polygenic disorder, that is, multiple genes contribute to its etiology. Moreover, a complex of environmental and developmental risk factors play an important role in the manifestation of SZ (1). SZ can be passed to the offspring, with a greater risk of occurrence among monozygotic twins than in first-degree relatives (13). More specifically, the risk for first-degree relatives is about 10% and just 3% for second-degree relatives. Dizygotic twins show a lower risk at 12% to 14%, whereas the risk is 48% for one monozygotic twin when the other has the disease (14,15).

Genetic factors play a major role in the emergence of schizophrenia, and heritability of the disease is about 75%. GWAS studies have identified genes and alleles associated with the disorder's risk. However many genes associated with schizophrenia overlap with those that are linked to neurodevelopmental diseases (16).

Disrupted-In-Schizophrenia-1 (DISC1) gene is associated with cortical layering, hippocampal formation, and neuronal migration (17), as well as synaptic plasticity. Duplications and deletions on this genetic variant are some of the changes that are present in 2% to 3% of schizophrenia cases. Particularly, a deletion on chromosome 22q11.2 is linked to the development of SZ at 30% to 40% risk, and it is known as velocardiofacial syndrome and DiGeorge (18). This syndrome is responsible for many disorders including SZ. Individuals with 22q11.2 syndrome manifest SZ at a rate of one-third. They present cognitive deficits and declined verbal IQ, mainly in childhood and adolescence (18).

Furthermore, catechol-O-methyltransferase (COMT) is an enzyme encoded by a gene located on chromosome 22q11. COMT is responsible for metabolizing catecholamines, dopamine, norepinephrine, and epinephrine. The main role of COMT is the clearance of dopamine from synapses (19,20). The activity of the enzyme is located in the prefrontal cortex (PFC), which is the region of the brain related to cognitive and executive functions and emotional regulation. Abnormalities in the enzyme activity,

driven by polymorphisms of the COMT gene, contribute to the pathophysiology of schizophrenia (21). The most studied single nucleotide polymorphism (SNP) is the Val158Met, where a substitution of valine (Val) with methionine (Met) occurs at position 158 of the COMT enzyme (22). The number of alleles of Val or Met on an individual's genome is associated with susceptibility to schizophrenia. More especially, a Val/Val carrier presents a decreased level of dopamine at PFC and shows increased risk for the illness whereas a Met/Met homozygote has lower susceptibility for SZ. So, the regulation of dopamine in the PFC is linked to the development of the disorder (21,22). Additionally, Val/Val individuals present cognitive deficits, particularly in working memory, while Met/Met carriers are prone to positive symptoms (22). On the other hand, the Met allele seems to be associated with chronic course and more severe symptoms (23,24) – that is, - this allele is linked to treatment resistance (25) despite its favorable influence on cognitive performance. The Val allele is associated with milder symptoms of the disorder (24).

Polygenic risk scores (PRS) define the risk of all genes in a given individual. PRS is referred to as a tool to predict genetic patterns into schizophrenia. Single nucleotide polymorphisms (SNPs) are genetic variants that vary among healthy individuals and patients with schizophrenia and are associated with the development of the disorder. GWAS studies have shown that, in the general population, schizophrenia PRS revealed deficits in social cognition and communication, and dysfunction in emotion and behavior in childhood (26). An additional factor that influences the development of schizophrenia is the advanced paternal age. This leads to a deterioration in epigenetic function, which regulates the appropriate role of DNA, genes, and molecules. As a consequence, the brain's neuroplasticity is compromised (26).

The biological and neurodevelopment profile of SZ are unclear, but some hypotheses could explain the molecular and genetic background of the disorder. Circuits affected are associated with genetic and cortical pathways (27). Dysregulation of dopamine and glutamate neurotransmission seems to be implicated in schizophrenia's pathophysiology. More specifically, the dopamine hypothesis is associated with positive psychotic symptoms, but it seems that glutamatergic dysfunction contributes to negative symptoms and cognitive abnormalities (28). Recent genetic studies have identified genes that play a role in brain and synaptic plasticity, in the immune system,

and finally, in functional activity (27). There are genes that contribute to neuroinflammation and oxidative stress (28).

2.1.1. Neurons & neurotransmitter circuits

The pathophysiology of schizophrenia is associated with abnormal glutamatergic transmission. N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) are two of the genes that participate in neuroplasticity (28). AMPA receptors are composed of four subunits, Glu1 to Glu4, which differ in their expression and are encoded by GRIA1 to GRIA4 genes, respectively (29). The GluA2 subunit is coded by the GRIA2 gene, which is located in the brain cortex and has an intense association with SZ (30). AMPA receptors contribute to neuronal maturation, memory formation, and synaptogenesis (31). Patients with schizophrenia present modified AMPA receptors both at the proteomic level and the synaptic level (32,33). AMPA receptors are associated with the cellular basis of cognitive functions, learning, and memory (34). AMPA and NMDA receptors are in interaction. NMDA receptors are composed of GluN1 subunit and GluN2 and/or GluN3 subunit. The role of these receptors is to improve glutamatergic transmission and to participate in memory and learning (35). At normal conditions, NMDARs function is inhibited by Magnesium (Mg^{2+}) at extracellular space. Dysfunction of AMPA receptors affects the normal function of NMDA receptors (29,33), because AMPAR allows NMDAR to be permeable, removing Mg^{2+} blockade (36).

2.1.2. Neurotransmitter system and schizophrenia

The neurotransmitter system associated with schizophrenia is the dopamine system and the “dopamine hypothesis” is the most common theory in the disorder. The “dopamine hypothesis” is referred to reduced dopamine function in brain regions. Imaging studies have shown that the density of dopamine receptors D2 is influenced in schizophrenia and more specifically, it is observed that increased levels in the striatum, a region associated with associative information processing (37). The hypofunction of the dopaminergic state in the frontal cortex and ventral tegmental area (VTA) has been associated with negative symptoms of schizophrenia, such as apathy, and alogia (38–40). On the other side, the hyperactivity of the dopaminergic system, mainly in the nucleus accumbens and limbic cortex, seems to provoke positive symptoms (39,40). Structural changes have been observed in hippocampus provoking decreased function in schizophrenic patients (41), while recent literature has shown increased activity in

hippocampal subfields (42). Studies, such as PET and contrast MRI where the blood flow and volume are measured respectively, demonstrate increased levels of regional cerebral (41).

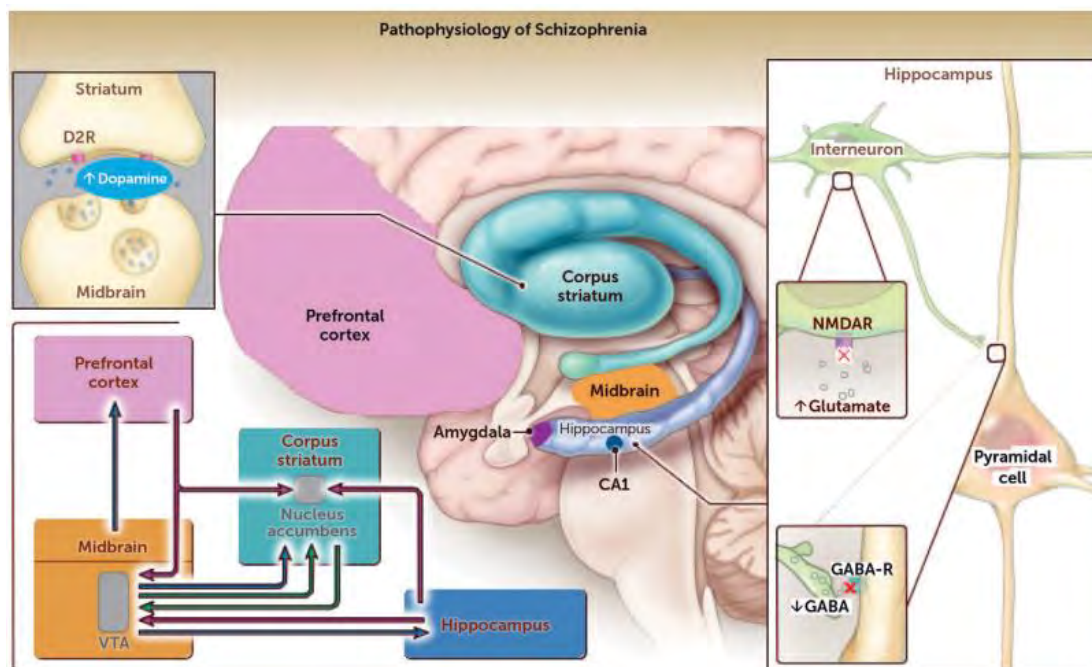


Figure 1: A diagram depicting the pathophysiological model in schizophrenia through dopamine and glutamate hypotheses. A sagittal view of the brain through the midline depicts the hippocampus, midbrain, corpus striatum, and prefrontal cortex, all regions that are implicated in the pathophysiology of psychotic symptoms in schizophrenia. In the pathophysiology of the disorder, neurotransmitters of dopamine (blue arrows), glutamate (purple arrows), and g-aminobutyric acid (green arrows) play a role. The symptoms of schizophrenia are believed to arise from the dysregulation of pyramidal cells that release glutamate onto cells located in and projecting from the CA1 region of the hippocampus caused by deficits in GABAergic interneurons and hypofunctioning N-methyl-D-aspartate glutamate receptors (NMDARs) (the red X denotes reduced neurotransmitter and receptor hypofunction). Shown in the enlargement of the hippocampus at right is a glutamate-expressing pyramidal cell and a GABA interneuron. There is underactivation of diminished numbers of interneurons because of hypofunctioning NMDARs. Also shown is the interneuron axon forming a synapse with the apical dendrite of the pyramidal cell. Because of its understimulation, due to a hypofunctioning NMDAR, less GABA is released by the interneuron, which in turn disinhibits the pyramidal cell and causes it to release more glutamate from hippocampal projections to the midbrain (ventral tegmental area, VTA) and the corpus striatum. Hippocampal overactivity augments dopamine release in the striatum either directly (at the level of the nucleus accumbens) or by stimulation of midbrain dopamine neurons, which project to the nucleus

accumbens and the prefrontal cortex. Midbrain dopamine neurons further promulgate the dysregulation of dopamine and glutamate through a projection back to the hippocampus. D2R denotes D2 receptor (39)

2.1.3. Glial cells

Alterations in the glia are observed in the pathophysiology of schizophrenia. Glial cells are distinguished into four types, oligodendrocytes, astrocytes, polydendrocytes, known as macroglia, and microglia (43). Microglia are the main innate immune effector cells of the Central Nervous System (CNS) and are associated with immune surveillance and defense against infections and injuries (44). The microglial cells seem to contribute to neuroinflammatory processes and synaptic dysfunctions. Many CNS disorders, such as schizophrenia, are characterized by microglial-cell activation (45). Studying these cells may reveal the mechanisms of neural degeneration and repair (43). Oligodendrocytes are the principal myelinating cells of the CNS (46). Increased levels of myelination in oligodendrocytes seem to be associated with the efficiency of new skills and abilities. Nonetheless, low levels of myelin lead to non-reversible myelination changes in the medial prefrontal cortex, provoking social and cognitive deficits (47). A reason why occurs apomyelination is the neuronal NMDA receptor inhibition (46). Studies have shown that deficits in attention, working memory, and cognitive functions are a result of decreased density of astrocytes in the prefrontal cortex (28,43). Schizophrenia disorder is associated with deficits in white matter integrity and myelination. Decreased volume in white matter in patients' brains is associated with the progression of negative symptoms.

Understanding the role of glial cell in the pathophysiology of schizophrenia is a relatively recent development in the field of psychiatric research. While much progress has been made, further investigations are necessary to elucidate the precise mechanisms by which glial cells contribute to the disorder.

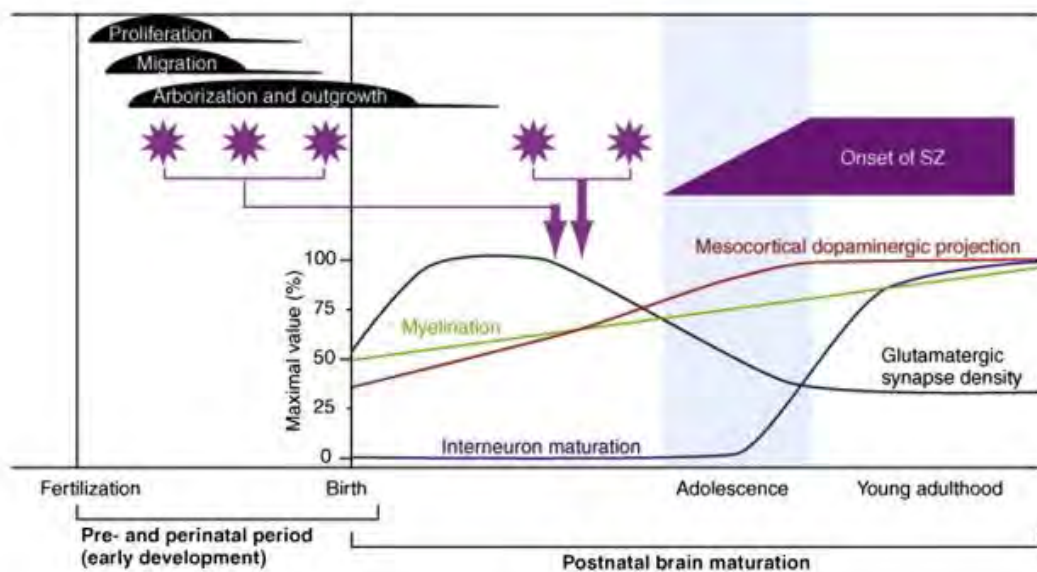


Figure 2: The manifestation of schizophrenia is observed in late adolescence or early adulthood. Factors that contribute to the progress are both neurodevelopmental and genetic. At the onset of schizophrenia in early development (imaging at the left of the diagram) and later in adolescence period (imaging at the right side of the diagram), it is observed neurodevelopmental deficits in progenitor cell proliferation, neuronal migration, dendritic arborization, and outgrowth. Such insults could lead to an overall disturbance of proper postnatal brain maturation, which includes maturation of interneurons and dopaminergic projections, pruning of glutamate synapses, and myelination (48)

Schizophrenia is distinguished in stages based on its progression. These stages are 1) the prodromal phase, 2) the onset of the first episode, 3) chronic SZ, and 4) individuals taking anti-psychotic medications (4). Although it is difficult to understand how SZ evolves, each stage and phase of the illness is characterized by different abnormalities both in the brain's function and structure (4).

2.2.Prodromal and premorbid phase

The prodromal phase or pre-psychotic phase of schizophrenia is a stage, where subtle changes in cognitive deficits (emotions, behavior, thoughts) are observed (49) leading to functioning abnormalities in everyday life. The duration of this phase is not specific, but it varies between some months or even years before the onset (50). The duration of this stage is about 52 weeks in people with SZ and psychotic symptoms are shown earlier than cognitive impairment in perception, belief, and thoughts (4). The age at which deficits are invisible either through neuroimaging or clinically varies. There is

evidence that these changes happen as early as prenatally (51). It has been observed that structural cranial changes in schizophrenia present after the age of six years. At this age, it is seem to have been completed the development of the cranium (51). Studying on prodromal phase, it could be predicted that schizophrenia's progression and who is going to manifest the illness (52). The prodromal phase is observed in 80-90% of schizophrenic patients (3). Indeed, children who have an affected parent show a higher risk of developing the illness and specifically, so early as the pre-teen years.

Prodromal period is characterized by sub-threshold features followed by psychotic symptoms (53). There is a state called "at-risk-mental-state" (ARMS), which is a situation characterized by cognitive impairments (54), lower social interaction and functioning. Moreover, the ARMS may outline the progression of illness and how it affects the patient.

Longitudinal studies revealed that in the prodromal phase neurodevelopmental abnormalities start (55). It is observed decreased volume of grey matter in frontal and temporal regions, specifically in right superior temporal gyrus in ongoing (54,56) patients and in left precuneus, bilateral (para)hippocampal areas and bilateral anterior cingulate (57). These regions contribute to normal function of attention and verbal memory. Reduced activation in the prefrontal cortex is observed in this phase and is associated with deficits in cognitive functions (56). Indeed, all the above impairments are evidence for the onset of schizophrenia. Furthermore, an MRI study demonstrated that decreased connectivity in white matter is observed in schizophrenic patients during the prodromal phase and provokes abnormalities in cognition (58).

2.3. Onset of the first episode

Manifestation of the first episode is the result of brain changes years ago. These patients are defined as being within 3 years of the onset of the first episode of psychosis (59). The first episode could appear either early on adolescence or late on adulthood. On that age, developmental changes are observed in the superior longitudinal fasciculus (SLF), corticospinal and corpus callosum. Moreover, volume of white matter is increased during that period of life and above changes are associated with the ongoing motor and language development (60,61). Investigating adolescence and early adulthood models, research revealed abnormalities in white matter organization. More specifically, fractional anisotropy studies associated with structural integrity of the tissues (62) was

increased in the left inferior longitudinal fasciculus (ILF) in adolescent patients (63,64). However, a recent study is claimed that evidences for the progression of white matter's volume are not important (54). Furthermore, the onset of schizophrenia is associated with grey matter deficits and the default mode network (DMN), in specific the prefrontal regions and the temporal lobe. In patients, it observed lower grey matter volume located to the insula, superior temporal gyrus and the anterior gyrus compared to healthy individuals (54). However, the exact role and how the activity of DMN is affected is not clear. Some studies support increased activation of DMN but others report decreased connectivity in the DMN (65,66). Moreover, it is showed that grey matter loss, throughout the brain keep increasing after the first episode (51,67). Indicatively, studies suggest dysfunction of oligodendrocytes as a cause to reduction of white matter in the superior frontal cortex and the bilateral hippocampus (54).

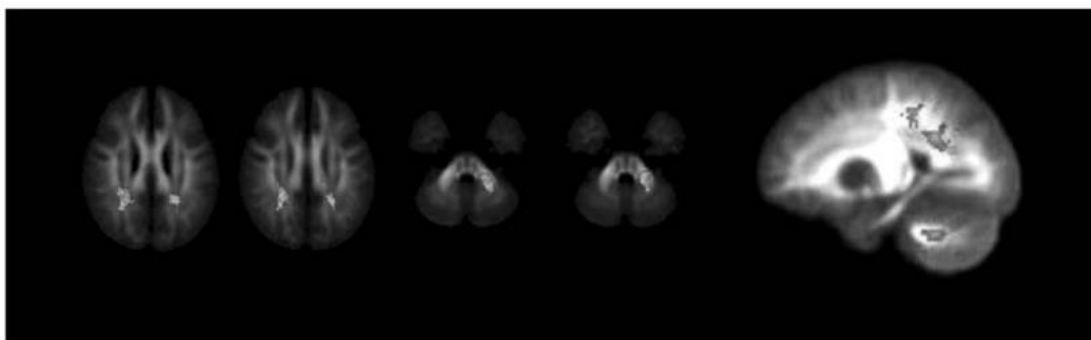


Figure 3: Diffusion Tensor Imaging studies show brain structure changes between patients with early onset schizophrenia and healthy individuals. Reduced FA is observed on the parietal and left cerebellar white matter regions (61)

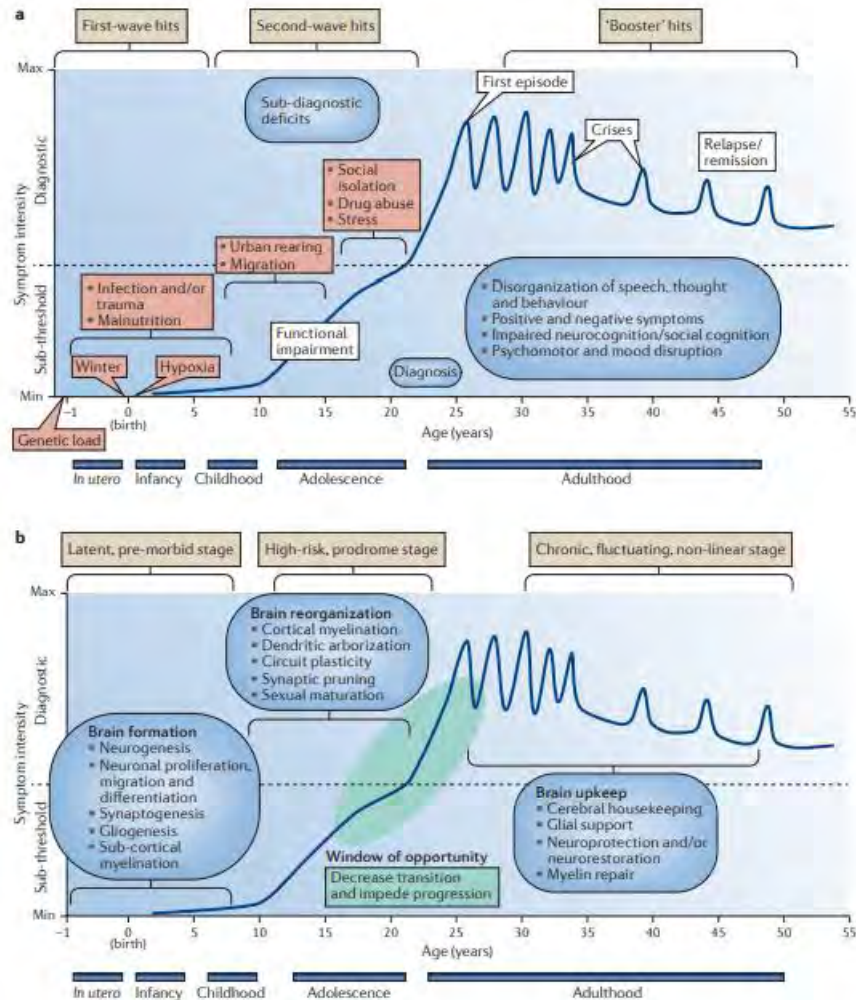
2.4.Chronic schizophrenia

In a patient who suffers by schizophrenia for years, it is observed limited ability of emotion and thinking (68). An individual who manifests the first episode of schizophrenia is called, from now on, a patient with schizophrenia. So, the disorder and its symptoms are developing. Brain structure present abnormalities in several regions, such as cerebral grey matter, where volume is lower in these patients than healthy individuals (69). Furthermore, Specifically, this density's reduction is detected mainly, in left hippocampus, right supramarginal gyrus, thalamus, temporal, occipitotemporal, precuneus and insular gyri bilaterally detected reduced density in patients (69). Furthermore, diffusion tensor imaging (DTI) studies reveal evidence about brain's abnormalities. According to Oestereich et al., 2017, it is observed reduced fractional

anisotropy (FA) in chronic patients but lesser deficits in extracellular volume (70). Indeed, research supports that white matter tissue volume in chronic schizophrenia is more localized (71). Furthermore, reduced FA is observed in specific regions which are the anterior limb of the internal capsule associated with episodic and declarative memory (72,73), the posterior thalamic radiation linked to distorted self-perception (74).

2.5. Intaking anti-psychotic medications

Schizophrenia's therapy is characterized by intaking antipsychotic drugs, which are categorized to 1st generation-typical and 2nd generation-atypical drugs. This categorization is defined by side effects and symptoms that are provoked to patients. As far as intaking medication, it is difficult to distinguish its effect on brain changes because patients receive medication at some point during their illness. However, there is evidence that second-generation treatment is associated with lower volume enlargement of the lateral ventricle than taking first-generation antipsychotic drugs (69,75).



(53)

Figure 4: Stages of schizophrenia. The picture above shows the onset of the illness and the evolution of schizophrenia through the years. Diagram a depicts how impairments and functional changes occur and how they evolve, what factors affect and contribute to symptomatology of the disorder. Diagram b depicts brain structure changes through the stages and when and how brain reorganization starts.

3. Cognitive deficits in schizophrenia

Schizophrenia is characterized by deterioration in some deficits, and functional and cognitive abnormalities, which are present and visible throughout the duration of illness. Cognitive impairment is intensively associated with functional aspects of the illness (76). Even if DSM-IV does not include as a requirement the cognitive impairment at diagnosis of schizophrenia, the main fields affected are verbal memory and fluency, processing speed, working memory, attention, reasoning and problem-solving (77,78), visual learning, and memory. Indeed, a recent umbrella review included 15 articles that revealed to what extent each domain is affected (79). More

specifically, memory is influenced at 34%, executive function at 27%, verbal fluency at 13%, processing speed at 13%, too and social cognition at 13% (79). The establishment of cognitive deficits occurs before the onset of psychotic symptoms (80). It is important to mention that scientists tried to include cognitive and functional deficits as a criterion on DSM-5, which provokes socioeconomic problems (78). However, this criterion is not included in DSM-5. Structural and functional deficits are dependent on patients' characteristics. Brain abnormalities are responsible for different intense impairments. There are some patients' characteristics that affect the course of the disorder. A few of them are, for example, the stage, on which individual is, the age, or other underlying diseases. According to Rajji et al., 2013, it seems that schizophrenic patients and healthy individuals didn't show different levels of cognitive decrease (81), and cognitive impairments occur at the same rate in both groups. However, other studies supported the opposite opinion of people showing cognitive declines in later adulthood (82). A study states that generally cognitive dysfunction is pre-existed in all age groups (49). However, neuropsychological tests lead to the result that cognitive changes associated with aging are more severe in patients than in healthy individuals. In particular, individuals with SZ succeed a score with on average between one and two standard deviations below compared to healthy ones in the same age group (82). Furthermore, an umbrella review studied many articles and concluded that several factors contribute to cognitive deficits in the disorder (79). The factors could be substance use, insight, childhood trauma, and aggressive behavior.

Cognitive deficits may be present before the onset of psychosis and remain stable or increase with the disease progression (83,84). Cognitive decline is observed in two different cognitive domains. One of them is neurocognition and the second one is social cognition (83). Neurocognition in schizophrenia is about brain functions that affect indirectly activities of daily living. A few of them are working memory, which has been studied the most, as visual, and verbal learning and memory. On the other hand, social cognition is associated with the Theory of Mind (ToM). The specific function presents an individual's ability to emotion perception, to understand facial expressions and the intentions and behaviors of others (83,85). Moreover, social cognition is categorized into four domains: emotion perception, social perception, theory of mind (ToM) (84,85). Social cognition and neurocognition are interrelated. There are four brain areas that participate in cognition and they are the fusiform gyrus (FG), superior temporal

sulcus (STS), the amygdala and the medial prefrontal cortex (MPFC) (85). FG is associated with facial identity while STS is linked to emotion processing and facial expressions. The amygdala is associated with negative emotions and MPFC with ToM.

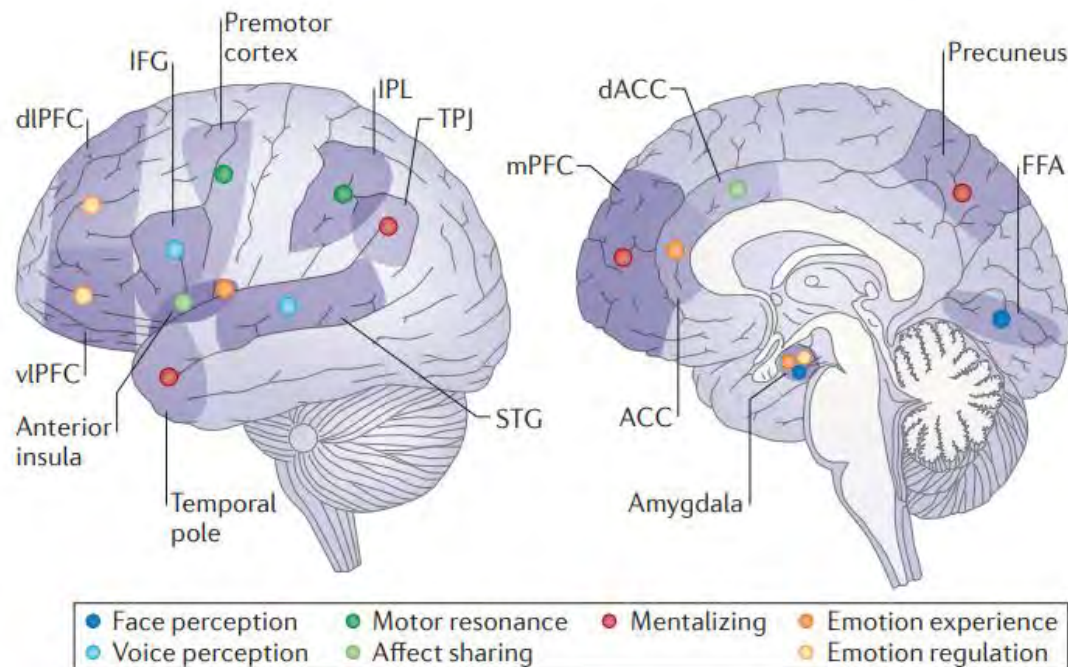


Figure 5: Here, it is depicted brain regions associated with social processes. Social cognition functions are overlapped and so, there are different brain regions participated in social processes. More specifically, activation of the amygdala and fusiform face area (FFA) is linked to face perception and activation of the superior temporal gyrus (STG) and inferior frontal gyrus (IFG) is associated with voice perception. Motor resonance functions activate the inferior parietal lobule (IPL) and premotor cortex, and affect sharing activates the dorsal anterior cingulate cortex (dACC) and anterior insula. Emotion experience activates the amygdala, anterior hippocampus (not shown), ACC and anterior insula, and emotion regulation activates brain regions including the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC) and amygdala. The anterior insula is involved in both affect sharing and emotion experience, and the amygdala is involved in face perception, emotion experience and emotion regulation. These regions represent a part of brain regions linked to social cognitive processes (86)

3.1.Cognitive deficits and neuroimaging

A cross-sectional study revealed cognitive impairment across stages of the disease (84). Even though cognitive performance is differentiated between patients and controls in the chronic schizophrenic individuals (84), it is yet, unclear in which stage of illness

impairment in cognition shows. Imaging studies underlie a relationship between functional changes and brain abnormalities. This relationship should discriminate the progress of cognitive deficits across the stage of SZ. As known, SZ is a neurodevelopmental disease, where abnormalities are manifested before the onset of SZ and changes are caused through the time. Indeed, social cognition and neurocognition are defined by different neural circuits on brain regions. As the disease presents cognitive deficits it is expected abnormal function of the corresponding regions. The frontal cortex and the temporoparietal regions are affected and associated with cognitive tasks (87,88), while the thalamus and anterior cingulate are influenced by performing attention tests (89,90).

Cognitive impairment shows an increased progression as schizophrenia ongoing. Firstly, people with first episode of schizophrenia manifest deficits in various cognitive domains (91,92) presenting worse performance than other psychotic disorders. Moreover, the cognition functions most affected seem to be the working memory, verbal memory, and processing speed. It should be underlined that cognition impairment is present to individuals non-taking a medication (79).

3.2. Verbal memory

Verbal memory is an additional cognition function impaired in schizophrenia. Verbal memory is associated with the ability to remember words, or linguistic information and the ability to store and recall information presented verbally. Verbal memory is categorized into 1) short-term, 2) long-term, 3) immediate and 4) working memory. It is known that the hippocampus is a brain structure associated with memory. So, there are imaging studies that reveal abnormalities on hippocampal and parahippocampal regions in schizophrenic patients. More specifically, it observed cortical thinning in main brain areas associated with verbal memory, namely the hippocampus, the parahippocampal gyrus and frontal lobes (93). However, other studies showed a similar cortical thickness between healthy controls and patients (94).

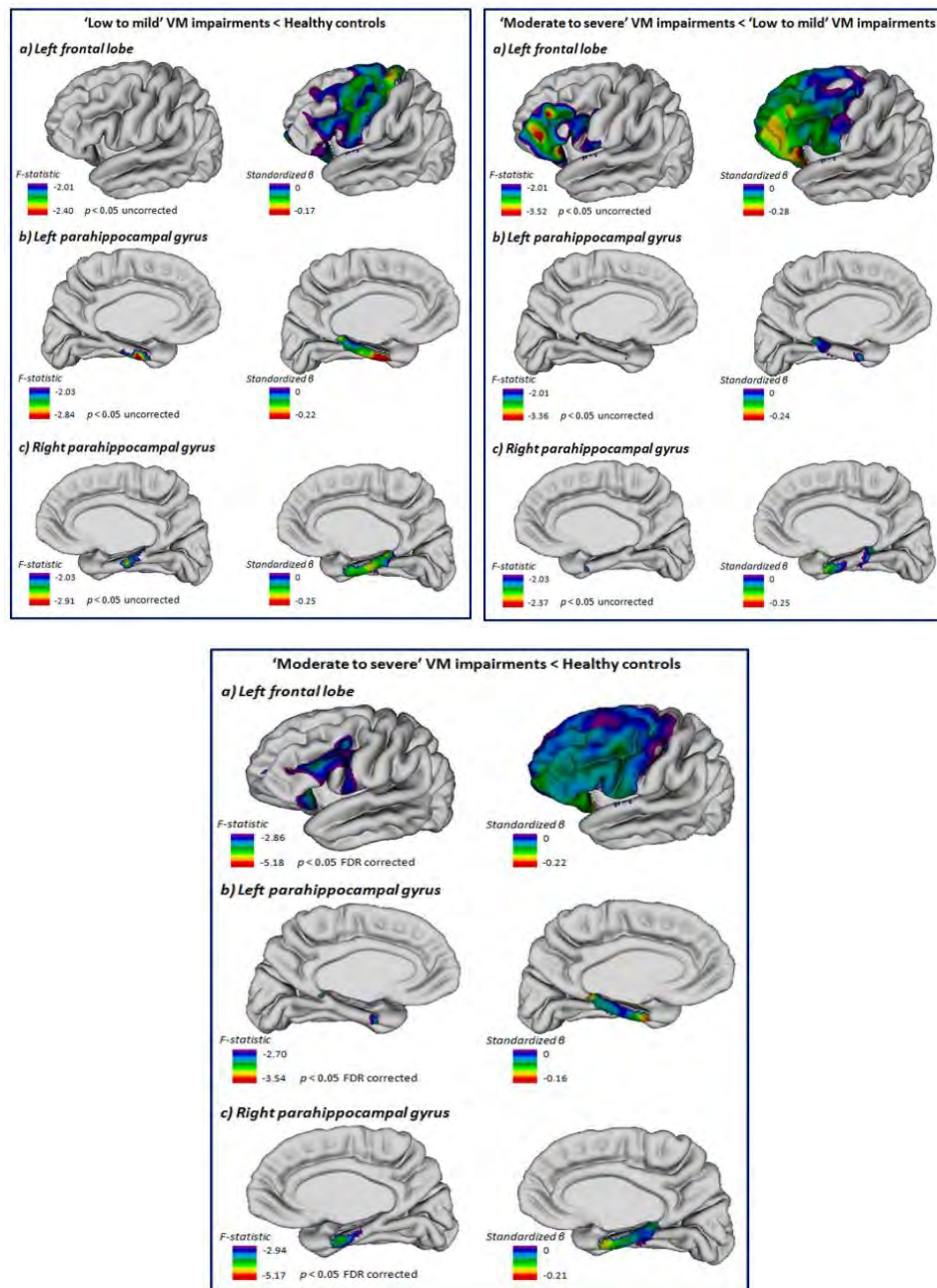


Figure 6: The statistical maps above depict cortical thickness changes on brain's patients and healthy ones, which are associated with verbal memory. More specifically, it is showed the differences between "low to mild" WM vs controls, "moderate to severe" WM vs "low to mild" WM and "moderate to severe" WM vs healthy ones (93)

3.3. Working Memory

Working memory (WM) is associated with temporary storage, manipulation of information for cognitive tasks (76,95). It is responsible for daily functioning, problem-solving, planning. Dysfunction of working memory is presented in increased level in schizophrenia. Schizophrenic patients show difficulties in all the above cognitive

abilities. Functional MRI findings show that the brain region responsible for working memory tasks, is dorsolateral prefrontal cortex (DLPFC) (95,96) and the PFC. The PFC is associated with executive functions which are underperforming in schizophrenia and DLPFC hypofunction is presented in patients compared to healthy ones and is associated with reduced working memory. Furthermore, neuroimaging studies have shown that a pivotal role on understanding the dysfunction of working memory in schizophrenia is the interaction among neuronal circuits in different brain regions (88). Structural and functional abnormalities are significant factors in clinical picture of schizophrenia. Additionally, schizophrenic show off reduced grey matter volume both on PFC and DLPFC, leading to hypofunction of cognitive tasks including working memory. Deficits in working memory is, also a result of neurochemical processing. PET imaging has revealed that dopaminergic circuits in striatum are hyperactivated and so, working memory is disrupted and has revealed that hippocampus and parietal lobes play a crucial role in WM functions (97). Decreased performance is observed on attention, executive functions, decision-making tasks, too (97). The functional abnormalities significantly impact individuals' daily life.

Working memory is categorized to the verbal and the visual-spatial one depending on how individual receiving the information. Symptoms on the verbal working memory are intensive in schizophrenia. Several tests evaluate the extent of functional disability on each memory task.

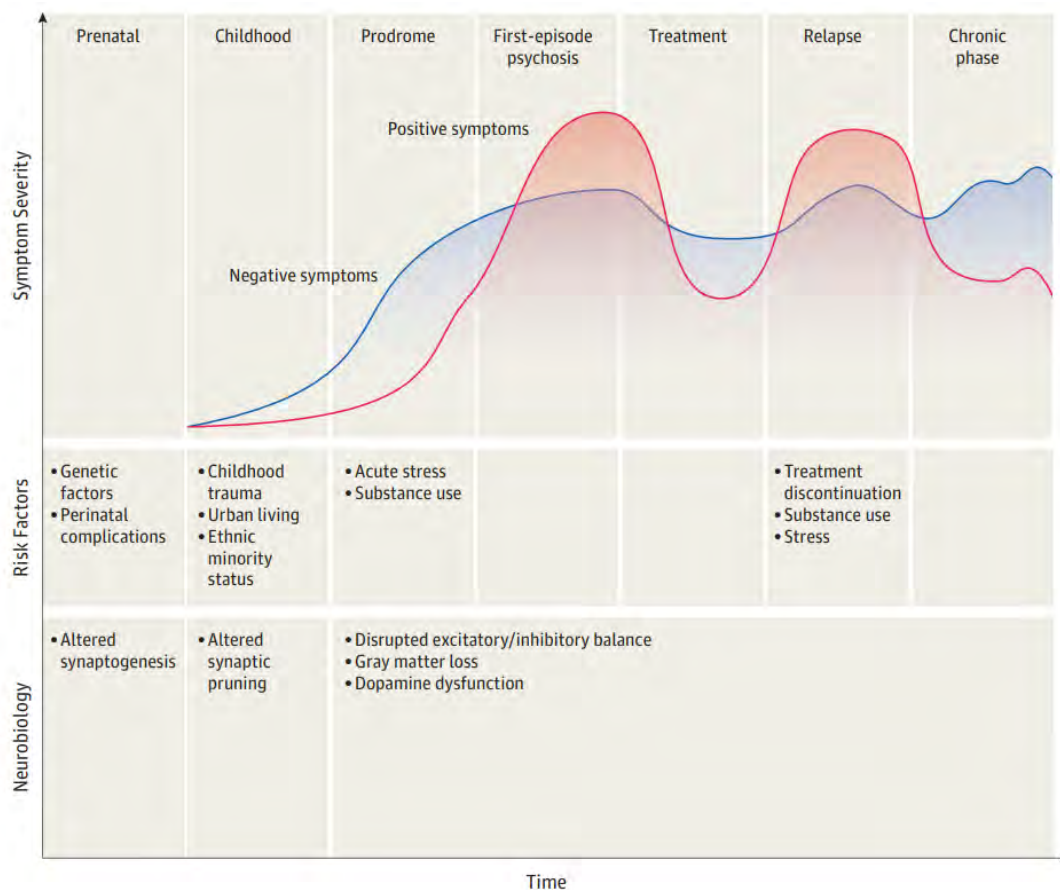


Figure 7: Diagram above depicts the molecular basis, the risk factors and, finally the clinical symptoms of schizophrenia. In prenatal and childhood period, several risk factors play a pivotal role, such as trauma, urban living, ethnic minority status, but genetic and biological factors associated with synapsis changes, contribute to manifestation of the disorder. Next, prodromal phase is associated with negative symptoms, where it occurs changes on volume of grey matter and dopamine function. Generally, it is depicted when symptoms are present in each stage.

3.4.Processing speed

Processing speed is the ability to process information efficiently and quickly, perceiving, recognizing, and responding to stimuli. In schizophrenia, patients exhibit deficits in processing speed leading to executive function impairments. Deficits in this cognitive domain manifest as reduced efficiency in information processing, delayed reaction times and impaired attentional resources. Impairments of processing speed have impacts on other cognitive domains, working memory and executive functions. Slower processing speed in patients reduces the ability to update and access information in working memory efficiently, influences cognitive flexibility provoking difficulty switching between cognitive tasks. Processing speed deficits in schizophrenia are

associated with brain's structure abnormalities. MRI studies have shown that reduced gray matter volume in the prefrontal cortex, anterior cingulate cortex and parietal regions is linked to the severity of processing speed deficits (98,99). Abnormalities in these brain regions are associated with other cognitive function, for instance, working memory and attention (100). Furthermore, DTI studies have revealed abnormalities in white matter volume in frontal and parietal lobes in schizophrenia, which are related to processing speed deficits (101,102). White matter plays a pivotal role on brain because the myelinated nerve fibers facilitate communication between brain regions. Moreover, the hippocampus is associated with the processing speed and in particularly, reduced hippocampal volume provokes slower processing speed in schizophrenia (103).

3.5.Negative symptoms and social cognition

Deficits in schizophrenia are associated with social cognition in a significant level. Social cognition influences mental processes, perceiving, responding to thoughts, emotions of others. Researchers studied the cognitive performance in SZ throughout neuropsychological tests and methodologies and study exhibited that there are three subtypes of cognitive performance in patients, which are depends on individuals' score on cognitive tests (77). The first subtype is characterized by less-impaired cognitive performance, the second one by intermediated impaired cognition and the last one shows an absolutely impairment. Cognitive impairment and negative symptoms seem to be in interaction and that is a reason why cognitive subtyping contribute to identify underlying profiles of illness (47). Theory of Mind is intensively associated with schizophrenia's abnormalities and social interaction. Decrease of this ability contributes to social isolation (104,105). More specifically, individuals present difficulties in functional systems, impairments in emotion recognition and usually struggle to be faced with the disappointed social footprint(outcome) (106). Furthermore, attributional style is a condition, with schizophrenic are deal, leading to paranoid thoughts, lower self-esteem and finally, to disturbed interpersonal relationships (107). Social perception is included in cognition performance and play a significant role in social cues and contexts. However, impairments in this field contribute to decreased sociality, as a result of misunderstanding of body language, facial expressions (84). Simultaneously, it could be said that schizophrenic patients are disabled to realize others' emotional situation. This disability could explain why

patients aren't acceptable by society and why it would be difficult to adapt in society (108).

Studies about structural and functional abnormalities in schizophrenia contribute to the better understanding of the neurobiological background of the illness. Neuroimaging studies are important for the development of targeted interventions and treatment for schizophrenia.

4. Diagnosis

Diagnosis of schizophrenia is based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Schizophrenia is discriminated among other psychotic disorder through some criteria. An individual should present the following six criteria. Criteria are (15,109):

- A. At least two of the following are present and at least for an one-month period.
 - ✚ Delusions,
 - ✚ Hallucinations,
 - ✚ Disorganized speech,
 - ✚ Catatonic behavior and
 - ✚ Negative symptoms.
- B. Social dysfunction effecting one or more functions such as interpersonal relations, self-care for a major section since the onset of the illness.
- C. Duration. The symptoms of the illness insist for at least 6-months. A that period, one of the Criteria A should be present.
- D. Schizoaffective and major mood disorder exclusion
- E. General mood condition exclusion
- F. Relationship to Global Developmental Delay or autism spectrum disorder. If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (109).

4.1. Prevention and early intervention

Prevention and early intervention in schizophrenia plays an important role, contributing in diagnosis and improving the upcoming treatment (39). The early detection of symptoms is helpful because it is possible an effective intervention on them An early

prevention could not only inhibit the suffering of patients but increase the prognosis and quality of their lives (39). A timely intervention usually includes receiving antipsychotic drugs, psychotherapy, and psychosocial enhancement (110). The development and the establishing of an intervention treatment is difficult because of the limited knowledge about the targets on prodromal stages of illness (39). Indeed, it is observed that early symptoms are stabilized on the ongoing of the disorder and for this reason intervention methods are more effective intervening on the fluid symptoms of individuals (110). According to Jaaro-Peled et al., 2020, it is significant a completely understanding of genetic contribution in schizophrenia and the contribution of several factors to be predicted the risk of disorder's development (16). On the below diagram (Figure 2), it is depicted a prevention strategy. More specifically, a universal intervention is associated with the general population, searching public health factors that could lead to the development of schizophrenia. For example, infections that affect pregnant individuals, influenza, toxoplasma, contribute to illness's profile and development. This strategy could predict the infection and so, one third of schizophrenia's causes could be eliminated (111). Moreover, universal strategy could offer the ability to be prevented childhood abuse and trauma improving individuals' social life and decreasing mental disorders.

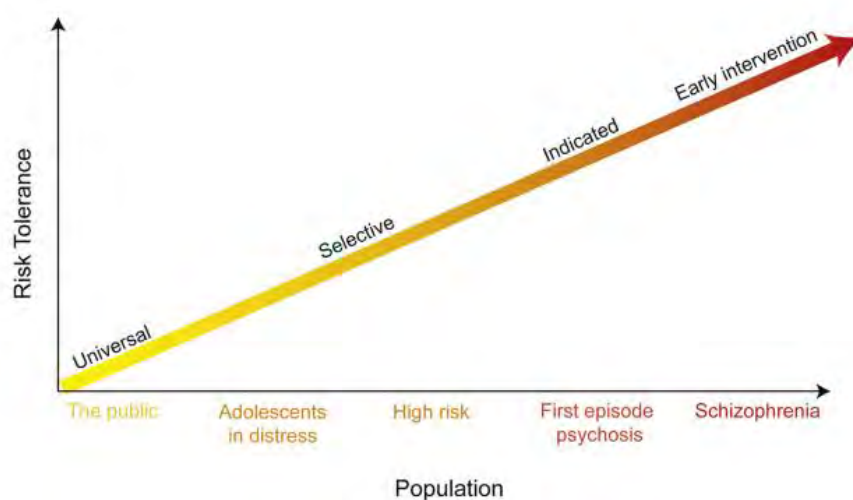


Figure 8: The diagram above depicts the risk that included in prevention strategies depending on the population group. As it is presented universal prevention strategies include the whole population, while as individuals show signs of psychosis, strategies should more specific and targeted (16)

However, limitations are that there aren't available sensitive and specific diagnostic criteria for pre-syndrome schizophrenia (39), so it isn't possible to be developed early detection and intervention models.

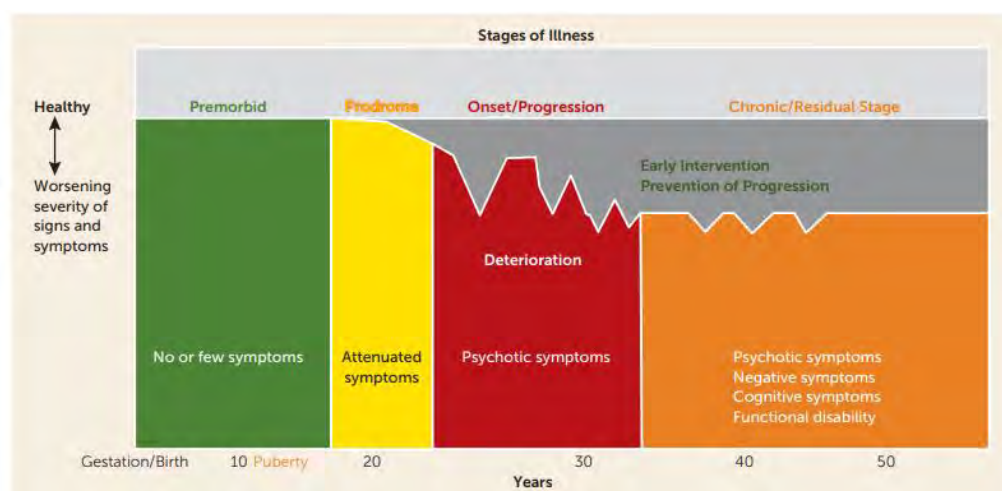


Figure 9: The picture above describes schematically the manifestation and progression of schizophrenia. It is presented the symptoms' worsening during over time and in the evolution of the stages of the disorder. The prevention of illness in the early stages is to prevent the progression of schizophrenia, ameliorate the symptoms and recurrences, so reducing the chronic effects (39)

4.2.Assessment of schizophrenia's cognition

The initial stage in the process of rehabilitation is a thorough and careful neuropsychological assessment. This will allow the identification of functional deficits, of potential strengths, and will make possible a conversation with the patient and management of possible lack of awareness of the deficits, feelings of depression, shame or inadequacy after the occurrence of the damage, and set the context of the intervention. Defining the specific targets of the rehabilitation, deciding the desired outcome, the setting of a personalized therapeutic plan, and the stepwise achievement of tactical and long-term goals in this direction, completes the first stage of the rehabilitative intervention. Contributing treatment modalities are the psychoeducation of the patient and his/her family, psychotherapy for behavioral and affective issues, occupational rehabilitation, learning skills for independent living (112).

The second phase of the intervention consists of three hierarchical stages: Acquisition, Application, Adaptation. The patient learns and practices the processes associated with the chose tasks (113). The favorable outcome is the adaptation and applying of the

acquired skills in the real-world environment, encompassing their home, workplace, and the entire social life.

5. Treatment of schizophrenia and Neurorehabilitation

Schizophrenia's treatment is difficult to eliminate completely the symptoms, but it could improve daily living of patient. Antipsychotic treatment is the most known, and the first-line therapy for illness (114). Drugs are categorized into the first-generation (FGAs) and the second-generation antipsychotics (SGAs). The FGAs, known as typical, target the dopamine D2 receptor inhibiting the dopamine activity (115,116). Aim of typical antipsychotics is to alleviate the positive symptoms of the disorder, hallucinations, and delusions. However, the administration of typical antipsychotics provokes extrapyramidal side effects in patients, who present dystonia, dyskinesia and parkinsonism events (116). One more disadvantage of FGAs is their incapability to ameliorate negative symptoms, leading to new therapies. So, a new approach to treating schizophrenia is the SGAs. Atypical drugs decrease the risk of extrapyramidal side effects and influence dopamine and serotonin systems (117,118). Furthermore, atypical antipsychotics target both positive and negative symptoms compared to typical ones (116) and improve cognitive function (119). A meta-analysis of the efficacy of SGAs revealed a functional recovery in patients' brain receiving SGAs (118). Some limitations of using SGAs are weight gain, metabolic disturbances (120,121). Overall, receiving antipsychotic therapy seemed not to contribute to the regulation of glutamate levels (122). The current treatment that targets D2 receptors may not be so effective (41). For example, clozapine is a second-generation antipsychotic drug, which is effective on antipsychotic-resistant schizophrenia (123). So, it is seemed that efficacy of clozapine is a result of its contribution to the reduction of cortical glutamate levels and the NMDAR activation (123). However, all type of symptoms are not improved at the same level in all schizophrenic patients (122).

5.1.Cognitive Therapy

Nowadays, treatment approaches have evolved, and so there are cognitive methods that contribute to psychosocial symptoms apart from medication treatments. Training approaches vary from paper-and pencil to computer assisted, from drill-and practice to therapist-guided strategy coaching, from bottom-up-starting from basic neurocognitive skill, such as attention and perceptual skill- to top-down techniques, from the higher order executive functions. There are several interventions contribute on improvement

in cognitive remediation in patients. For instance, Cognitive Enhancement Therapy (CET), Cognitive Behavioral Training (CBT), Cognitive Remediation Therapy (CRT), Cognitive Adaptation Training (CAT) and Social Skill Training (SST) is some of cognitive interventions. Cognitive treatment is a trial to strengthen the patients' quality of life additional to antipsychotic therapy.

Firstly, Cognitive Enhancement Therapy is the most frequently used therapy. It involves a multifaceted strategy that enhances cognitive abilities targeting both neurocognitive and social cognitive domains, through training exercises. It is a computer-assisted technique and has effective results, applying bottom up and top-down strategies. The first strategy aims to critical stimuli and the second one tries to manage distractions and emotional responses through executive control (124,125).

Cognitive Behavioral Training is a therapeutic intervention, which is based on Cognitive Behavioral Therapy (114). CBT is associated with 1) improvement of positive and negative symptoms in schizophrenia (126), 2) improved stress levels of auditory hallucinations (127), 3) addressing and improvement of medication adherence issues (128). Recent studies demonstrated advantages of virtual reality-based cognitive behavioral therapy (VR-CBT). This therapy may offer individualizing treatment targeting not only a specific symptom but a range of behavioral functions.

Additionally, one more cognitive therapy is the Cognitive Remediation Therapy (CRT). CRT is a behavioral-based intervention training, which target functional abnormalities in cognition. This method is neutral, it doesn't focus on individual needs but it seem to influence the main cognitive impairments in schizophrenic population (129). CRT utilizes various protocols and tests of tasks, teaching "thinking skills" (129). Recently, new computer software programs have been developed, and so, patients respond immediately to CRT therapy (119,130). CRT therapy contribute to cognition domains that are impaired in schizophrenia applying the appropriate training approach. Training methods are divided into bottom-up and top-down (119). There are specific programs for the therapy which are the RehaCom Cognitive Therapy Software (131), the REHACOP rehabilitation cognitive program (132), CogPack and CogRehab (133).

Cognitive Adaptation Training is a cognitive rehabilitation approach giving the possibility of a remotely training that offers to patients access from their homes. This

program is personalized to the daily life of each patient and targets to improve daily functions.

Social Skill Training (SST) is a psychological intervention, and a promising therapeutic approach in schizophrenia's treatment. SST is an evidence-based intervention and personal-guided improving interpersonal communication, reducing symptoms severity, enhancing individuals' sociality (134). This cognitive improvement is achieved through group therapy, problem-solving tasks, and the result is presented on patients' social daily life interactions (134). Moreover, an advantage of SST, as CBT, is that ameliorates positive and negative symptoms in contrast with CRT (135). the Neuroimaging studies confirm positive structural changes in brain regions associated with cognition affected by SST (9,136). More specifically, fMRI showed increased volume in the prefrontal, while DTI revealed increased white matter volume in superior longitudinal fasciculus. Superior longitudinal fasciculus is a numerous of fibers between two hemisphere and connects all the lobes together (137).

Social cognition training is an intervention method targeting to all core domains of social cognition, and training usually includes the Social Cognition and Interaction Training (SCIT), the Social Cognitive Skills Training (SCST), and the Social Cognition Enhancement Training (SCET) (138). More specifically, there is an online intervention, the SocialVille, where personalized exercises are based on principles of cognition and neuroplasticity (139).

Intervention	Target	Duration	Setting	Type
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CET	Cognitive functions and Theory of Mind	45 min sessions, 2/week, 24 months	Individual	Computer-assisted and non-computer-assisted sessions
CBT	Cognitive behavioral functions		Individual	Computer-assisted sessions (and through VR)
CRT	Cognitive functions		Group (on the whole schizophrenic population)	Computer-assisted sessions
CAT	Cognitive functions	30-minute sessions, 1/week, variable duration	Individual	Non-computer assisted sessions
CogPack	Cognitive functions	Variable	Individual	Computer-assisted

Table 2: The most frequently used cognitive remediation treatment in schizophrenia.

5.1.1. Impact of cognitive rehabilitation on brain's reorganization

Studies have shown that cognitive therapy improves cognitive functions and daily life of patients with schizophrenia. Emotion management is a cognitive domain that is improved by Cognitive Enhancement Therapy. Imaging studies have shown that the ventrolateral prefrontal cortex and the dlPFC are associated with the ability to manage emotions. In schizophrenia, the amygdala and prefrontal cortex present function abnormalities presenting reduced connection between these regions (140–142). Receiving CET, patients in early course schizophrenia present improved connectivity between the two regions referred to above. On the other hand, EST therapy is associated with lower improvement in emotion management performance, but it seemed to increase the functional connectivity between bilateral amygdala and the right dlPFC. However, it should be clearly understood the role of the amygdala and the dlPFC on

cognitive domains. Nonetheless, future studies should be focused on investigating the whole brain connectivity and how it is affected by CET and EST.

Furthermore, according to fMRI studies, CET provokes important increased function levels associated with working memory (143). Cognitive Remediation Program For Schizophrenia and Other Related Disorders (RECOS) using verbal mediation techniques, contributes to the activation of Broca's area. This area is associated with language-related functions, speech function, and speech production. More specifically, the production of constructed sentences followed by the rules of syntax and grammar.

It is very important to underline that in schizophrenia there isn't language lateralization. According to Weiss et., 2004, Broca's area is activated through verbal tasks but in a different way between healthy controls and patients. In healthy controls, it is observed activation mainly in the left hemisphere, while in patients this activation is observed more bilateral. Applying RECOS, there is a lateralized language activation in the left inferior frontal gyrus. Social cognitive dysfunctions should be a reason why there isn't language lateralization (144,145)

Cognitive rehabilitation and therapy have demonstrated a positive impact on cognitive and functional outcomes in individuals with schizophrenia. Neuroimaging studies have contributed to our understanding of how interventions could lead to brain reorganization, changes in functional connectivity and neuroplasticity. The literature underpinned that cognitive interventions enhance cognitive functions facilitating individual's daily life, as a result of brain reconstruction.

5.2.MATRICES

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) contribute to the effective treatments. The MATRICS initiative participates to guide the development of neuropsychological test batteries for preclinical research in schizophrenia. More specifically, cognitive domains that are improved are working memory, reasoning and problem solving, processing speed, visual learning and memory, verbal memory, attention, and social cognition (146). The advantage of MATRICS is that offers specific neuropsychological tests to improve these functions. Describing how MATRICS improve the symptoms, tests for working memory involve the N-back task, where participants should hold and manipulate information in their short-term memory. So, some of daily routines, such as making

decisions and planning are improved reducing disorganized thinking. Moreover, reasoning and problem solving is a domain, which is disorganized in schizophrenia and Wisconsin Card Sorting Test (WCST) allows cognitive flexibility and problem-solving skills. Another test battery is the Trail Making Test Part A, which enhances the processing speed contributing individuals to process information more quickly and reduce delays in decision-making. Another cognitive domain that is strengthened, is visual and verbal memory. Here, it is used the Brief Visuospatial Memory Test (BVMPT) enhancing navigation to the physical word, recognition faces and reduction confusion and paranoid feelings. Neuropsychologists apply the Hopkins Verbal Learning Test (HVLT) to improve individual's ability to remember and recall verbal information and finally, HVLT contribute to social life improving communication skills and reducing social withdrawal. Addressing the domain of attention, Continuous Performance Test (CPT) improve attention vigilance, requiring participants to respond to respond to specific stimuli while ignoring distractions. Social cognition as a basic disorganized function in schizophrenia, is improved through Reading the Mind in the Eyes Test (RMET). This technology evaluates the individual's ability to infer emotions from facial expressions (146–148).

6. Discussion

Here, we have discussed neurobiological background and some of the mechanisms underlying cognitive impairment and the reorganization of cognitive networks in schizophrenia. Then, we mentioned the implementation of neurorehabilitation and neuromodulation, clinically. Schizophrenia as a neurodegenerative and psychopathological disease is a challenging issue for the neuroscientists. Although its etiology and physiopathology are not fully clear, there are studies that investigate the neurobiological background in order to explain the clinical symptoms of the disorder.

Neuron circuits on brain play an important role on the development of schizophrenia and neurotransmitters that are involved are NMDA and AMPA. Dysfunction of neurotransmitter contributes to the symptoms' manifestation. Furthermore, glial cells and their function are associated with the manifestation of schizophrenia. More specifically, myelination of glial cells plays a role in cognition and changes on it affects cognitive functions. Genetic background of schizophrenia is extensive because the disorder is referred as polygenic. Several genes are involved in the development of schizophrenia. Many studies have shown that the number of alleles that individuals carry influence the severity of symptoms.

Pharmaceutical treatment, antipsychotic drugs, try to eliminate positive and negative symptoms. Current treatments can be effective, but they are often insufficient to alleviate the full range of symptoms. The administration of FGAs and SGAs offers provoke many positive results and improve few of the positive and negative symptoms. However, cognitive symptoms that are present from the onset of the disorder till chronic schizophrenia, seem to be an issue to be resolved. Recently, it started to focus on the cognitive deficits of schizophrenia, which are very decisive in the daily life of individual. Cognition is a function that affect several domains of social life of patient. Behavior, thoughts, emotion, the ability to understand the other's emotional status are fields that a patient should face in daily routine with. However, the elimination of cognitive impairments is a major subject to the treatment of schizophrenia so, to improve cognitive functions in individual's life.

Cognitive neurorehabilitation is a systematic intervention personalized to functionality and needs of patients, focusing on individuals' impairments. Scientists have been tried to suggest therapies to eliminate cognitive abnormalities not only improving patients'

functionality but provoking brain reorganization. Cognitive therapies include activities based on behavioral training in order to improve or reorganize cognitive deficits. Moreover, neurorehabilitation aims to establish new cognitive habits, to train the brain step by step and improve the neuronal function. This kind of treatment offers many advantages to patients. The basic characteristic is that side effects are eliminated. The interaction between patient and therapist offers the possibility to be controlled all stages of the process. Each one of the therapies follows protocols and is appropriate for different cognitive domains.

Neuroimaging studies have shown that each cognitive treatment target to reorganize different brain structures and neuronal circuits. For example, the prefrontal cortex is a key focus of cognitive neurorehabilitation, as it is associated with executive functions, such as decision-making, problem-solving (149). CRT seem to contribute to the dorsolateral prefrontal cortex improvement (124). CBT as an effective therapy reducing symptoms of anxiety and depression by modifying dysfunctional thought patterns improve activity in the prefrontal cortex, too. The anterior cingulate cortex and the anterior insula is the target of SST.

Cognitive neurorehabilitation is an important tool, using the brain's neuroplasticity to improve cognitive function in patients with schizophrenia. Neuroplasticity is a very important ability of the brain and therapies of several degenerative diseases benefit from this ability. Neuroplasticity should be the tool of the following treatments in schizophrenia because a therapy that eliminate the side effects should be applied early onset of the disease.

7. Conclusion

Cognitive therapies are promising to the improvement of schizophrenia's symptoms. Moreover, they are a low-cost approach to the treatment compared to conventional pharmaceutical treatment. Studying schizophrenia, more research on neurorehabilitation and neuromodulation should be the aim of next studies, because they seem to be in part effective, even in advanced stages. However, the introduction of cognitive rehabilitation, exclusively, in clinical routine to schizophrenia's treatment is far away because it is impossible to include each case of schizophrenia in a pattern of cognitive therapy.

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