UNIVERSITÀ DEGLI STUDI DI GENOVA

Scuola di Scienze Mediche e Farmaceutiche

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e scienze Materno-Infantili

CORSO DI LAUREA IN MEDICINA E CHIRURGIA

TESI DI LAUREA

"SPATIAL PERCEPTION AND THE ROELOFS EFFECT IN SCHIZOPHRENIA AND BIPOLAR DISORDER"

Relatore

Chiar.mo Prof. G. Serafini

Correlatore

Prof. A. Escelsior

Candidata

Lisa Rognoni

Matricola N° 4556268

Anno Accademico 2022/2023

SUMMARY

1. ABSTRACT

Background - It is known from previous research that schizophrenia and bipolar disorder share some perceptual dysfunctions. We focused on the visual system and especially on the role of spatial context on visual perception and processing, utilizing an illusion known as the Induced Roelofs Effect. This illusion refers to the spatial mislocalization of a target within a shifted frame, with the target perceived as mislocated towards the opposite direction of the frame offset.

Methods – We enrolled 46 subjects: 15 healthy controls (HC), 13 bipolar-I patients (BD-I), 9 bipolar-II patients (BD-II) and 9 schizophrenia patients (SZ). Subjects were submitted to a visual task, consisting of a training and an experimental session, divided into a preliminary left-right discrimination assessment and the Induced Roelofs effect assessment. Visual stimulus consisted of a frame with an encoding target (a dot), subjects were asked to discriminate the dot position with respect of their perceived midline, ignoring the frame. They were offered a two-alternatives-forced-choice response pattern (left/right).

Results - Results showed the highest frequency of correct answers when frame and dot shifted in opposite directions with respect of the monitor midline. On the contrary, subjects obtained the lowest possible frequency of correct answers when both items shifted towards the same direction. SZ patients experienced the biggest variation in the proportion of correct responses as a function of the stimulus value, therefore their Induced Roelofs effect size is the bigger compared to all other groups.

Conclusions – We replicated literature findings of greater magnitudes of the Induced Roelofs effect in SZ, resulting from altered center-surround interaction with increased surround suppression and augmented spatial contextual processing. Moreover, we demonstrated augmented Induced Roelofs effect in BD, supporting the notion of spatial processing's dysfunctions in other major mental illnesses.

2. INTRODUCTION

2.1 Bipolar Disorder

Bipolar disorder (BD) refers to a psychiatric, chronic affective disorder. It is characterized by recurring depressive and manic or hypomanic episodes [1]. Patients usually show fluctuations in mood state, energy, speech, thought and psychomotricity [2].

2.1.1 History

The concept of bipolar disorder has its roots in the works of the ancient Greeks, who observed morbid mood states alterations such as depression and exaltation. Later, thanks to Hippocrates's works, it was possible to introduce and describe the concepts of mania and melancholia, which fell under the first classification of mental disorders along with paranoia [3].

The term "melancholia" has a clear etymology (melas means black and cholé means bile) and it was based on the pre-Hippocratic Greeks' studies, especially Alcmaeon of Crotona's. They believed that mental disorders could be explained by the interaction between body liquids, such as the bile, and the brain [3]. Specifically, they theorized that excessive concentration of black bile and yellow bile could be found respectively in melancholia and in mania [4]. The origin of the term "mania", however, is much less clear. Caelius Aurelianus, Roman physician, in his book "On Acute and Chronic Diseases" resumed the views and works of Empedocles and was able to describe at least seven different etymologies. Moreover, he cited Plato's "Phaedrus" describing two different kinds of mania, one originated from bodily distress and the other one caused by divine intervention.

During the classical period mania and melancholia still weren't considered linked to one another. It was Areatus of Cappadocia, in the 1st century AD, the first to describe these two states as different expressions of the same disease and, accordingly, to introduce the first conception of bipolarity. In particular, he believed mania and melancholia to have the same aetiology, traceable to brain disfunction, and that mania was nothing but a worsening of the disease [3].

In the 18th and initial 19th century more studies were conducted by German and French psychiatrists, but it wasn't until 1851 that bipolar disease started to be considered an entity on its own. This was possible thanks to the works of Jean-Pierre Farlet, physician at the Salpêtrière Hospital, who introduced the concept of "folie circulare", characterized by the alternation of recurring mood episodes (melancholic depression, hyperactivity mania, free intervals) [3,5]. In particular, he considered these free intervals to be an important part of the disease, that he defined a long-term illness. This also led to questioning the separation between mania and melancholia as different entities. Farlet's views were in contrast with the theories of his colleague and contemporary Jules Baillarger, who described the so called "folie à double forme", a disease in which mania and melancholia switch to one another but without the need for a free interval [5].

We can trace back the first classification of psychiatric disorders at the end of the 19th century. In 1863 Karl Kahlbaum distinguished between two groups of mental disorders: vecordia, a limited disturbance of the mind with a continuous remitting course, and venania, a complete disturbance with a progressive course, leading to dementia [6]. He was also the first to introduce the term "cyclothymia", grouped along with "dysthymia" and "hyperthymia" in the so called "partial mental disorders" [7].

His works inspired Emil Kraepelin, today considered the father of modern psychiatry, who theorized a "dichotomy" of psychoses into two main clinical entities: "manic-depressive insanity" (today known as bipolar disease) and "dementia preacox" (the modern schizophrenia). Specifically, manic-depressive insanity represented the first attempt to include all types of affective disorders into one category. Kraepelin believed that all pathological mood alterations, such as single/recurrent episodes, depression and mania, psychoses, severe and mild forms along with subsyndromal forms and mixed states could all be traced back to the same common disease. In conclusion, he created a spectrum of affective disorders [8].

Many years after Kraepelin's studies, in 1966, bipolar disorder experienced a rebirth thanks to the works of Jules Angst and Carlo Perris. In opposition to Kraepelin, both the authors supported the distinction in pathophysiology and course between unipolar and bipolar depression, leading to its modern concept [6].

2.1.2 Diagnosis

In the 1st edition of the American Diagnostic and Statistics Manual of Mental Disorders (DSM-I, 1952) manic depression was classified as a psychotic disorder. Although mania's symptoms were similar to the modern description, sensory deceptions such as hallucinations and illusions were also considered possible additions to the disease. Three different types of mood disorders were described, in opposition to Kraepelin's singular category: manic, depressed and others (mixed type, circular type) [9].

In the DSM-II (1968) it was introduced the so called "manic depressive illness" as part of the "Affective Disorders" category. This clinical entity was defined by recurrent mood fluctuations and divided into three categories: manic, depressive and circular. The term "circular" meant characterized by "at least one attack of both a depressive episode and a manic episode". Mixed type became part of the "Other major affective disorder" category [10].

Bipolar disorder was then fully shaped into its modern definition with the publication of the DSM-III (1980). In particular, the major deviation from the previous versions was the separation between bipolar and unipolar depression as different kind of mood disorders. Spatial deceptions, if present, became a specifier of the mood episode. It was also introduced the term "hypomania" to describe a mild version of mania [11].

In the DSM-IV (1994), finally, mixed episodes acquired their own diagnostic criteria. These required the presence of both a manic episode and a major depressive episode for nearly every day for at least a week [12].

In the latest edition of the Diagnostic and Statistics Manual of Mental Disorders (DSM-5, 2013) bipolar and related disorders are found to be a bridge between "schizophrenia spectrum and other related disorders" and "depressive disorders". In this chapter seven different diagnostic subtypes of bipolar disorder are described: bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance and medication induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder and unspecified bipolar and related disorder.

Bipolar I disorder diagnostic criteria include at least one lifetime manic episode (*Table A*) not better explained by schizoaffective disorder, schizophrenia spectrum or other psychotic disorders. The manic episode could be preceded or followed by hypomanic or major depressive episodes. Lastly, during the diagnostic process, it should be specified the type of current or most recent episode, and it should be considered current severity/psychotic features/remission specifiers.

Bipolar II disorder is characterized by at least one hypomanic episode (*Table B*) and one major depressive episode (*Table C*), not better explained by schizoaffective disorder, schizophrenia spectrum or other psychotic disorders. A manic episode has never occurred, and the symptoms should lead to significant distress or impairment in different areas of functioning. The diagnosis should also specify if the current or most recent episode is hypomanic or major depressive, if it is in full or partial remission and its severity (mild, moderate, severe).

Cyclothymic disorder is diagnosed if, for at least 2 years (1 year in children and adolescents), there have been periods with hypomanic or depressive symptoms that do not meet criteria for, respectively, a manic episode or a major depressive episode. These symptoms should be present for at least half the time during the 2 years, and there should not be a free interval longer than two months. Again, this condition is not better explained by schizoaffective disorder, schizophrenia spectrum of other psychotic disorders; and it is not imputable to the effects of an abuse substance or another medical condition.

Substance/medication-induced bipolar and related disorder consists in a mood disorder that is prominent in the clinical picture of a patient whose symptoms developed after exposure, intoxication or withdrawal from a substance or a medication. Evidence of an independent bipolar or related disorder, such as symptoms which precede or persist for about one month after the substance/medication's use should not be present.

Bipolar and related disorder due to another medical condition is diagnosed when a persistent disturbance in mood is the direct consequence of another medical condition, not better explained by a psychiatric condition.

"Other specified bipolar and related disorder" category applies to patients whose symptoms are typical of bipolar and related disorder but do not meet full criteria for any of the previously cited

classes. It differs from the "Unspecified bipolar and related disorder" category because, in this case, clinicians explain how the condition does not fit into any other class. Examples of this category include: short duration hypomanic episodes (2-3 days) and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, hypomanic episode without previous major depressive episode, short duration cyclothymia and manic episode superimposed on the schizophrenia spectrum [13].

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

***Table A**: diagnostic criteria for a manic episode in DSM-5*

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external
stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or
psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g.,medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

***Table B**: diagnostic criteria for a hypomanic episode in DSM-5*

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly everyday. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A–C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

***Table C**: diagnostic criteria for a major depressive episode in DSM-5*

2.1.3 Epidemiology

Overall, most of the studies on BD estimates a lifetime prevalence approximately around 1-2% in the general population. It has been suggested a lifetime prevalence of 0.6% for bipolar type I disorder, 0.4% for bipolar type II disorder, 1.4% for subthreshold bipolar disorder and 2.4% for bipolar disorder spectrum. The 12-months prevalence for both BD types is slightly lower than the lifetime prevalence (0.4% for BD-I, 0.3% for BD-II and 0.8% for subthreshold-BD) [14].

Nevertheless, it is possible that the true prevalence of bipolar disorder could be higher, as a lot of BD-II, subthreshold-BD and cyclothymic disorder remains under diagnosed. In fact, research has shown that between 30% and 40% of patients with bipolar disorder who presented hypomanic episodes or depressive features has been wrongly diagnosed with unipolar depression [15,16].

Moreover, it has been observed an increase trend in prevalence of bipolar disorder with the use of DSM-IV in comparison with DSM-III and DSM-III-R. This could be a result of the use of different assessment scales for BD-I diagnoses and of the changes in diagnostic criteria for BD-II [17].

The prevalence ratio between men and women is almost equal (1.1:1). Women usually have a higher prevalence of BD-II diagnoses [13,18].

2.1.4 Course and outcome

Research shows that the age of onset of bipolar disorder is early; it has been observed the highest rate of 12-month prevalence in subjects aged 18-34 years. The mean ages at onset are 18.4 years for BD-1, 20.0 years for BD-II and 21.9 years for subthreshold-BD. It seems that the first hypomanic and manic episodes occur much earlier, during lifetime, than depressive episodes [14,19].

At onset, bipolar disorder could present with either a manic/hypomanic or depressive episode. There is a strong association between the polarity at onset and later depressive versus manic morbidity. Bipolar disorder is known to be a recurrent condition: almost 70% of patients have

experienced more than 7 episodes and 42% more than 11, with a mean of 8 episodes per patient [18].

There are different course patterns in bipolar disorder, these are known to be predictors of treatment responses and outcome. Most patients experience the so called DMI pattern or its opposite, the MDI pattern.

DMI pattern identifies patients who experience a sequence of depressive episodes preceding manic or hypomanic states, then followed by an illness free interval (Depression-Mania-Illness free interval). DMI patients are more likely to be women diagnosed with BD-II, with a later onset-age and they typically experience a first episode characterized by depression or anxiety. In these subjects, manic morbidity is less frequent than depression during a long term follow up. DMI pattern is also associated with a reduced response to mood stabilizer long term treatments, especially lithium, resulting in an inferior clinical outcome and in an insufficient protection against recurrences of bipolar depression. This could be explained by a much more severe and agitated presentation of depressive episodes in DMI patients than in MDI patients, often improperly treated with antidepressants firsts [20]

On the other hand, MDI patterns refers to a sequence of manic/hypomanic episodes followed primarily by a depressive episode and secondly by an illness free interval (Mania-Depression-Illness free interval). Patients who experience this sequence are usually diagnosed with BD-I and have an onset characterized by mania, hypomania, mixed states or psychosis. MDI pattern also have a better response to long term mood-stabilizing treatments, supporting the hypothesis that the best possible outcome for BD patients is obtained by suppression of manic/hypomanic episodes [20].

A smaller proportion (28%) of patients follow a continuous circular course sequence (CCC), defined by < 4 episodes/year without euthymic intervals. This subtype of subjects, in comparison with the non-continuous circular course (N-CCC) ones, have a later onset-age and a higher number of total mood episodes, of polarity switches and of recurrences. Mixed states are less frequent. The absence of a free interval is associated with a reduced response to maintenance therapy [18,21].

Another subcategory of patients (22.3% 12-months prevalence and 35.5% lifetime-prevalence) develop rapid cycling bipolar disorder (RC-BD), defined by the occurrence of at least 4 mood episodes (manic/hypomanic, depressive or mixed states) within the previous 12 months. Strong evidence supports the association of RC-BP with suicide ideation as well as greater illness severity, work impairment, and poor response to mood-stabilizer therapy. Ulterior associated factors include being a female diagnosed with BD-II and the co-presence of other medical disorders such as hypothyroidism [22].

Furthermore, around 35% of bipolar patients develop the DSM-5 "mixed features" specifier during a mood episode, defined as the presence of at least 3 signs or symptoms of opposite polarity to that of the current episode [23]. These subjects typically have an earlier onset-age, a longer time to symptoms resolution and shorter illness free intervals. They also experience a higher rate of comorbidities (especially substance abuse), and, given the diagnostic and therapeutic challenge, worse outcomes including suicide. Antidepressants are usually not indicated, as they aggravate symptoms. The first line treatment at the moment is second-generation neuroleptics, eventually associated with mood stabilizers. Electroconvulsive therapy (ECT) is helpful if first line treatment fails or cannot be used [24].

In conclusion, bipolar disease often reduces psychosocial functioning, and it is associated with a high economic cost, mainly due to chronic comorbid diseases, especially cardiovascular's. Cardiovascular comorbidity is also the most frequent cause of premature mortality in bipolar disease. Life expectancy is considerably shorter than the general population, studies show approximately a loss of 10-20 years of life. Furthermore, these patients are 20-30 times more likely to die by suicide, which has been demonstrated to be the cause of death in approximately 15-20% of people affected by this condition [25].

2.1.5 Aetiology and pathophysiology

Thanks to extended genetic epidemiological research, inherited factors are known to play a key role in the aetiology of bipolar disorder. Estimated heritability is around 59%, first degree relatives of a bipolar proband have a significantly increased risk (5-10%) of suffering of this condition. This risk decreases with genetic distance. On the other hand, monozygotic twins'

studies show a much higher risk (40-70%) than the general population and an estimate 89% heritability [26]. Relatives of a BD proband are also at increased risk of other psychiatric conditions, such as unipolar depression, schizoaffective disorder and especially schizophrenia, as demonstrated in a large Swedish population-based study. In fact, due to genetic and environmental common effects, it seems that genetic susceptibility is partially overlapping in both bipolar and schizophrenic patients [27].

As most psychiatric disorders, there is no evidence in BD of a mendelian pattern of inheritance or of highly penetrant susceptibility genes. There are, instead, multiple associated susceptibility loci of small effect, a part of them which have been identified thanks to genome-wide association studies (GWASs) [28]. Genes contained in the identified loci have been linked to different cellular pathways, for example calcium signalling (CACNA1C, encoding the alpha-subunit of L-type voltage-gated Ca2+ channels), synaptic plasticity proteins (ANK3, encoding ankiryn 3), neuronal signalling and pathfinding (OZD4, encoding a member of the teneurins, surface cell proteins) and neuronal modelling and adhesion (NCAN, encoding neurocan, a chondroitin sulphate proteoglycan also involved in schizophrenia pathogenesis [29]*)* [26]. These single nucleotide polymorphisms (SNPs) only explain 30% heritability in BD. Several other mechanisms can, indeed, contribute to inheritance of this condition, for example copy number variants (CNVs), epigenetic variations and mitochondrial dysfunction. CNVs, in particular, cause cognitive problems and are carried by subjects at higher risk of suffering from neurodevelopmental and mental disorders [26,30], while mitochondrial DNA variations are known to play a role in treatment response and phenotypic presentation in BD [31]. Mitochondria dysfunction could also explain the presence of oxidative stress in bipolar disorder, demonstrated by increased lipid peroxidation and nitric oxide compared to healthy controls [32].

It is also essential to consider the interaction between these genetic factors and the environment, childhood trauma in particular. It has been demonstrated that a history of severe childhood abuse could be found in approximately 50% of patients suffering from BD. Sexual, physical and emotional abuse is associated with an earlier age of onset, rapid cycling, higher rates of lifetime suicidality and comorbid substance abuse [33] .

The pathophysiology of bipolar disorder is yet not fully clear, it is known to be a complex multifactorial disorder. Research focused on genetic, inflammation, oxidative stress and

mitochondrial dysfunction; then leading to abnormalities in neurogenesis and increased neuronal apoptosis [25]. These factors are different between early and late stages of the disease and could be considered the first biomarkers of the staging model in BD, along with structural brain-alterations such as ventricular enlargement and loss of grey matter thickness [34]. The fact that these patients may present progressive neurobiological, structural and cognitive changes as an expression of illness duration and past episodes goes by the definition of neurobiological progression hypothesis [25].

Immuno-inflammatory dysfunction appears to be a major contributor in the pathophysiology of bipolar disorder. Mechanisms involved in this hypothesis include direct effects of inflammatory cytokines on monoamine levels (with decreased serotonin during depressive episodes and increase dopamine during manic episodes [35]), dysregulation of the HPA axis (with increased CRH, ACTH and cortisol levels) and pathological microglial prolonged activation [36]. The immunological abnormalities could help explain the correlations between BD and several medical comorbidities in which inflammation plays a key role, such as cardiovascular diseases, obesity and metabolic syndrome. This idea is reinforced by an increased risk for autoimmune diseases in bipolar patients, who tend to develop organ-specific autoantibodies such as TPOA (associated with thyroid dysfunction), H/K ATPase (associated with autoimmune atrophic gastritis) and GAD65A (marker of type I DM) [37]. Moreover, immunological and inflammatory biomarkers that increase during systemic inflammation (in particular CRP, TNF-α, IL-1β, IL2 and IL6) could also be found higher in patients suffering from mood episodes. Changes in serum marker levels seem to be related to symptoms' worsening and different stages of bipolar disorder [36,37].

2.1.6 Therapy

Treatment of bipolar disorder aims to gain euthymia during an acute mood episode, to prevent recurrences, to reduce subthreshold symptoms and suicidality and to improve social functioning. These objectives are often difficult to achieve due to the risk of rebound episodes of opposite polarity during acute phases [25,38]. It is also important to emphasize the necessity of an early treatment of the first lifetime-episode of BD, both with pharmacological and psychoeducational

programs, as a delay in diagnosis and intervention is associated with a higher tendency to relapse and progression of the disease [39].

As regards acute mania, antimanic efficacy has been demonstrated for lithium, atypical antipsychotics, valproic acid and carbamazepine [25]. First-line treatment should prioritize monotherapy; combination therapy, which is associated with more side effects, should be reserved to patients who do not respond to the previous treatment and who suffer from psychiatric comorbidities or severe presentation [40]. Second generation antipsychotic drugs, especially Olanzapine and Risperidone, have demonstrated better efficacy and faster onset of action than mood stabilizers [38]. Lithium, on the other hand, is still an effective treatment option in patients with family history of BD who do not experience mixed episodes, rapid cycling and psychotic features. Antimanic efficacy is achieved when lithium blood levels range from 0.8 to 1.2 mEq/L [41].

Acute bipolar depression represents a more difficult clinical and therapeutical challenge, in particular because of the controversial role of antidepressants. These drugs, in fact, are associated with polarity switch to manic episodes (especially in BD-I), induction of dysphoria and suicidality; therefore, their use should be limited to patients who do not present with rapid cycling and mixed features and they should be associated to an effective mood-stabilizing treatment [25,42]. Second-generation antipsychotic, including Olanzapine combined with Fluoxetine, Lurasidone and Quetiapine are approved by FDA for short-term treatment in acute bipolar depression [38,42]. Lamotrigine, as well as Lithium, have shown efficacy in preventing recurrences of bipolar depression and are approved for long-term prophylaxis in BD. Lithium, in addition, is also useful to prevent suicidal behaviour [42].

In conclusion, during remission it is necessary to continue pharmacotherapy that was effective during acute phases in order to prevent relapses. Maintenance therapy could be potentially prolonged for indefinite time but, typically, for at least 6-12 months. Lithium, Lamotrigine and atypical antipsychotics (especially Olanzapine, Quetiapine and long-acting injective Risperidone) are approved for long-term use in BD. These medications have been associated with adverse effects and thus, drugs blood levels testing and clinical periodic monitoring is required. It is also important to combine psychotherapy, along with pharmacotherapy, in BD to reduce morbidity and to improve quality of life and social functioning. Group psychoeducation,

cognitive-behaviour therapy, interpersonal and social rhythm therapy and family therapy may be particularly effective in BD [41,42].

2.2 Schizophrenia

Schizophrenia is a highly complex psychiatric disorder with wide heterogeneity in onset, clinical symptoms, course and outcome. Its main features include negative, positive and disorganised symptoms, along with a variety of less prominent dysfunctions involving cognitive, affective, behavioural and perceptual-sensory domains. This illness represents a diagnostic and therapeutic challenge; it also has significant impact on the patients in terms of social functioning and stigma [43].

2.2.1 History

Schizophrenia was originally addressed as "dementia preacox", as it began early in life (praecox) and led to an impairment in cognitive and behavioural skills (dementia) [44]. This term was firstly coined by Kraepelin who, in the fourth edition of his textbook, introduced a category called "psychic degeneration processes", that included dementia praecox (referring to Hecker's hebephrenia), catatonia (a term adopted from previous studies by Kahlbaum) and dementia paranoides. Ulterior editions of Kraepelin's textbook further developed these concepts and culminated in the sixth edition with a new nosologic entity, dementia praecox, divided into hebephrenic, catatonic and paranoid subtypes. In this same edition the author also separated dementia praecox from manic-depressive insanity, today known as bipolar disorder. In the seventh edition, Kraepelin identified 10 forms of dementia praecox: dementia simplex, silly deterioration, depressive deterioration with delusional manifestations, circular, agitated, periodic, catatonic, paranoid and schizophasia. Finally, in the eighth edition, he gave a comprehensive definition of dementia preacox, described as different clinical conditions characterized by a destruction of the internal connections of the psychic personality [45]. Kraepelin, in his works, focused on avolition, poor social and functional outcome and chronicity of the disease; moreover, he did not consider psychosis as a main defining feature of

schizophrenia but delineated primarily the cognitive and social decline that precedes other symptoms [46,47].

Ulterior studies on schizophrenia were carried out by Bleuler, who replaced "dementia praecox" with the current term, referring to a group of psychoses sharing anomalies in thinking, feeling and interaction with the external world. Bleuler emphasized primarily signs and symptoms, rather than course and outcome [44]. He differentiated between the physical disease process (unknown at the time) and its symptoms, furtherly divided into primary symptoms (caused by the underlying illness, specific of schizophrenias and present throughout the course of the disorder) and secondary or accessory symptoms (a result of psychic reactive mechanisms) [48]. Primary or basic symptoms were identified with the four A's: autism, ambivalence, loosening of associations and inappropriate affect [45]. In summary, he focused on dissociative psychopathology identifying fragmentation of thought as the most important symptom (the term schizophrenia itself refers to splitting of associations). Moreover, he viewed negative symptoms as main features of schizophrenia while affective, catatonic, psychotic symptoms along with speech, written language and memory impairment as accessory symptoms of the disease [47,49].

Bleuler's four A's were broadly employed in the diagnosis of schizophrenia until Schneider introduced the so called first-rank symptoms (FRS): audible thoughts, auditory hallucinations (voices arguing, discussing or commenting), somatic passivity experiences, influenced thoughts (e.g. thought withdrawal, insertion or interruption), thoughts broadcasting, delusional perceptions, made volition, thought, affect and impulse (experienced as influenced by others) [45]. FRS, when unequivocally present, had diagnostic preference over second-rank symptoms such as delusional notions (e.g. paranoid or persecutorial delusions) or depressed /elated moods, which can also be found in other psychoses [50]. Like Bleuler, Schneider attempted to identify features strictly specific to schizophrenia that occurred often enough to be useful as diagnostic tools, however he focused mainly on specific delusions and hallucinations rather than dissociative processes. He was the first to introduce a cross-sectional assessment for differential diagnosis based on highly defining symptoms. Schneider's ideas of FRS as pathognomonic for schizophrenia and of a poor outcome prognosis based on specific schizophrenia's features were later abandoned in follow-up studies [44].

Schizophrenia was furtherly studied by Kleist, who identified four different subtypes of schizophrenia: paranoid, hebephrenic, catatonic and confused. He also divided typical and atypical schizophrenias depending on whether one or more neurological systems were involved. Kleist's dichotomy was replaced by Leonhard's systematic vs unsystematic schizophrenia, the first characterized by insidious onset, long course and moderate-severe impairments, the latter referring to a milder syndrome with rapid onset, episodic course and mild defects. Moreover, he identified too different subtypes of schizophrenia: catatonia, cataphasia and paraphrenia. Both Leonhard's and Kleist's contribution were not furtherly considered valid in the major classifications in use today (ICD-10 and DSM) [45].

2.2.2 Diagnosis

The definition of schizophrenia has evolved through the different editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). The main defining features of this illness have their roots in the works of Kraepelin, Bleuler and Schneider; however, the influence of these different perspectives varied during the years with the evolution of DSM. For example, Bleulerian focus on dissociative psychopathology and accent on negative symptoms had major influence in DSM-I and DSM-II, leading to a broader definition of schizophrenia in the US vs UK and Europe [46].

In order to narrow and homologate the definition on schizophrenia internationally, DSM-III eliminated non-psychotic forms of schizophrenia, focused on Schneiderian FRS and expanded psychotic features to other psychiatric diseases, such as affective disorders. Bleuler's four A's symptoms were deemphasized, with less relevance given to negative or deficit features and to social and functional impairment. Moreover, the new definition of schizophrenia required chronicity (6 months duration criterion) and poor functional outcome [44,46].

DSM-IV slightly modified DSM-III schizophrenia's chapter to provide a more adequate coverage of different symptoms. DSM-IV's definition had high diagnostic stability, reliability and validity, therefore, its core diagnostic domains were maintained in DSM-5. In the latest edition of DSM (DSM-5) in fact, only a few changes were made to obtain simplicity and add new information gained on the disorder during the years. The six criteria (A-F) (*Table D*) for

the diagnosis of schizophrenia, introduced by DSM-IV, were maintained in DSM-5. Criterion A "characteristic symptoms" added the requirement of at least one out of two demanded symptoms being hallucinations, delusions or disorganized speech. Less prominence was given to Schneiderian FRS and to special treatment of bizarre delusions and hallucinations. Criteria B-E (B: social/occupational dysfunction, C: duration of 6 months, D: schizoaffective and mood disorders exclusion, E: substance/general mood condition exclusion) did not change. Criterion F "Relationship to a global development disorder or autism spectrum disorders" is clarified adding "other communication disorders at childhood onset" to its description. Moreover, classic DSM-IV's subtypes of schizophrenia were furtherly revised in DSM-5 as they were found poorly predictive of treatment response and course, did not explain the wide heterogeneity of the disease and had low diagnostic stability. Psychopathological dimensions were used as a substitute to subtypes. In conclusion, DSM-5 added course specifiers to allow clinicians to characterize the patients both in a cross-sectional and longitudinal pattern of illness, the latter requiring an observation period of at least one year. Ulterior specifiers include with or without catatonia and current severity (*Table E*) [46] .

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

***Table D**: diagnostic criteria for schizophrenia in DSM-5*

Specify if:
The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.
First episode, currently in acute episode: First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An acute episode is a time period in which the symptom criteria are fulfilled.
First episode, currently in partial remission: Partial remission is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.
First episode, currently in full remission: Full remission is a period of time after a previous episode during which no disorder-specific symptoms are present.
Multiple episodes, currently in acute episode: Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, a remission and a minimum of one relapse).
Multiple episodes, currently in partial remission
Multiple episodes, currently in full remission
Continuous: Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.
Unspecified

Specify if:
With catatonia (refer to the criteria for catatonia associated with another mental disorder, p. 135, for definition).
Coding note: Use additional code F06.1 catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.

Specify current severity:
Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). (See Clinician-Rated Dimensions of Psychosis Symptom Severity in the chapter “Assessment Measures.”)
Note: Diagnosis of schizophrenia can be made without using this severity specifier.

***Table E**: schizophrenia’s specifiers in DSM-5*

DSM-5 chapter “Schizophrenia spectrum and other psychotic disorders” include schizophrenia, other psychotic disorders and schizotypal personality disorder. All disorders share abnormalities in five domains: delusions, hallucinations, disorganized thinking, speech or motor behaviour (including catatonia) and negative symptoms. Main features of these condition, useful for differential diagnosis, are described in the following lines.

Schizotypal personality disorder is better described in “Personality Disorders” chapter. It consists of a pervasive pattern of social and behavioural abnormalities and cognitive or perceptual deficits, below the threshold for a diagnosis of psychotic disorder.

Catatonia and delusional disorder are two conditions with an impairment only in one out of five psychotic domains, disorganized motor behaviour and delusions respectively. Delusional disorder consists of at least one month of delusions without other psychotic symptoms, catatonia refers to a condition that may be associated with different psychiatric disorders, characterized by marked psychomotor disturbance (e.g. decrease or excessive motor activity or reduced engagement during clinical assessment).

Brief psychotic disorder requires the presence of defining symptoms lasting at least one day but less than one month.

Schizophreniform disorder shares clinical presentation with schizophrenia but lasts at least one month and less than 6 months. It is not associated with poor functional outcome.

In schizoaffective disorder active-phase symptoms of schizophrenia happens simultaneously with a major mood episode. Two or more weeks of psychotic symptoms usually precedes or follows these clinical manifestations, in the absence of a major mood episode. Clinical specifiers include bipolar or depressive type and with or without catatonia.

Psychotic disorders may also be induced by substance, toxins, or medication abuse, as well as a consequence of another medical condition. Symptoms recedes after removal of the agent.

Other specified or unspecified schizophrenia and related disorders refers to condition that do not meet criteria for any specific psychotic disorder [13].

2.2.3 Epidemiology

For decades, lifetime risk prevalence of schizophrenia was though being around 1% across, time, geography and sex. To date, studies have reevaluated schizophrenia's epidemiology and found more accurate estimates of incidence, prevalence and mortality [51].

Overall, estimated incidence per year of schizophrenia is around 15/100.000 men and 10/100.000 women, with the central 80% of estimates distribution varying over a fivefold range. Concerning prevalence, the median lifetime risk is around 4/1000 (with a range between 0.3-0.7% [13]) while median morbid lifetime risk is 7.2 on 1000. Therefore, the traditional statistic that "one in a hundred" people will be affected by schizophrenia was more accurately replaced by "seven individuals per 1000" will develop schizophrenia during their lifetime. Mortality is 2-3 times higher in patients with schizophrenia compared with healthy controls, as a result of both increased suicide risk (around 5% of patients [52]) and increased risk of comorbid somatic conditions.

Concerning sex differences in the incidence of schizophrenia, evidence suggests a higher frequency in men, with a male: female rate ratio of 1.4/1. Prevalence, however, appears to do not differ between sex [53].

Moreover, studies have shown an increased incidence and prevalence of schizophrenia based on migrant and refugee status, ethnicity, social and economic status and latitude of the country. Nutritional factors, social defeat and infections have been investigated as underlying causes of the association between migration and schizophrenia. Incidence increases in urban settings, developed nations and higher latitudes.

2.2.4 Course and outcome

Schizophrenia typically develops in early adult life, between late teens years and mid-thirties. Men show an incidence peak in their early twenties and a steady decline soon after, while in women the peak is less sharp and new cases onset until late forties. Occurrence in childhood (before 13 years old) is unusual [52]. Most individuals manifest an insidious onset, characterized by slow development of different prodromal signs and symptoms, which last a median of 12

months. These symptoms include feelings on inner change, emotional changes (e.g. anger, anxiety, depression, irritability), cognitive changes and especially initial social withdrawing and functional deterioration. Prodromal symptoms are followed by frankly psychotic ones, which may remain episodic or become persistent leading to chronic schizophrenia i.e. defined by continuous clinical course and functional impairment cause primarily by negative symptoms [13,52].

A chronic course is common in 20% of patients while others, despite having long-term psychiatric illness, experience periods of remission and recovery [51]. Remission rate, defined as absent or reduced symptoms for at least 6 months, is around 56% after the first episode. Recovery rate, defined as clinical and social/functional improvement for at least 2 years, is 30% or 13.5% if only schizophrenia or the whole spectrum is considered, respectively [13].

Psychotic symptoms are main features of the disease but reduce during late life. Cognitive impairment onsets during development, before full psychosis, and remains stable in the following years. Negative symptoms tend to be stable or to be more variable depending on whether they were present during development or began later [13].

In conclusion, schizophrenia is a long-term illness and the most disabling among psychiatric disorders, leading to social and occupational disfunction. Patients need long-term mental health care and, in some cases, living support. These challenges reflect in high unemployment rate (around 70-90% in Europe), social isolation, with reduced prospect of finding a partner [52]. Life expectancy is around 60 years in men and 68 years in women. Schizophrenia is associated with 13-15 years of potential life lost, compared to healthy subjects. Premature death has been linked to higher frequency of somatic disorders, especially cardiovascular and metabolic diseases, poor dietary habits and increased use of abuse substances as tobacco, drugs and alcohol. Finally, patients with schizophrenia have a 12 times higher rate of suicide than controls, especially within 1 year from the first hospitalization. Suicide risk is higher in younger patients, suffering of comorbid substance use and experiencing negative symptoms. Men appears to lose more years of potential life than women, as they more commonly present with prominent negative symptoms and longer course of illness, leading to poorer outcome [13,54].

2.2.5 Aetiology and pathophysiology

Both genetic and environmental factors have a role in the aetiology of schizophrenia.

Genetic factors contribute, even if not in an exclusive way, to the underlying causes of schizophrenia, as evidenced by a tenfold increased prevalence of schizophrenia in first-degree relatives of patients. Estimated heritability for schizophrenia is around 64%, and even higher (81%) in twins.

Genetic transmission does not appear to follow a Mendelian pattern of inheritance, as in most psychiatric disorders. Genome-wide association studies (GWASs), on the other hand, pointed out the contribution of specific DNA common variants and more than 100 loci, containing risk alleles of small effect associated with schizophrenia [51,52]. To date, SNPs account for the biggest single contribution to heritability (25%). Therefore, schizophrenia is considered a polygenic disease resulting from the small effect of hundreds of different genes. The association is stronger with genes expressed in the brain and involved in neuronal and synaptic function such as DRD2 (dopamine receptor D2 gene), genes encoding voltage-gated calcium channels proteins or implicated in glutamatergic neurotransmission (GRIN2A, GRIA1, SRR, CACNA1C). Strict association has also been found between schizophrenia and genes expressed outside the CNS involved in acquired immunity, such as B lymphocyte lineages and variants enriched in genomic regions outside major histocompatibility complex (MHC) [43,51,52]. In addition to SNPs, genomic studies have also identified 12 rare but recurrent copy number variant (CNVs) and gene-disrupting variants, including rare-coding variants (RCVs) and protein-truncating variants (PTVs). These variants occur de novo, account for 2% of heritability but are also the strongest individual risk factor identified so far. In summary, only 10% of heritability is explained by findings that meet stringent criteria for a strong association with schizophrenia [43]. Finally, genomic studies had a key role in demonstrating extensive overlap in common risk variants between different psychiatric disorders, suggesting that genetic risk seems to be pleiotropic. Significant sharing of risk variants has been shown between schizophrenia, bipolar disorder, major depressive disorder and neurodevelopment disorders [27,51].

A significant proportion of the variance in liability for schizophrenia is due to gene-environment interaction and environment-environment interaction. Multiple environmental factors are

known to have additive effect on risk of psychosis. The neurodevelopmental hypothesis, that has been for years the main paradigm to understand environment's contribution to schizophrenia, focused on risk factors that affect early neurodevelopment during pregnancy and childbirth, e.g. maternal stress and infections, IUGR, fetal nutritional deficits, pregnancy complications (e.g. preeclampsia and bleeding) and hypoxic-ischemic obstetrics complications. However, not only biological but also psychosocial risk factors can be linked to schizophrenia, such as childhood adversity (sexual, physical or psychological abuse, neglect, death are associated with increased risk of positive symptoms), immigration (with higher risk in refugee-migrants both first, second and third generation) and socioeconomic factors (social inequality, disadvantage, isolation). Increased risk of schizophrenia has also been found in individuals who grew up or lived in an urban area, born in late winter or spring and who used cannabis, especially earlier in life or with a high concentration of THC. Moreover, advance paternal age is associated with higher risk of developing schizophrenia, due to increased sporadic de novo mutations in male germ cells [51,55].

Pathophysiology of schizophrenia can be link both to structural and functional brain alterations. CT and MRI studies of schizophrenia's patients show lateral ventricular enlargement (25% compared to controls) and a reduction in brain volume of around 2%. Reduction in brain volume is progressive, it is active especially in early stages of illness and affects primarily the gray matter, involving specific cortical areas such as the frontal lobe, temporal lobe and the limbic system [52]. Superior temporal lobe (STG) is particularly affected by gray matter's reduction and changes in its volume have been linked to severity of positive symptoms. Excessive tissue loss is demonstrated in the left rather than the right hemisphere, supporting the finding of abnormalities in asymmetries in chronic schizophrenia's brain. Antipsychotic treatment is a confound factor of the time course of brain abnormalities, in particular second-generation antipsychotics seem to have a neuroprotective effect and to counteract the progressive cortical gray matter loss, especially in the temporal lobe [56]. Nevertheless, brain volume reduction is also evident in drug-naïve patients, particularly in the thalamus and caudate nucleus, with effect sizes of total brain and gray matter volume up to 30% lower compared to medicated patients. Therefore, the largest part of brain volume reduction happens at onset, before treatment [57]. Concerning functional brain alterations, functional imaging in schizophrenia patients has established reduced activity in the prefrontal cortex (hypo frontality), especially its dorsolateral

division, both at rest and during executive tasks. On the contrary, during the execution of cognitive tasks, patients showed hyper-frontality in the medial frontal cortex and lateral prefrontal regions. Simultaneous presence of both hypo and hyper frontality could be explained by a third anomaly in brain functionality, that is failure of deactivation of the medial frontal cortex during cognitive tasks, an area known to be part of the default-mode network, active at rest and that should be deactivated during performance [52].

Furthermore, brain imaging and pharmacological studies suggest that schizophrenia might be explained by an underlying neurochemical disbalance. Dopamine and glutamate are the two main neurotransmitters involved. The "dopamine hypothesis" suggests a dysregulated modulation of dopamine neurotransmission within the mesolimbic and mesocortical pathway, leading to positive and negative symptoms respectively. This theory is supported by the fact that blockage of dopamine D2-like receptors by antipsychotic drug treatment improve symptoms, while raising striatal dopamine signalling via psychostimulants (Amphetamine) or via dopamine D2 receptors overexpression induces a psychotic-like clinical picture. To date, dopamine dysfunction seems to be caused by increased dopamine synthesis capacity and increased number of presynaptic D2 auto receptors. The "glutamate hypothesis", on the other hand, rose as a result of the observation that antagonists of N-Methyl-D-Aspartate (NMDA) receptors (a class of postsynaptic glutamate receptors), such as ketamine and phencyclidine induced schizophrenia-like symptoms, suggesting that deficient glutamate function may be involved in schizophrenia. In particular, a disturbance in the interaction between dopamine and glutamate may be responsible for negative and cognitive symptoms, as the dopamine hypothesis alone does not explain them completely. This idea is backed by a dysfunction in parvalbumin-positive interneurons, sensitive to alterations in NMDA receptors and involved in the generation of gamma oscillations critical to cognitive functions [51,58].

In conclusion, genetic studies along with brain imaging and postmortem studies underlie the importance of abnormal synaptic function in schizophrenia's pathogenesis. Molecular pathways involved in development and maintenance of normal synaptic function are affected by genetic and environmental risk factors, as mentioned in the previous paragraphs. Moreover, signalling cascades involving oxidative stress and inflammatory processes are also known to have a role in synaptic function of the developing brain and may be involved in schizophrenia's

pathogenesis [51]. In particular microglia, MCH class 1 and complement are implicated in synaptic maintenance and plasticity. Inflammation, infections and immune dysfunction may have an effect on neurotransmitters, neurodegeneration and neurodevelopment. For example, early life infections with associated proinflammatory immune response have a priming effect on microglia and might lead to CNS alterations, making individuals susceptible to psychotic illnesses later in life. Moreover, microglial activation, which is a key factor in many degenerative diseases, interferes with neuronal survival by increasing oxidative stress and decreasing neurotrophic factors. In summary, immune dysfunction might contribute to positive, negative and cognitive symptoms of schizophrenia [59].

2.2.6 Therapy

The therapy of schizophrenia consists of both pharmacological and psychological treatment.

Concerning the pharmacological treatment, the main class of drugs in use for schizophrenia are antipsychotics, both first (FGA) and second (SGA) generation (also known as typical or atypical antipsychotic respectively). These drugs have been in use since chlorpromazine was discovered, more than 50 years ago. A person presenting with a first episode of psychosis should be treated with a drug of this class titrated to its therapeutical dose and, if response is not complete after 4-6 weeks, a shift to another drug with different receptor-binding profile should be considered.

Almost all antipsychotic works by blocking D2 postsynaptic dopamine receptors (DRD2), as dopamine excess is responsible for psychotic symptoms. Antipsychotic action occurs when the occupation of striatal DRD2 is at least 65%, further increases in D2 blockage does not improve drug efficacy and it is associated with major side-effects. In fact, while FGA are very effective in reducing positive symptoms, they also cause relevant side-effects, particularly hyperprolactinaemia and extrapyramidal side effects (EPSEs) such as parkinsonism, akathisia, acute dystonic reactions and tardive dyskinesia. The latter is especially severe as it is usually irreversible. Response to treatment is often incomplete and almost 30% of patients are totally resistant. Clozapine is the main antipsychotic drug approved for treatment-resistant patients, it can improve their response to treatment, and it is not associated with major extrapyramidal side-effects. Nevertheless, Clozapine does not lack side-effects, indeed its use require constant blood

monitoring as it is associated with almost 4% risk of neutropenia and agranulocytosis. Clozapine's effect occurs when less than 65% of DRD2 are blocked, suggesting that other mechanisms and receptors (such as serotonin receptor 2 5-HT2R) are implied [52,60]. SGA, on the other hand, may show modest therapeutic advantage over typical antipsychotics (particularly Amisulpride, Clozapine, Risperidone and Olanzapine) but cause limited EPSEs at moderate doses and have differentiating receptor profiles. Concerning side-effects, atypical antipsychotics are associated with higher rates of metabolic dysfunction and weight gain, especially within the first 6 weeks of treatment. Greatest weigh gain potential is met by Olanzapine and Clozapine as they have the greatest affinity for 5-HT2C and H1 receptors [61].

Treatment should be continued for at least 1 year after the first episode of psychosis and at least 5 years in those with multi-episodes. Longer-term maintenance treatment is also recommended based on the severity of acute episodes. Non-adherence or discontinuation of treatment is associated with higher rates of relapse, rehospitalization and worse prognosis. Strategies to support treatment adherence are fundamental, especially in early stages of illness, for example psychoeducation or the use of long-active injection antipsychotics (LAIs or depot) [60].

Regarding psychological and social support interventions, studies have demonstrated that family interventions, family psychoeducation, cognitive behavioural therapy (CBT) and patients' psychoeducation are efficient in relapse prevention and improving symptoms. These programs require a multidisciplinary approach conducted in community-care settings. In the absence of resources, simple family psychoeducation and family intervention is the minimum solution offered to patients. CBT should be also offered to all patients in association with pharmacotherapy as it resulted efficacious in reducing relapses, improving positive symptoms such as delusions and hallucinations, adherence and social functioning [62].

2.3 Visuospatial perception and processing

2.3.1 Visual system basics

The visual system consists of channels involved in the transmission of different visual information, magnocellular (or transient) and parvocellular (or sustained) are the main pathways. Both start in the retina, pass through the thalamus and end up in the primary vision cortex V1. In the thalamus visual information cross by the lateral geniculate nucleus (LGN), whose two inner layers receive projections from the M ganglion cells in the retina, while layers 3 through 6 receive projections from P cells in the retina. These projections remain distinct even in the primary vision cortex, where the M-pathways terminates in layer 4Cα of V1 (involved with measuring local motion) and P-pathway terminates in layer 4Cβ (involved in orientation and size recognition) [63] *(Fig.1).* Neurons in magnocellular pathway send their axons through the parieto-occipital cortex (the dorsal-stream), transport low-resolution visual information, are involved primarily in the earliest stage of visual processing and, in particular, in attentional capture, global analysis of the visual field, motion perception and action guidance. Moreover, magnocellular system is activated by low luminous-contrast stimuli, responds to contrast gain in a nonlinear way and it is more sensitive to large objects (low spatial frequencies). Parvocellular neurons, on the other hand, transport high quality visual information through the temporal cortex (the ventral-stream), are focused on the identification of fine objects details (in fact are used in the latest stages of visual processing) and are primarily activated by higher-contrast stimuli. Parvocellular system is also more susceptible to smaller objects in the visual field and to high-spatial frequencies. In the parietal-occipital cortex, the dorsal stream incorporates areas V3 and MT/MST (middle temporal/medial superior temporal lobe), involved in global motion processing; in the temporal cortex, the ventral stream incorporates areas V2, V4 and Inferotemporal lobe, involved in contour, shape and objects/faces recognition respectively (*Fig. 2*). These areas are part of a higher-level visual system [64,65].

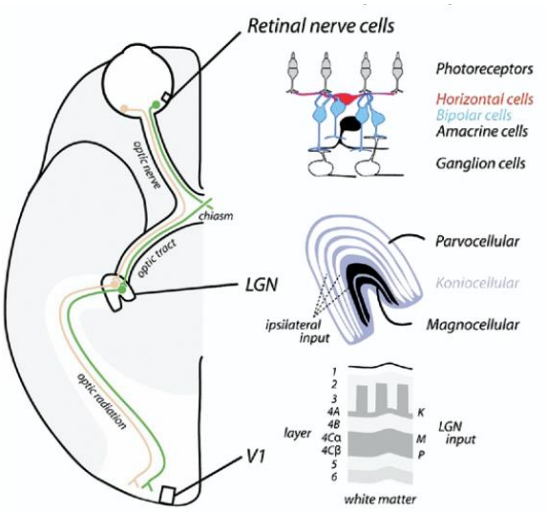

Fig. 1 *– Early visual system basics.*

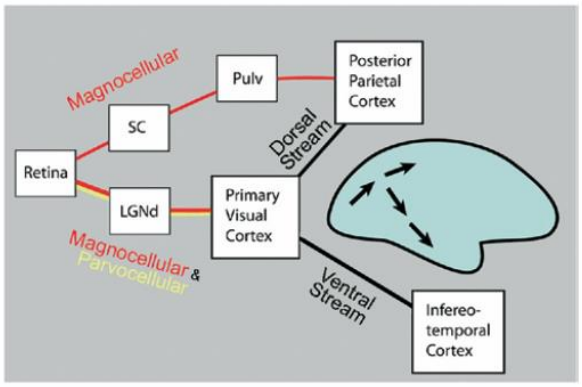

Fig. 2 *– Magnocellular and parvocellular pathways transport different visual information through dorsal and ventral streams.*

2.3.2 Spatial context in visual perception and processing

The role of spatial context on visual perception has been greatly studied. Spatial context include sensory, cognitive and behavioural cues that influence the way every sensory feature is perceived, in order to identify the meaning of these visual image features. Center-surround interaction is fundamental to organize spatial distributed stimuli for perception.

To understand how neurons respond to visual information, it is important to underlie that when a visual stimulus fell into a functionally independent, spatially restricted region of space known as classic receptive field (RF) it induces neurons to fire. However, our perception is based on the interaction between proximal and distant point in our visual field, requiring short and long-term neural connections. Therefore, local RF properties are not enough to completely analyse the visual field, global features integration is required. Visual information outside this field represents surrounding stimuli that, if processed, influence perception and identification of stimuli in the RF [65]. Contextual cues from the surround are also useful whenever circumstances intrinsic to the visual scene or to the visual system leads to full or partial loss of the visual information. This process is known as context-mediated recovery process. Surround modulation allows a scission of each image value into perceptually distinct properties and to fill-in

informational gaps with contextual cues. These informational gaps could be caused, e.g., by acquired/induced scotomas, or transient occlusion of the visual field. Neurons at early stage of visual processing, V1 or V2, are responsible for the detection of these contextual cues useful to recover visual images [66].

Traditionally, visual information has been seen as ascending though a hierarchy of different cortical areas, with different cells processing stimuli for increasingly larger areas of the visual field. Long distance integration of visual stimuli, however, can occur at early stages of visual processing. Anatomical structure of center-surround interaction (*Fig. 3*) typically consists of the RF, whose size and complexity increases progressing through the visual hierarchy from areas V1 to V4, near surround and outer surround. Research typically attributes RF to feed-forward information from LGN, near surround to cortico-cortical inputs from within V1 and outer surround to feedback from extrastriate areas. In particular, neural circuitry underlying center-surround interaction in V1 is based on intrinsic horizontal/lateral cortico-cortical connection between different laminae of the visual cortex. V1 receive feedforward (FF) inputs from the LGN and, likewise, sends FF inputs to extracortical striate areas, which, in turn, sends feedback inputs to V1.

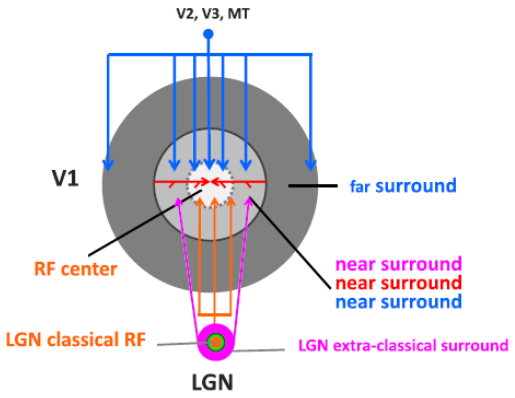

Fig. 3 *– Anatomical circuits for the RF and the surround*

As stated above, contextual information from the surround modulates the neuronal response to the RF stimulus. There are various ways in which surround can influence the RF. The most well-known nonclassical RF effect is the modulation of neuronal responses in the MT visual area

(typically very selective for the direction of motion of a stimulus), obtained by moving the surround. Motion outside the RF, in fact, modulate MT neuronal response to a stimulus within the RF. In particular, when center and surround motion are in the same direction, neural response to the classical RF motion is suppressed; while when center and surround motion move in opposite directions, neural response to central RF motion is facilitated. This phenomenon could be considered a motion-dependent surround suppression *(Fig. 4-5)* and it happens because direction-selective neural units play a key role in mediating perceptual responses to visual motion [66–68].

.

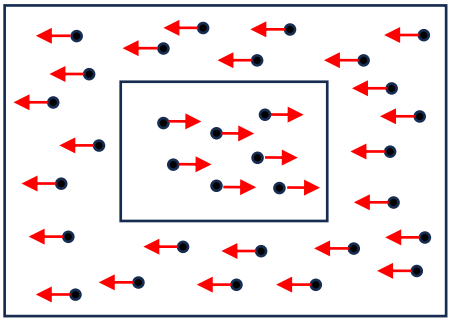

Fig. 4*- Enhanced neural responses to RF motion*

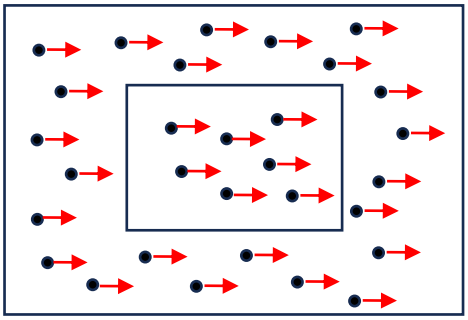

Fig. 5 *- Suppressed neural responses to RF motion*

2.4 The Roelofs Effect

Roelofs effect refers to a perceptual phenomenon that tend to bias the observers' sense of straight ahead. The subject, otherwise in darkness, is presented an illuminated rectangular frame whose centre is located leftward or rightward from the midline, one edge is aligned with the subject's median plane (*Fig. 6A*). The Roelofs illusion leads the observer to underestimate the frame's offset and to do not perceive that edge as straight ahead (*Fig.6B*).

A related phenomenon is the *Induced* roelofs effect, in which the observer is presented a target enclosed by the same rectangular frame (*Fig. 7A*). This target is perceived by the subject as mislocated in an opposite direction compared to the frame offset (*Fig. 7B*). For example, a rightward-shifted frame will led the observer to perceive the target located to his left. As previously mentioned, the offset frame induce a bias in the subject's midline (*Fig. 7C*) [69,70].

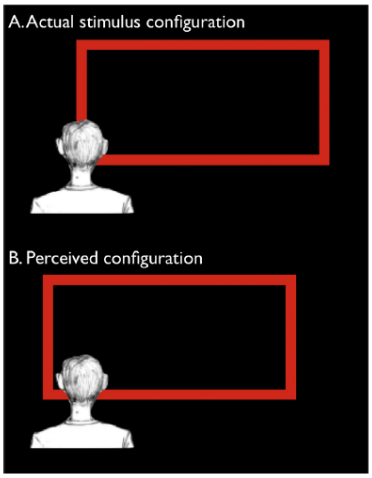

Fig. 6 *– The Roelofs effect*

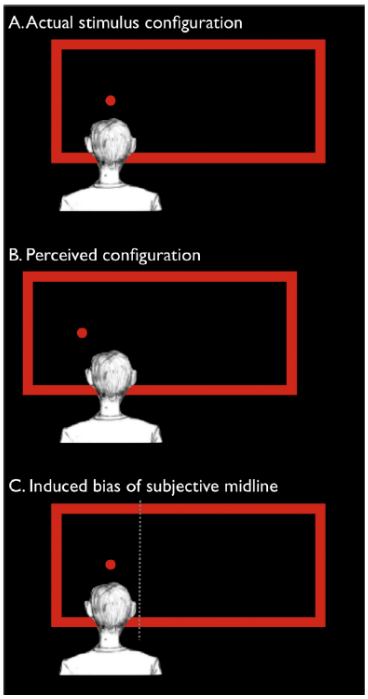

Fig. 7 *– The Induced Roelofs effect*

2.4.1 History

Theories on how objects are perceived and localized by an observer's eye are dated long back in time. Initial studies focused on the "theory of local signs" by Lotze, who found a correlation between an image on the retina and a corresponding object in the world. Later on, it became clear that localization of an object was also influenced by other objects in the visual field, the state of the oculomotor system and the body posture [69].

Duncker (1929) was the first to introduce the idea of induced motion , also known as "Duncker illusion", which stated that perception of the motion of a target results from the motion of the background in the opposite direction. [71]. He was able to prove that movement of a large object could led to the visually perceived motion of a smaller object (located in its surroundings) in the opposite direction, therefore he assumed an object-relative source of mislocalization. Roelofs's work on optical localization was published in 1936 and claimed that true motion has a relevant influence on oculomotricity and on mislocalization of a target; a theory that was later abandoned. His studies and experiments, along with Dietzel's (who described a similar

perceptual illusion), led to the so called “Dietzel-Roelofs effect” which suggests that perceived location of objects in space can be manipulated, inducing the impression of motion [69,72].

In 1953, Werner, Wapner and Bruell carried out further experiments in order to explain this illusion quantitatively. They focused on the effect of a fixated object, located asymetrically, and on the effect of eye and head movement on the perceived position of the observer’s median plane. It turned out that the apparent median plane followed the direction of eye torsion towards the target, while, with eyes closed, it shifted in the opposite direction of eye and head movement. Apparent median plane shifts were therefore ascribed to changes in fixation and not to the location of the target [73].

Bruell and Albee performed another experiment in 1955 in order to gain ulterior informations on how the apparent median plane deviate from the objective median plane. They found out that this condition only occure when retinal stimulation is asymmetrical and that the magnitude of this effect depends on the degree of the asymmetry. This theory is based on two hypothesis: that a fixated target is seen in a specific visual field (e.g. the left one) if fixation is maintained by voluntary innervation of respective eye muscles (e.g. levo-rotators), and, consequently, that a fixated target is perceived as straight ahead solely when fixation does not require voluntary innervation. The latter condition is called “Reflex equilibrium” and it is met when two neurological reflexs, the fixation reflex (which causes eye movements to follow objects in the peripheral visual field) and the postural reflex (which return the eyes to their primary position) are equal in strenght [74].

The hypothesis of the observer’s midline used as a source of target’s localization was carried on widely during the following years. Thanks to additional studies, Harris (1974) proved that visual context could bias the observer’s perception of the median plane; in particular, the apparent midline was biased in the direction of a rotation [69].

In conclusion, these experiments led to two discordant views on motion perception. The first one assumed an object-relative source of mislocalization, as stated by Duncker, who focused solely on the target’s motion in relation to other objects in the surrounding visual field. The other one, on the contrary, focused on the role of eyes-head movement and of target’s change of position with relation to the observer as possible factors of (mis)perceived motion, therefore suggesting a subject-relative source of mislocalization. Brosgole, in 1968, conducted several

experiments in order to evalute the role of both these theories on visual perception. His results led to the conclusion that a displacing field can induce motion to a stationary object as far as it shifts the apparent straight-ahead and that the degree of this displacement was related with the amount of induced motion and with the size-of-field. E.g., an apparent median plane shift to the left correlate with an induced motion to the right in equal measure. Moreover, he found out that perception of motion does not depends upon the relationship between that object and its surroundings; instead it results from a subjective displacement of objects in space. Ultimately, perceived motion in a given direction resulted from spacial displacement in that direction during a limited period of time [72].

2.4.2 Dissociation of action and perception

In modern times Roelofs effect has been reevaluated and it was discovered that Roelofs illusion has a different effect in perceptual and motor tasks. In fact, despite the perceptual mislocalization of a target, a guided movement in its direction appear accurate under specific conditions. Many experiments were performed to understand the underlying causes of this phenomenon.

An initial hypothesis introduced to explain the presence of a dissociation between perception and action was the two visual-systems theory. This theory states that visual system is composed of two different branches, differentiating after sharing an early vision input in the primary visual cortex: a "cognitive system", which focus on perception, and a "sensorimotor system", specialized for visually guided motor activity, which is active even when an object's location is not perceived and therefore available in the cognitive system. On support of this hypothesis, it has been demonstrated an anatomical dissocation between different cortical areas encoding visual informations in primates: the cognitive system appears to be located in the temporal lobe, while sensorimotor functions refers to posterior parietal areas. Human patients who suffers from neurological diseases showed a similar pattern: some experienced visual ataxia, characterized by a damage in the sensorimotor system that prevented them to accurately grasp or reach an object despite being able to identify it; meanwhile others had a damage to the cognitive system that caused impairment in objects's perception, but not in visually guided behaviour. The two

visual-systems theory therefore assumes that correct visual perception is not mandatory in order to produce effective motor activity, and that a subject does not need to perceive a target's location to engage with it [75].

Different experiments, especially of saccadic suppression and induced motion, have been successfully conducted to prove the dissociation between cognitive and sensorimotor systems, but they mostly required movement of the target. In order to eliminate motion (of target, background or eyes) as a confounding factor, induced Roelof's perceptual illusion was applied to these studies [76]. A rectangular frame, with an eclosed target, was presented asymetrically in the subject's visual field; the target's location was misperceived in the opposite direction of the offset frame. This perceptual mislocalization was noticeable when subjects were asked to address the target verbally, showing that the cognitive system was prone to the illusion. However, if subjects were requested to physically make open-loop pointing movements towards the target, once it disappeared, they were able to accurately identify its location. It was later demonstrated by a subsequent series of experiments that accuracy in pointing/reaching behaviour towards a target increase linearly with distance of the hand from the body [77]. The motor task involved the sensorimotor system, proving that motor behaviour was not affected by the illusion. Sensorimotor system appears to be less prone to the illusion because it is mostly based on egocentric localization rather than on objects' qualities recognition; moreover, the sensorimotor system does not require to make decisions about objects identity because it works on a 1:1 relationship between the target's position and the position of the finger during the pointing behaviour [75]. The opposite effect of Roelofs illusion on perception and action was important evidence to support the hypothesis of two different paths of visual processing [69].

A further experiment introduced a 4-seconds delay between the target disapperance and the subject's pointing action. In this case, in all subjects tested, both cognitive and sensorimotor representation were affected by Roelofs illusion, in particular motor behaviour towards the target was biased by the frame's displacement [76]. This event could be explained as a loss of accurate visual and spatial informations in the sensorimotor system after a limited period of time (studies showed Roelof's illusion onset after a 2-seconds delay), which resulted in forcing subjects to import data from the cognitive system, including the perceptual illusion, in order to guide a delayed movement [75].

An alternative explanation for the different effect of Roelofs' illusion on action and perception was produced by Dassonville and Bana, whom took up Werner, Bruell and Albee's studies on the biased-midline hypothesis. They aimed to prove that Roelofs' perceptual and motor effects were traceable to a frame-induced bias in the observer's apparent midline, and not to a two visual-systems theory. Under normal visual conditions, the center of the visual field reflects the apparent median plane of the subject. During the experiment, subjects were asked to look straight ahead after an offset frame was presented to them in surrounding complete darkness, it was indeed showed that the frame was able to bias the observer's apparent midline in its direction (*Fig. 8A*). Moreover, it was also possible to explain how the sensorimotor system appeared to be immune to Roelofs' perceptual illusion. When a target was presented within the rectangular frame and the subjects were asked to point at it, the sensorimotor response was accurate: assuming that motion behaviour is guided within the same distorted reference frame already used to identify target's location, the error in target encoding was cancelled by the error in motor guidance (*Fig. 8B*) [78].

Dassonville and Bana were also able to demonstrate that the effect of the distorted frame on the subject's apparent straight ahead was transient: after the frame disappeared, in fact, its influence on mislocalization decreased, allowing proprioceptive and vestibular cues to return dominant. During the experiment, a few seconds after the removal of the Roelofs-inducing frame, the apparent midline shifted back towards its right position, taking the misperceived memory of the target location with it. Accordingly, the delayed motor response towards the target was directed in its incorrect location (*Fig. 8C*), proving that sensorimotor response after a few seconds delay is affected by Roelofs' illusion, as previously stated by Bridgeman [78]. The disperceived frame reference in which occured the encoding error of the target is not the same used to guide the motor behaviour, therefore one error does not cancel the other [69].

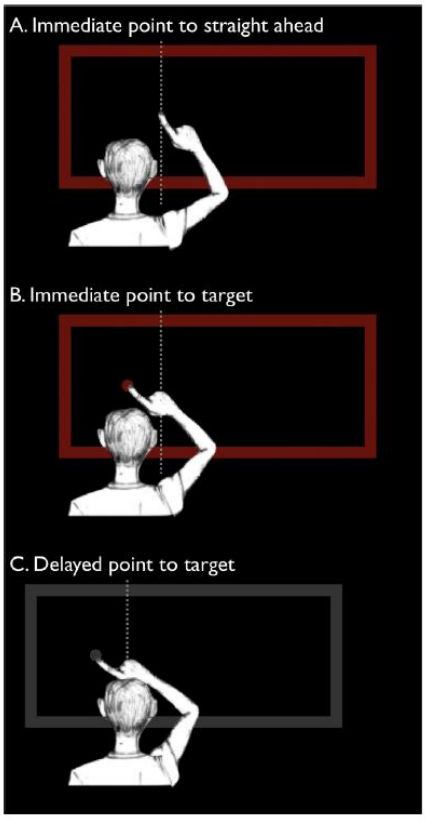

Fig. 8 A *- When subjects were asked to point to straight ahead immediately after the disappearance of the reference frame, the observer's motor response was biased. The frame induced a deviation of the subject's apparent midline in its direction.*

Fig. 8 B *- A target was presented within the offset frame, e.g. on the left of the subject's apparent midline. If asked to point at the target, the subject's motor response was accurate, as the target encoding and motor guidance happened in the same distorted reference fame, cancelling each other out.*

Fig. 8 C *- With an imposed delay of more than 2 seconds between the frame's disappearance and the motor response, apparent midline shifted back towards the objective midline, taking misperceived target's location with it. The motor response, as it happens in a veridical reference frame, is incorrect, reflecting the original error in target encoding.*

2.4.3 The Roelofs effect on levels of visual processing

Recent works on Roelofs effect have tried to understand the responsible mechanism for the distortion of the subject's apparent midline. To do so, it was studied the level of processing at which the illusion-causing reference frame has its effect. Different studies led to different results. Lathrop and Bridgeman focused on "inattentional blindness", a phenomenon characterized by failure in noticing an unexpected stimulus when a subject is fully focused on an attentional demanding task. In their experiment, Roelofs effect was used to demonstrate if a big illusion-inducing stimulus presented unexpectedly such as the frame can go unnoticed due to inattentional blindness during an attentional task and, if that happens, if it will still produce its illusory effects. Subjects were asked to make a judgement on target's location during an additional attentional task. Results showed no difference in perceptual mislocalization of the target between those who did and did not report the reference frame, demonstrating that the frame did not need to be consciously perceived to cause a bias in the observers' apparent midline [79]. Moreover, awareness of the illusion-inducing contextual cue was insufficient to even modulate Roelofs effects' magnitude. In conclusion. this study suggested that early visual processing was involved in processing information from contextual cues and that it had a role in illusions susceptibility.

These results were opposed by many other studies which suggested how the magnitude of a wide range of visual illusions could be modulated by attentional tasks. A main experiment led by Lester and Dassonville demonstrated that features-based attentional processes have effect on the magnitude of Roelofs effect. They asked patients to search for a target of a certain colour (among distracting-coloured items) and obtain a much greater effect of Roelofs illusion (causing an enhanced shift of the perceived straight ahead) when a reference frame of the same colour was added to the visual field. These findings supported the idea that even if Roelofs illusion can be obtained without conscious awareness of the illusion-inducing spatial context, it is also possible to modulate its magnitude using attentional processes. The role of feature and space-based attentional processes implicate that, not only early, but also later stages of visual processing are involved in illusions susceptibility. In summary, both bottom-up (environmental visual cues) and top-down (task-relevant) attentional information influence Roelofs effect [80].

2.4.4 Roelofs effect in psychiatry

Roelofs effect, along with other perceptual illusions, has been tested in some psychiatric disorders in order to evaluate visuospatial perception and visual guided motor behaviour towards a target. To date, researchs focused primarly on autism spectrum disorders and schizophrenia.

2.4.4.1 Visuospatial processing in ASD

Abnormalities in perceptual processing are not a diagnostic key trait of autistic spectrum disorders (ASD), but in these patients it has been demonstrated an impairment in visual recognition of motion behaviour. In particular, child with autism have shown a deficient perception of human motor behaviour, presumably due to a deficit in integration of local movements into a global coherent pattern, while the visual identification of an inanimate object's movement appears to be more accurate. This hypothesis is supported by a typical feature of ASD such as impaired recognition of emotional facial expressions, which could be considered a subtype of biological motion and could be explained by a difficult integration of motion signals from eyes, mouth and forehead [81].

2.4.4.2 Roelofs effect in ASD

Studies were performed in order to prove that the inability of ASD patients to integrate contextual elements into a general pattern could be associated with a reduced susceptibility to visuospatial illusions. Walter and Dassonville, for example, focused on the impact of autism in visual processing assuming that illusion susceptibility depends on the extent to which autism traits are exhibited among individuals. To do so, they tested Roelofs effect along with a battery of other perceptual illusions in ASD patients. Their studies showed a significant negative correlation between a typical autistic trait such as systemizing (i.e. the ability or drive to analyse and construct complex systems in order to control them) and susceptibility to a series of tested illusions, not only Roelofs but also Ponzo, rod-and-frame, Poggendorff and Zöllner illusions.

This decreased susceptibility could be related to the inner tendency of this trait to focus on the target per se and not on the context that cause the illusion (e.g. the reference frame in Roelofs effect). All these visual illusions appear to be caused by a mislocalization of the observer's sense of straight ahead, vertical and horizontal directions and can all be considered tilt-inducted illusions, suggesting that they probably share a common underlying cause [82].

2.4.4.3 Visuospatial processing in schizophrenia

Schizophrenia is associated not only with deficits in information processing on a cognitive level, but also with a series of sensory-perceptual dysfunctions; deficits have been found in olfactory, auditory and somatosensitive systems and, of course, visual processing.

Studies suggest that, in schizophrenia, magnocellular pathway (see 2.3) seems to be dysfunctional while parvocellular stream appears to be intact. Magnocellular impairment results in deficits in motion processing, low-contrast and low-resolution visual detection [83]. Contrast gain and contrast sensitivity are factors that increase neural response to motion signals and are crucial in the early visual processing. On the contrary, in a later stage of visual impairment neural responses are not-contrast dependent but sensitive to velocity or direction of the target. As a result, velocity discrimination of a target presented at low or high contrast is a marker able to detect what stage of visual motion processing is impaired in schizophrenia. Studies showed a reduced velocity discrimination in both low and high contrast in patients compared to healthy controls, patients were found lacking in the ability to improve velocity discrimination when the target's contrast increased. Therefore, an impairment in both early (contrast-dependent) and late motion processing (contrast-independent) may be involved in schizophrenia [84].

Magnocellular pathway deficits suggest that gain control, which refers to the ability of the sensory systems to adapt and optimize their neural responses to the surrounding context, is compromised. Gain control is able to reduce the impact of undesired or unhelpful sensory input and at the same time amplify or facilitate salient signals, adjusting to environmental demands [85]. This mechanism operates at a low-level visual processing and enable the identification of basic visual stimuli; it is also a necessary ground in order to reach a higher-level visual processing, in which integration of local visual inputs conveys into a global complex structure

with recognition of faces, objects and movement [65]. Low-level processes are mediated by the early structures of the visual system (from the retina to the primary visual cortex), while higher-level processes are handled by the middle temporal area (MT), an extra-striate cortical area involved in global motion processing [84,86]. Studies showed an impairment not only in the low-level system, but also in the integration process in schizophrenia, as demonstrated by a deficient object recognition, face processing and contour identification. Gain control has been studied in motion processing tasks. Motion is signalled by direction-selective neural units in V1 and later pooled by MT neurons, with larger RF and center-surround antagonism. Impaired gain control leads to motion processing deficits. Pathophysiology of both gain control and integration dysfunction seems to be related to NMDA/GABAergic dysfunctions and dopamine deficiency. Gain control and integration (which represents lower and higher-level visual processing respectively) are necessary to obtain correct visual perception, that indeed result compromised in schizophrenia [65].

Perceptual-sensory deficits in schizophrenia have been widely investigated thanks to visual illusions, which helped provide information on how schizophrenic patients perceive the visual world and insight on possible underlying causes of psychotic visual symptoms. As previously stated, perceptual processes are divided into a low-level and a high-level system based on what visual features need to be recognised and, consequentially, on what cortical areas are involved. Low-level visual illusions such as contrast illusions rely on early visual processing structures that perform gain control. Schizophrenia patients showed a specific resistance to some, but not all, of these illusions and, opposed to healthy controls, exhibit a weakened gain control mechanism that does not allow them to optimize visual discrimination. High level illusions, on the other hand, require a cognitive control to completely understand more complex visual features. Patients showed an increasing trend in resistance to these illusions. Perceptual impairment in cognitive-level visual features has been linked to reduced social functioning in schizophrenia. Supporting evidence of increased resistance to higher-level visual illusion is a reduced "top-down modulation" i.e. integration of high-level information such as contextual cues with lower-level visual perception [86].

Regarding spatial context processing (see 2.3), several studies suggested that schizophrenic patients' visual processing was not as influenced by spatial context as healthy controls, resulting

in a more accurate and enhanced visual performance (limited to some task) [87]. Patients were found in fact less susceptible to the "surround-suppression" phenomenon, in which the neural response to a visual stimulus is reduced by a co-stimulation in the surrounding context *(Fig. 9).* For example, perception of a central region's contrast is reduced in the presence of a high contrast surround. If this mechanism, as theorized, is reduced in schizophrenia, visual perception of the central region is more accurate [88]. To date, spatial context seems to have the same effect as healthy controls on orientation, luminance, size and motion, while contrast has weakened contextual modulation. In summary, reduced contextual modulation it is likely not a general impairment in schizophrenia, but it is limited to some specific visual tasks [89].

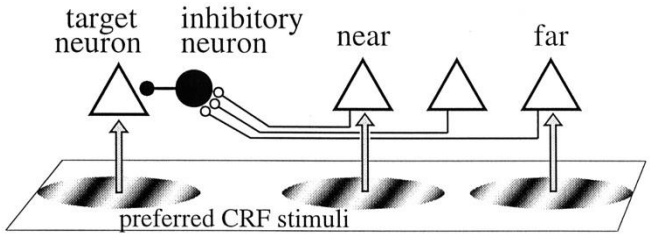

Fig. 9 *– Surround suppression.*

Other research, on the contrary, stated that spatial contextual processing may be greater, and not weakened as previously theorized, in schizophrenia. For example, a study submitted patients to a visual task involving randomly moving dots in the surround, while motion perception was measured in the center. It was demonstrated an increased perceptual shift of central motion perception in the opposite direction of the surround, especially when the center and the surround moved in the same direction. This result was considered coherent with an increased surround suppression in schizophrenia [90]. The opposite hypothesis on the effect of spatial context in schizophrenia may be explained by a change in brain activity levels when different kind of visual stimuli are presented to patients. In fact, whether similar (e.g. gratings used in previous studies) or different/global stimuli (e.g. frame and target/moving dots) for the center and the context were used, separate mechanisms of visual processing were activated and eventually impaired in opposite ways [91].

The hypothesis of a greater spatial contextual effect in schizophrenia has been furtherly researched with the help of Roelofs effect.

2.4.4.4 Roelofs effect in schizophrenia

Roelofs effect has been tested in patients with schizophrenia to gain information on visual perception and visuomotor processing in this mental disorder. A rectangular offset frame (left-shifted, central and right-shifted) with an eclosed target was presented to the observer on a black background; subjects performed a visual task, an immediate and delayed visuomotor task and a contrast detection task. Tests showed a significant greater effect of the Roelofs illusion in patients in the first three tasks, compared to healthy controls. This result underpins the idea that visual and visuomotor processing share a common underlying mechanism, likely an incorrect inhibitory control over the illusion-causing spatial context (i.e. the reference frame that causes the illusion in not completely suppressed in the perceptual process). This study, as stated above, suggested that the spatial contextual effect on schizophrenia patients' visual system seemed indeed to be augmented and this may be associated with a reduced filtering of not useful visual information (also known as hyper-responsiveness to the environment). This could explain the excessive effect of irrelevant stimuli, such as the reference frame, over the relevant task, which is the target [91].

The pathophysiological neural substrate for the augmented effect of Roelofs illusion in schizophrenia patients has been linked to the superior part of the parietal cortex. An fMRI study has demonstrated that this part of the parietal cortex, along with the precuneus, is particularly active when the subject is asked to determine if a target is located left or right of the apparent straight ahead, in the presence of an offset rectangular illusion-inducing frame. Therefore, this cerebral area has been associated with visuospatial context processing and with identification of a target's location in the presence of contextual cues. Additional results support the idea that perceptual location tasks are predominantly associated with activation of the dorsal visual system, rather that ventral system as it was previously stated in the two visual systems hypothesis [92]. A subsequent study showed that the suppression of neural activity in the superior parietal lobe in the right hemisphere, but not the left, led to a significant reduction of

susceptibility to illusions caused by a distortion of the egocentric reference frame, while illusions based on different mechanism were unaffected. These findings proved that this area is involved in processing visual contextual information in order to maintain perception of egocentric space [93].

In summary, it is possible that the augmented Roelofs illusion in schizophrenia may not be completely related neither to the ventral system (i.e. the temporal cortex) nor to the dorsal system (i.e. dorsal parietal cortex). This conclusion is supported by another study that demonstrated how a patient suffering from bilateral lesion of the dorsal system showed the same sensitivity to visual illusions as healthy controls, suggesting that visuomotor behaviour may be executed independently of the dorsal pathway [94].

2.5 Visuospatial processing in bipolar disorder

Bipolar disorder and schizophrenia share genetic risk factors and some clinical features, however abnormalities in sensory and perceptual processes, well established in schizophrenia, have been less studied in BD. Bipolar disorder is characterized not only by mood alterations, but also cognitive and sensory dysfunctions. Different studies have tried to identify disturbances in sensory processes in BD, in particular visual perception. Visual processing has been assessed in BD on a set of tasks to evaluate different stages and channels implicated in the identification and transmission of visual cues.

For example, to assess integrity or disruption of magnocellular and parvocellular pathways different visual tasks were submitted to BD patients. As mentioned above, the M-pathway can be probed presenting stimuli with low-luminance contrast, low spatial frequencies and high temporal frequencies while the P-pathway responds to static stimuli, high spatial frequencies and low temporal frequencies. Studies showed a generalized deficit in moving performances at all temporal frequencies and intact threshold for a static and high-spatial frequency stimulus. Moreover, dot motion discrimination (that involves the dorsal cortical pathway and the MT area) was impaired while form discrimination (conveyed by the ventral stream) appeared intact. All these results led to the conclusion that the M-pathway is primarily dysfunctional in bipolar disorder as it is in schizophrenia [95].

Further studies were conducted to define if a deficit in early visual processing and thus visual discrimination was present in bipolar disorder. To do so, a low-level visual sensory domain such as spatial frequency was studied. Results showed an increased discrimination threshold in both schizophrenia and bipolar disorder patients, suggesting worse performance than healthy controls. Discrimination threshold was negatively associated with IQ in both controls and bipolar patients, backing the notion that early visual processing is a precursor to higher-level cognitive functions. Moreover, in both groups of patients, a disruption in early visual processing was related to worse psychosocial and daily functioning, as a result of reduced ability to encode information and direct attention to relevant targets in the surroundings [96]. Ulterior evidence of early visual processing deficits and its association with clinical symptoms in BP and SZ have been investigated using the contrast sensitivity function (CFS), a measure that identify the threshold between visible and invisible and correspond to the reciprocal of the contrast threshold. CFS differs with spatial frequencies. Both groups of patients demonstrated lower contrast sensitivity to low, moderate and high spatial frequencies compared to healthy controls. Comparing the two groups of patients, however, SZ showed lower sensitivity to high spatial frequencies. Moreover, clinical variables as treatment (especially lithium and typical antipsychotics), illness duration and symptoms' severity had a high and moderate influence on BD and SZ respectively [83].

Another domain known to be reduced in schizophrenia is velocity discrimination, a measure of late visual system functionality, which is involved in global motion processing. Velocity discrimination is mediated primarily in the middle temporal extra-striate cortex that, if damaged, lead also to impairment in eye tracking and motion discrimination. Studies were conducted to evaluate if velocity discrimination threshold was elevated in other psychotic conditions such as bipolar disorder. Bipolar patients showed deficits in velocity discrimination only at high velocities, patients with schizophrenia instead showed deficits along all the range of velocities tested (low, intermediate and high). A direct measure of the integrity of motion processing only happens at intermediate velocities, when the velocity signal of a target is dominant compared to its other features, such as position, contrast or temporal frequency (which intervene at low or high velocities). Since bipolar patients did not show reduced velocity discrimination at intermediate velocities, it is possible to conclude that motion processing is not impaired in these patients. Furthermore, considering that at fast velocities temporal changes in visual contrast (a

non-visual cue) is dominant, the selective velocity discrimination impairment in BD at this velocity range may be due to a temporal visual processing disruption rather than a motion processing deficit per se [97].

In conclusion, contextual processing and its influence on visual targets has been investigated in subjects suffering with other forms of psychosis than schizophrenia, for example bipolar disorder. Results suggested normal magnitudes of spatial contextual effects on all visual domains tested. The contextual contrast illusion, in particular, is different between the two groups. While in schizophrenia contrast had global weakened contextual modulation (resulting in a more accurate discrimination), bipolar disorder patients did not. Yet, the latter group experienced the same effect when suffering severe manic states. This event may be related to abnormal gain control mechanism in early visual areas caused by hyperdopaminergia during mania, since dopamine levels are associated with contrast gain control. Furthermore, the strength of context effects such as motion or orientation may be modulated by clinical symptoms severity, both in SZ and BD [87].

2.6 Psychophysics

Psychophysics aims to evaluate the mathematical relationship between physical stimuli submitted to observers and the resulting perceptual responses. The purview of psychophysics is to analyse the outward human behaviour as an indirect measure of inner perception. Visual psychophysics, in particular, provides a set of useful tools to analyse the processes underneath visual perception and their neural substrates. We introduce these concepts as the experimental task submitted to the patients in our study (see 4.3.2.2) followed standard psychophysical procedures.

During psychophysical procedures, physical stimuli are presented to observers, who need to indicate if they experience detection (i.e. they perceive the stimuli) or discrimination (i.e. they differ from a reference stimulus). Different psychophysical methods have been developed to explore the limits of detection and discrimination. These methods are structured systematic procedures in which many samples of a given behaviour are observed in response to given stimuli; changes in stimuli's characteristics lead to changes in detection and discrimination. One

of the classical psychophysical procedures is the constant stimuli method (CS, see 4.3.2.2), others are called adaptive psychometric procedures and are designed to maintain accuracy and reliability of psychophysical measures while reducing experimenter's and subject's time and effort (see 4.3.2.1) [98].

A core feature in the theory and practice of psychophysics is a psychometric function (*Fig. 10*), which describes the relationship between a physical measure of a stimulus (e.g. stimulus strength) and the subject's response. The latter variable is represented by the probability of success on a certain number of trials at that stimulus level, where the response is expected to be a two-alternatives-forced-choice response pattern (e.g. yes/no, correct/incorrect) [99].

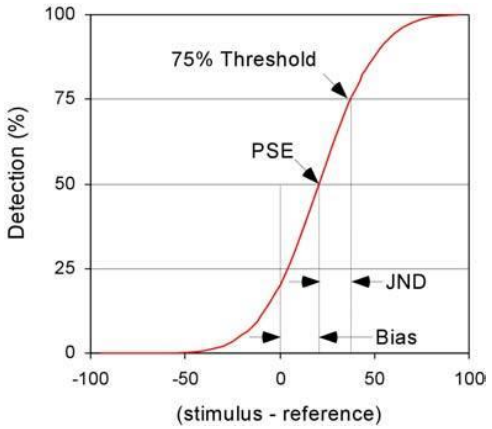

Fig. 10 *– A generic psychometric function*

There are two important parameters of a psychometric function: Point of Subjective Equality (PSE) and Just Noticeable Difference (JND). PSE is the point at which a given stimulus is considered equal to a reference stimulus, therefore there is an equal 50% probability to give a correct or an incorrect answer. The detection rate at PSE corresponds to equiprobable random guessing. PSE gives information about the accuracy of the results (that is high when the PSE is close to its actual value) and about possible response bias. In fact, the difference between PSE and the reference stimulus level correspond to judgement bias. JND, on the other hand, is the smallest difference that is detectable between two stimuli, and it corresponds to the stimulus values at which the probability of a correct response is about 65-70%. It is a measure of results' precision, that is high when the JND is smaller [98,100].

3. AIMS OF THE STUDY

It is known from few previous research that schizophrenia is associated with altered visuospatial processing and perception, and that some visual dysfunctions may be present in bipolar disorder too. This study aims to add further evidence to this statement, utilizing a visual illusion known as Induced Roelofs Effect. We compared Induced Roelofs effect in patients with bipolar-I, bipolar-II and schizophrenia, in order to demonstrate a bigger effect size in patients than healthy controls. Moreover, we aimed to demonstrate differences in Induced Roelofs effect size between the three groups of patients tested and especially an augmented effect size in bipolar disorder, in order to add further evidence to previous findings suggesting spatial processing's dysfunctions in major mental illnesses other than schizophrenia.

4. MATERIALS AND METHODS

4.1 Subjects

Forty-six patients *(Table F)* were enrolled in the study: 15 healthy controls (HC), 13 bipolar-I patients (BP-I), 9 bipolar-II patients (BP-II) and 9 schizophrenia patients (SZ). Each subject was submitted firstly to a training and secondly to an experimental session. Subjects were recruited over a period of almost 2 years, starting in December 2020 and ending in September 2022.

All patients were hospitalized and received a diagnosis of bipolar disorder or schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders criteria [13] . Exclusion criteria included the following: psychiatric disorders other than SZ or BP, history of drug and alcohol addiction, neurological disorders, and severe somatic diseases. All healthy individuals had no history of psychiatric, neurological, or cognitive disorders. All participants were Italian native speakers. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Individuals provided written informed consent prior to testing.

Subjects were also submitted to a psychodiagnostic evaluation using the NIMH-MATRICS Consensus Cognitive Battery and a series of both self-rated and clinician-based questionnaires, in order to assess different clinical and neurocognitive domains.

	N°	Gender	Age (min-max)	Age mean
HC	15	10 M	26 – 48	33,73
		5 F		
BP-I	13	9 M	21 – 68	36,31
		4 F		
BP-II	9	3 M	20 – 67	47,89
		6 F		
SZ	9	6 M	23 – 65	45
		3 F		

***Table F**: number (N°), gender (M: males, F: females) and age data from the subjects enrolled in the study.*

4.2 Stimuli and setting

The experimental sessions were conducted in the ANTARES (Applied Neuroscience for Technological Advances in Rehabilitation Systems) JointLab, located in the Psychiatry Department of the San Martino Hospital in Genoa and co-directed by both the Italian Institute of Technology (IIT) and the Psychiatry Section of the University of Genoa's Neuroscience Department (DINOGMI-UNIGE).

Observers were placed in a darkened room, where the only lighting available was the one provided by a computer monitor. They sat at a table, with their heads stabilized using a chin rest. A keyboard was placed on their frontal plane, at an accessible length. A 60 Hz, 19" HP monitor (model L1940T, aspect ratio 5:4, dimension 29.4 cm × 29.4 cm, resolution 1280×1024 pixel) was positioned 57 cm far from the subjects. The middle point of the chin rest was used as a reference to accurately locate the computer monitor, so that the participants' head midline was

aligned with the monitor midline. The distance between the superior left edge of both the chin rest and the computer monitor (a) and between the superior right edge of both the chin rest and the computer monitor (b) should range between 62-65 cm. It was required that a and b had the same length *(Fig. 11)*. The examiner sat near the patient, in front of a laptop connected to the 19'' monitor. This laptop was used to control trial presentation and to collect data from subjects' responses.

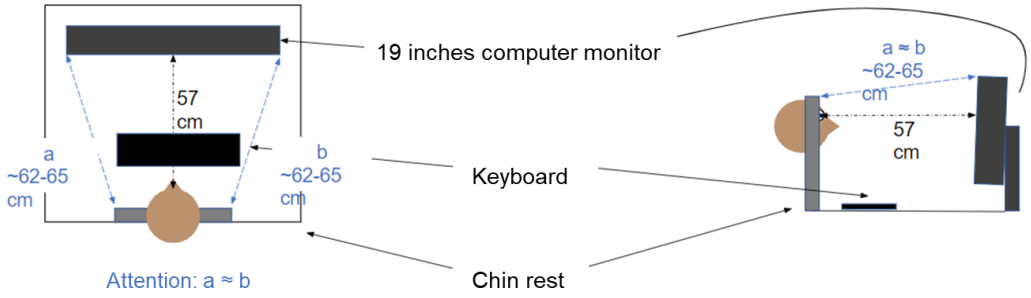

Fig. 11 *- Setting*

The stimulus *(Fig. 12)* consisted of a target (dot) enclosed by a reference frame. The spot had a diameter of 0.15°, while the frame measured 20° horizontally and 10° vertically.

Visual stimuli presented to the subjects were generated and controlled by MATLAB (The MathWorks Inc., 2022) with the Psychophysics Toolbox, a software package that support visual psychophysics and that can provide an interface between a high-level platform-independent language like MATLAB and the video display hardware [101,102].

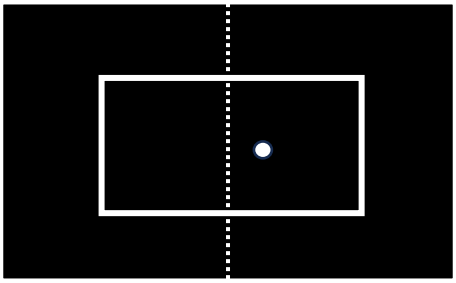

Fig. 12 *- Stimulus*

4.3. Procedure

The task presented to the patients consisted of two different parts: a training and an experimental session. In the training the examiner verbally explained the task to the subjects and let them perform some orientation trials. The experimental session consisted of two different blocks: a preliminary assessment of the subjects' left-right discrimination abilities and the Induced Roelofs effect assessment.

4.3.1 Training

Subjects were submitted to a training before starting the experimental session. The first part of this training consisted of a verbal explanation of the task, presented by the examiner. Subjects were asked to look straight towards the 19 inches monitor where the stimulus, consisting of a dot within a reference frame, appeared. These two items were presented with no correlation to one another, the dot could be shifted to the right or to the left with respect of the midline. The stimulus presentation lasted 1 second and then expired. Subjects were informed that during the task they needed to judge the position of the dot with respect to their midline, ignoring the frame. In particular, subjects should identify if the chosen item was located leftwards or rightwards compared to their nose. They were asked to respond using the keyboard located in front of them. To answer "left" subjects were required to press the left arrow key with their index finger, to answer "right", likewise, to press the right arrow key with their middle finger. This motor task should be executed as quickly as possible, but only after the stimulus offset.

In the second part of the training subjects were asked to sit at the desk and find a comfortable position, adjusting both the sitting height, to fit in the chinrest, and the keyboard position. Once that was achieved, the examiner started some orientation trials so that the subjects could acquire confidence with the task and demonstrate to have fully understood the assignment. Finally, the examiner instructed the participants that, in case they had difficulty in pressing their response on the keyboard, they could answer verbally and the experimenter himself would enter the response manually.

4.3.2 Experimental session

As mentioned above, the experimental session consisted of two blocks: a preliminary left-right discrimination assessment and the Induced Roelofs effect assessment. Both blocks had the same trial structure: the stimulus was shown to the patients for 1 second, it appeared on the monitor located in front of them. They were asked to discriminate the dot's position with respect of their perceived midline, ignoring the surrounding frame. Their motor response could be executed only after the stimulus' disappearance. A response to every current trial, and its respective collection, was necessary to start the following one. An inter-trial interval between every trial was sampled randomly from the range [1, 1.5] s *(Fig. 13).* No feedback was offered by both the monitor or the examiner regarding the accuracy of the subjects' responses. The only difference between the two blocks was the number of trials and the position of the two presented items. First block lasted about 2 minutes and the second one lasted about 10 minutes, therefore the whole procedure, including breaks that participants were free to take if needed, lasted about 15-20 minutes.

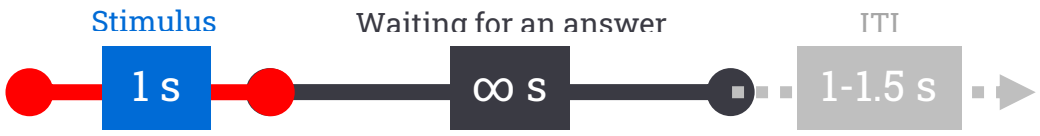

Fig. 13 *– Stimulus presentation*

4.3.2.1 Preliminary left-right discrimination assessment

The preliminary assessment consisted of 40 trials, lasting about 2 minutes. The stimulus consisted of dot, whose position could range between -2° and 2°, surrounded by a frame, located at 0°, i.e. in the center of the screen. The dot position was determined by a QUEST routine on a trial-by-trial basis; QUEST is an adaptive psychometric procedure that use a Bayesian approach to locate the dot position.

Bayesian approach differs from classical statistical methods because it incorporates subjective beliefs about the parameter being evaluated and include prior knowledge and experience to the

estimation process, therefore it does not rely solely on the information from the data. In Bayesian inference prior distribution of a given parameter, i.e. the degree of belief of the parameter before observing the data, is updated with observed data using Bayes' theorem to calculate the posterior probability of the hypothesis. The posterior probability distribution, i.e. the degree of belief of the parameter after observing the data, becomes the new prior in the next round of inference. In summary, compared to classical statistical methods, loss of information in the process is reduced[103,104].

QUEST is an algorithm used in psychophysics and it is part of adaptive procedures developed to obtain valid threshold estimation (i.e. stimulus values leading to a given percentage of determined levels of detection or discrimination) while reducing observers' effort and experimental time, compared to other methods such as constant stimuli (CS). To do so, adaptive procedures concentrate stimulus presentation near subjects' threshold and do not require responses to a larger set of stimulus values. In particular, adaptive parametric procedures assume beforehand the underlying psychometric function (i.e. observers' response as a function of stimulus value) and after each trial one or more parameters of the function are estimated and used to determine the most informative stimulus to present next [98]. In all adaptive procedures, knowledge of the outcome increases as the procedure is in progress as stimulus placement is driven by the algorithm and located towards the selected measurement point [105]. QUEST is a Bayesian variant of these procedures; in fact, it introduces the concept of a prior probability density for the psychometric function parameters [98]. Main characteristics of this algorithm include assuming a single stimulus dimension, sampled periodically, and two only possible trial outcomes (e.g. yes or no). Moreover, it assumes a constant slope (i.e. how rapidly performance change with changes in stimulus values) for the psychometric function, therefore it only estimates one parameter that is the threshold, defined on the stimulus dimension [99,106]. The application of the QUEST algorithm to our study allows to define the position of the dot and its distance from the midline using information available from previous trials, along with prior knowledge derived from the literature. QUEST is able to identify the ideal dot position as to obtain 65-70% of correct answers.

In this first part of the experimental session standard psychophysical procedures were followed by using the just noticeable difference (JND) as an index of the observers' discrimination ability.

JND equals the standard deviation (SD) of the Gaussian cumulative distribution, fitted on the proportion of correct given answers with respect of the dot position.

4.3.2.2 Induced Roelofs Effect assessment

In the assessment of the Induced Roelofs effect, the frame could appear on the monitor in different positions with respect to the monitor midline: -3.2°, -1.6°, 0°, +1.6°, +3.2°. The dot, on the other hand, could appear in only two positions: to the left or to the right of the monitor midline. Frame shifts towards positive numbers (+1.6°, +3.2°) are ipsilateral to the dot shift, frame shifts towards negative numbers (-1.6°, -3.2°) are contralateral to the dot shift. In particular, at -3.2° and -1.6° dot and frame shifts are in opposite sides from the monitor midline but at -3.2° the frame is far from the monitor midline while at -1.6° their distance is reduced. At 0° the frame midline corresponds to the monitor midline. At +1.6° and +3.2° dot and frame shifts are in the same side of the monitor midline but at +1.6° the frame midline is closer to the monitor midline compared to their distance at +3.2°.

As shown in the following image (*Fig.14*) ten different combinations of dot and frame shifts could be projected on the monitor (five frame shifts combined with two possible dot shifts). Each combination was presented 20 times, for a total of 200 stimuli in about 13-15 minutes.

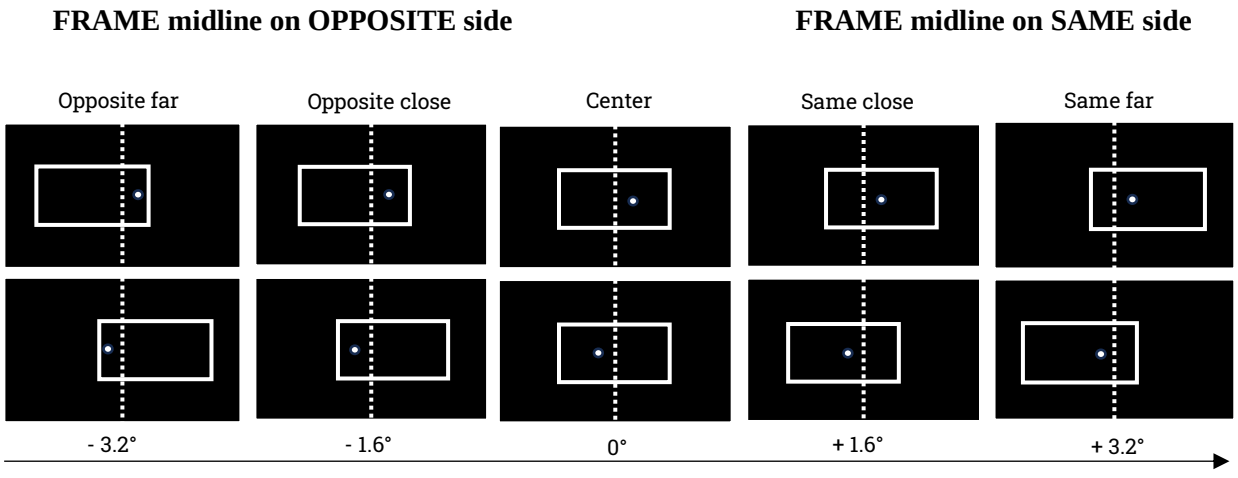

Fig. 14 *– Ten possible combinations of frame and dot shifts.*

As opposed to the preliminary assessment, in this part of the experimental session the stimuli for each trial were selected with the constant stimuli method (CS). This procedure is a psychophysical method that requires response to a large set of stimulus values, whose are specified before the experiment. This method allows to fully develop the psychometric function and to accurately determine both the threshold and the slope. Although this function underlies the perception of sensory stimuli, it is often unnecessary to obtain all parameters of the function, the threshold is typically enough. Moreover, this procedure can be more time consuming and stressful for the patients and the examiner. In fact, unlike adaptive procedures that are known to concentrate stimulus presentation near the patient's threshold, with the CS method many trials are far from the observers' threshold. Additional information about performance at these off-threshold levels is necessary to develop the psychometric function but it is often not worth the extra-experimental time [105,106].

Finally, participant's JND obtained during the preliminary assessment, i.e. the stimulus values at which the probability of a correct answer in 65-70%, was used to determine the dot's distance from the monitor midline in this second part of the experiment. JND, as mentioned above, is the smallest difference detectable between two stimuli and it is a measure of response's precision, that is high when the JND is smaller.

5. RESULTS

Following standard psychophysical procedures, the preliminary results of our study can be summarized in the following figure (*Fig. 15*), in which we observe a Gaussian cumulative distribution function.

.

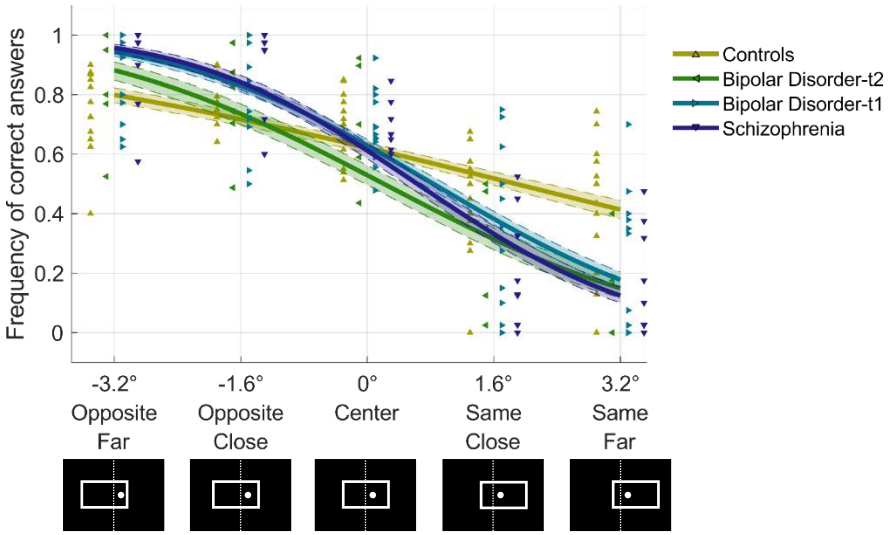

Fig. 15 *– Gaussian cumulative distribution function of tested subjects and groups data*

On the x-axis we observe five out of ten different combinations of dot and frame shifts that could be showed to patients in the Induced Roelofs effect assessment (see paragraph 4.3.2.2). As we already know, at negative numbers dot and frame shifts are contralateral (e.g. see at -3.2° that the dot is on the right of the monitor midline while the frame left-shifted). The opposite happens at positive numbers of the x-axis, e.g. at +3.2°, where dot and frame shifts are on the same side of the monitor midline.

The observers' response is the variable located on the y-axis, measured as the frequency of correct answers given by the subject at a given stimulus level. The answer is expected to be a two-alternatives-forced-choice answer, in this case if the dot is located left or right compared to the subject's perceived midline.

In the graphic we observe the Gaussian cumulative distribution of preliminary data of every tested subject and every tested group (BD-I, BD-II, SZ, HC). The function is the mean value of

the Gaussian cumulative distribution of every tested group. The dots represent raw data of every tested subject, in other words the percentage of right responses of every subject with respect of the dot and frame shifts' combination.

0° (i.e. when the frame is in the center) corresponds to the JND, the stimulus value at which the probability of a correct answer is 65-70%. In particular, 0.68 is the probability that a value drawn from a cumulative normal distribution centered at 0° is larger than the cumulative normal distribution's standard deviation, i.e. the proportion of a correct answer when the frame is in the center. QUEST adaptive algorithm, used in the preliminary assessment, allows to identify the ideal distance between the dot and the midline as to obtain 65-70% of correct answers, in order to equalize task's complexity between all tested groups of patients.

In the left part of the diagram, we observe that all four tested groups gave a higher percentage of correct answers. Dot-discrimination task was easier when dot and frame shifts were on opposite sides of the monitor midline, far from each other (-3.2°). In particular, SZ and BP-I patients had the highest frequency of correct answers, followed by BP-II and then HC. On the contrary, subjects gave the lowest possible frequency of correct answers when frame shifts were ipsilateral to the dot shifts, i.e. when both items were on the same side of the monitor midline, far from each other (+3.2°). In fact, if the frame shifted towards the dot, perceived observers' midline shifted too, leading to a more difficult dot-discrimination task. Again, SZ patients had the lowest frequency of correct answers, followed by both BD groups and lastly by HC.

Induced Roelofs effect is known to let observers perceive a target enclosed by a frame as mislocated in the opposite direction compared to the frame offset. Our results demonstrate that all four group of patients experience in some measure Induced Roelofs effect. At -3.2°, where the frequency of correct answers is the highest, a leftward shift of the frame induce a mislocation of the subject's perceived straight ahead and a perception of the dot on the opposite side, that in this case is the right of the monitor midline. Therefore, in the required two-alternative-forced-choice answer left/right, subjects would likely answer right, i.e. the correct answer. On the contrary, at +3.2° the frequency of correct answer is the lowest because a rightward shift of the frame induce an altered perception of dot in the opposite side of the monitor midline, that is the left, while it really is located on its right. Because of this misperception, subjects would likely answer incorrectly.

Moreover, despite all subjects experienced Induced Roelofs effect, its size is different not only between patients and HC but also between all three groups of patients (*Fig. 16*).

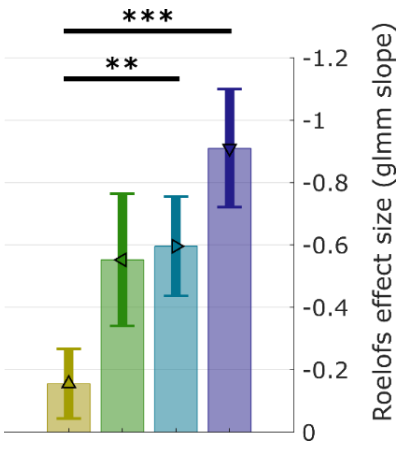

Fig. 16

The link between Roelofs effect size and diagnosis was quantified as the variation in the proportion of correct answers as a function of the stimulus value. To do so, probit regression was used (i.e. a nonlinear type of regression where the dependent variable can only take two values). The model outcome's variable was the proportion of correct responses (y-axis). SZ patients experienced the biggest variation in the proportion of correct responses as a function of the stimulus value therefore their Induced Roelofs effect size is the bigger compared to all other groups tested. BD-I and BD-II patients had similar effect size (slightly inferior in the latter group of patients) but both experienced lower effect size compared to SZ patients. As hypothesised, HC had the smallest variation in the detection of correct answers with the variation of the stimulus value and thus it is possible to conclude that are significantly less prone to Induced Roelofs effect compared to all groups of patients.

6. DISCUSSION

This study was based on the assumption that schizophrenia and bipolar disorder share not only genetic risks factors and some clinical features, but also abnormalities in sensory and perceptual processing. We focused on the visual system, and especially on the role of spatial context on visual perception and processing, researching previous studies that tried to identify disturbances common to both illnesses.

As mentioned in paragraphs 2.4.4.3 and 2.5, both schizophrenia and bipolar disorder have been linked to a primarily dysfunction in the early visual system, reflecting a disturbance in the magnocellular visual pathway that starts in the retina, constitutes the dorsal visual information stream, and end up in the primary vision cortex. When altered, the M-pathway leads to deficits in low-resolution visual information, initial attentional capture, global analysis of the visual field, motion perception and action guidance. Moreover, deficits in early-stage neurophysiological function contribute to dysfunctions in lower-level visual sensory domains, such as contrast sensitivity or spatial frequency [64,65]. The present study was not designed to address a specific M-pathway deficit in both illnesses; however, these kinds of dysfunctions have a large influence on our main point of interest that is spatial contextual processing and center-surround interaction in the visual system.

A dysfunction in early visual processing results in compromised gain control, a mechanism able to adapt and optimize sensory responses to stimuli within a particular surrounding context. Abnormal gain control is linked to a more difficult modulation of neuronal responses to take advantage of the surrounding context. Dysfunctions can also be found in integration, the higher-level visual process that conveys local visual inputs, obtained with gain control, into a global complex structure. Neurophysiology of gain control dysfunction can be linked to NMDA and GABAergic dysfunction [65].

The role of spatial contextual processing on visual perception in SZ has been widely examined in literature, while fewer studies were conducted on BD. Contextual cues' processing enables perception and identification of visual features to be influenced by the surrounding spatial context. Both abnormally strong or abnormally weak spatial contextual modulation typically leads to non-veridical visual performance, however, this process is often considered functionally

advantageous as it is useful to enhance different visual features. Our literature's analysis showed that the role of spatial context on visual perception and processing in SZ is still not completely clear, in fact two opposite theories emerged. The opposite hypothesis on the effect of spatial context in schizophrenia may be explained by an activation, and eventually an impairment, of separate mechanisms of visual processing when different kind of visual stimuli are presented to the patients [91].

Some studies suggested weakened connection of collateral neural units involved in processing central and surrounding stimuli, resulting in diminished contextual modulation in patients compared to controls. Therefore, patients were found experiencing a more accurate and enhanced visual performance in some specific visual sub modalities, e.g. contrast detection [89]. Others research, on the contrary, found greater contextual modulation in SZ leading to abnormal visual perception and especially misperception of central stimuli. Excessive spatial contextual effects may be associated with a reduced filtering of irrelevant visual information (also known as hyper-responsiveness to the environment). Our study supports the latter theory because significantly augmented magnitudes of the Induced Roelofs Effect, as found in our results, indicates in fact the existence of excessive spatial contextual effect of the reference frame during a visual task. Greater contextual modulation, in fact, allows amplification of irrelevant visual information, such as the reference frame, over the relevant task, which is localizing the dot. This may be influenced by reduced tod-down modulation in filtering out irrelevant stimuli.

Abnormal information processing and the consequent overflow of sensory stimuli in schizophrenia indicates a multi-faced abnormal inhibitory control in processing visual information. Weakened contextual modulation has been liked to reduced GABA levels in the primary vision cortex while other studies, suggesting greater contextual modulation, hypothesised excessive GABA inhibitory control of motion processing [90].

In other words, SZ patients suffers from abnormal surround suppression. Surround suppression is a phenomenon in which the neural response to a visual stimulus is reduced by a co-stimulation in the surrounding context, i.e. outside the classic receptive visual field. It is a fundamental property of visual neurons, useful to obtain efficient information processing. Surround suppression has been found altered in SZ when salient motion stimuli activate the neural circuitry. However, previous studies found different results regarding the nature of this

abnormal suppression. Surround suppression has been considered weakened in SZ compared to healthy controls in a wide range of studies, mainly regarding orientation-specific or contrast-specific surround suppression. This would allow patients to perceive the central region of the visual field more accurately [88,89]. Other studies instead (see [90]) found stronger surround suppression, proved by the perceptual shift towards the opposite side of central motion experienced by patients when observing a moving surround. Our results seem to agree with the latter findings, as it was indeed demonstrable that the presence of a moving surround, the frame, shifted the perceptual judgment of central motion, the dot, towards the opposite direction from the surround. Altered interaction between a moving surround and the center is likely linked to MT area dysfunctions, as this higher-level visual processing area is very selective for the direction of motion of a stimulus. It may be interesting submitting our patients to an fMRI study in order to evaluate MT area and the parietal cortex that, along with the precuneus, has been previously linked to visuospatial processing and activation during Induced Roelofs Effect tasks [92].

To better understand how spatial context modulation influence visual perception, and its role in visual illusions such as the Induced Roelofs Effect, the concept of center-surround interaction needs to be addressed. Center-surround interaction is fundamental to organize spatial distributed stimuli for perception. Surround could either be suppressed or enhanced on neural responses to central motion. In other words, neural responses are suppressed by a surround with the same direction of motion as the center or enhanced by a surround with the opposite direction of motion to the center. This happens because direction-selective neural units play a key role in mediating perceptual responses to visual motion (see 2.3.2). In SZ, alteration of center-surround interaction is likely due to a suppression rather than facilitation from surround because a perceptual shift towards the opposite direction of central motion occurs mostly when center and surround move in the same direction [90]. Our study is able to replicate these literature findings, as the highest frequency of correct responses was obtained when frame and dot shifted in opposite direction, i.e. when neural response were enhanced by the surround, while subjects obtained the lowest possible frequency of correct answers when both items shifted towards the same direction, i.e. when neural responses were suppressed by the surround.

Strictly regarding BD, our literature research found few studies concerning anomalies in motion and spatial processing. Regarding motion processing, previous research focused on velocity discrimination, mediated primarily in the middle temporal extra-striate cortex and a measure of late visual system functionality. BD patients did not show reduced velocity discrimination; therefore, motion processing appears to not be impaired in these patients. Moreover, focusing on spatial processing's influence on visual targets in subjects suffering with major psychiatric illnesses such as BD, results suggested normal magnitudes of spatial effects on all visual domains tested except that in contrast-detection tasks during manic states, when BD patients experienced weakened contextual modulation. In other words, manic bipolar patients with psychotic symptoms may experience the same dysfunctions as SZ patients. This event has been linked to abnormal gain control mechanism in early visual areas, caused by hyperdopaminergia during mania, since dopamine levels are associated with contrast gain control [87]. Our study suggests that abnormal spatial processing may be detectable even in motion-detection tasks such as the Induced Roelofs effect. BD patients, in fact, experienced augmented Induced Roelofs Effect in the submitted task compared to HC. However, BD patients gave smaller proportion of correct answers as a function of the stimulus value, therefore their Induced Roelofs Effect size has been proved smaller compared to SZ.

Finally, literature findings suggested that abnormally strong motion surround repulsion was linked to greater symptoms severity in SZ and that this relationship remained significant even in BD. Doses or type of current medication, instead, was not proved to correlate with contextual modulation. It may be interesting evaluating how clinical state and current medication in our enrolled patients influence the Induced Roelofs Effect size.

7. CONCLUSION

We tested patients and HC with the Induced Roelofs Effect. We replicated literature findings of greater magnitudes of the Induced Roelof Effect in schizophrenia compared to healthy controls, adding further evidence in support of abnormal visuospatial perception and processing in this illness. Our results agree with previous studies describing altered center-surround interaction, greater spatial contextual processing and increased surround suppression in schizophrenia.

Direction-selective neural units play a key role in mediating perceptual responses to visual motion and neural responses to central motion are suppressed by a surround with the same direction of motion as the center. In our study we were able to support these findings as we proved that in the presence of a surround (the frame) moving in the same direction as the center (the dot), patients suffered of a perceptual shift towards the opposite direction of central motion, localizing the dot in the opposite side of the midline with respect of the frame offset. We also witnessed that happen in BD. Moreover, we found that greater contextual processing may be held responsible for the amplification of irrelevant visual information such as the frame, perceived outside the classical receptive visual field, over the relevant and central task, which is the dot. It may be interesting evaluating how clinical state and current medication influence these dysfunctions. Finally, we also found supporting evidence to few previous studies stating the presence of abnormal spatial processing in BD. In fact, we proved increased Induced Roelofs Effect in bipolar disorder type I and II, with an augmented effect size compared to healthy controls but reduced effect size compared to schizophrenia. Therefore, we suggest that it may be useful to extend additional research on these visuospatial dysfunctions to other major mental illnesses.

8. ACKNOWLEDGMENTS

Ringrazio la Clinica Psichiatrica dell'Ospedale San Martino e in particolare il Direttore Gianluca Serafini e il Professor Andrea Escelsior per la disponibilità e l'aiuto fornitami.
Ringrazio inoltre il Dott. Davide Esposito di IIT per il supporto nella raccolta dati e nella stesura della parte sperimentale di questo elaborato.

Ringrazio la mia famiglia per avermi sempre dato una fiducia e una libertà tali da permettermi di fare le mie scelte, e crescere sbagliando. Grazie per avermi fornito gli strumenti per la mia istruzione, che spesso dimentichiamo essere un grande privilegio.
Ringrazio i miei quattro nonni, a cui dedico questa tesi di laurea, che non hanno potuto studiare ma sono stati i miei migliori insegnanti.
Ringrazio la Dott.ssa Giovanna Zuin che, anche se non lo sa, tanti anni fa all'Ospedale Pediatrico Buzzi di Milano per prima mi ha ispirato a fare questo lavoro.
Infine, ringrazio la mia famiglia acquisita di Genova, nelle persone delle mie amiche e delle mie coinquiline, che mi hanno donato una casa lontano da casa e che mi hanno amato "così come sono" (semicit).

9. REFERENCES

1. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet*. 2013;381(9878):1663-1671. doi:10.1016/S0140-6736(13)60989-7

2. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet*. 2016;387(10027):1561-1572. doi:10.1016/S0140-6736(15)00241-X

3. Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord*. 2001;67(1-3):3-19. doi:10.1016/s0165-0327(01)00429-3

4. Laios K, Tsoukalas G, Kontaxaki MI, Karamanou M, Androutsos G. Suicide in ancient Greece. *Psychiatriki*. 2014;25(3):200-207.

5. Haustgen T, Akiskal H. French antecedents of "contemporary" concepts in the American Psychiatric Association's classification of bipolar (mood) disorders. *J Affect Disord*. 2006;96(3):149-163. doi:10.1016/j.jad.2006.09.014

6. Angst J. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. *Schizophr Res*. 2002;57(1):5-13. doi:10.1016/s0920-9964(02)00328-6

7. Brieger P, Marneros A. *Dysthymia and Cyclothymia: Historical Origins and Contemporary Development*. Vol 45.; 1997.

8. Zivanovic O, Nedic A. Kraepelin's concept of manic-depressive insanity: One hundred years later. *J Affect Disord*. 2012;137(1-3):15-24. doi:10.1016/j.jad.2011.03.032

9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-I, 1st Ed.; Washington, DC, USA, 1952*.

10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-II, 2nd Ed.; Washington, DC, USA, 1968*.

11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-III, 3rd Ed.; Arlington, VA, USA, 1980*.

12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, 4th Ed.; Washington, DC, USA, 1994*.

13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 5th Ed. (2013)*.

14. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011;68(3):241-251. doi:10.1001/archgenpsychiatry.2011.12

15. Angst J, Gamma A, Lewinsohn P. The evolving epidemiology of bipolar disorder. *World Psychiatry*. 2002;1(3):146-148.

16. Fagiolini A, Forgione R, Maccari M, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*. 2013;148(2-3):161-169. doi:10.1016/j.jad.2013.02.001

17. Clemente AS, Diniz BS, Nicolato R, et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Braz J Psychiatry*. 2015;37(2):155-161. doi:10.1590/1516-4446-2012-1693

18. Oswald P, Souery D, Kasper S, et al. Current issues in bipolar disorder: a critical review. *Eur Neuropsychopharmacol*. 2007;17(11):687-695. doi:10.1016/j.euroneuro.2007.03.006

19. Pini S, de Queiroz V, Pagnin D, et al. Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol*. 2005;15(4):425-434. doi:10.1016/j.euroneuro.2005.04.011

20. Koukopoulos A, Reginaldi D, Tondo L, Visioli C, Baldessarini RJ. Course sequences in bipolar disorder: Depressions preceding or following manias or hypomanias. *J Affect Disord*. 2013;151(1):105-110. doi:10.1016/j.jad.2013.05.059

21. Tundo A, Calabrese JR, Marchetti F, Dell'Osso L, Proietti L, De Filippis R. Continuous circular cycling in bipolar disorder as a predictor of poor outcome. *J Affect Disord*. 2013;150(3):823-828. doi:10.1016/j.jad.2013.03.006

22. Miola A, Fountoulakis KN, Baldessarini RJ, et al. Prevalence and outcomes of rapid cycling bipolar disorder: Mixed method systematic meta-review. *J Psychiatr Res*. 2023;164:404-415. doi:10.1016/j.jpsychires.2023.06.021

23. Vázquez GH, Lolich M, Cabrera C, et al. Mixed symptoms in major depressive and bipolar disorders: A systematic review. *J Affect Disord*. 2018;225:756-760. doi:10.1016/j.jad.2017.09.006

24. Fagiolini A, Coluccia A, Maina G, et al. Diagnosis, Epidemiology and Management of Mixed States in Bipolar Disorder. *CNS Drugs*. 2015;29(9):725-740. doi:10.1007/s40263-015-0275-6

25. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841-1856. doi:10.1016/S0140-6736(20)31544-0

26. Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet*. 2013;381(9878):1654-1662. doi:10.1016/S0140-6736(13)60855-7

27. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373(9659):234-239. doi:10.1016/S0140-6736(09)60072-6

28. Harrison PJ, Geddes JR, Tunbridge EM. The Emerging Neurobiology of Bipolar Disorder. *Trends Neurosci*. 2018;41(1):18-30. doi:10.1016/j.tins.2017.10.006

29. Mühleisen TW, Mattheisen M, Strohmaier J, et al. Association between schizophrenia and common variation in neurocan (NCAN), a genetic risk factor for bipolar disorder. *Schizophr Res*. 2012;138(1):69-73. doi:10.1016/j.schres.2012.03.007

30. O'Connell KS, Coombes BJ. Genetic contributions to bipolar disorder: current status and future directions. *Psychol Med*. 2021;51(13):2156-2167. doi:10.1017/S0033291721001252

31. Andreazza AC, Duong A, Young LT. Bipolar Disorder as a Mitochondrial Disease. *Biol Psychiatry*. 2018;83(9):720-721. doi:10.1016/j.biopsych.2017.09.018

32. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res*. 2014;218(1-2):61-68. doi:10.1016/j.psychres.2014.04.005

33. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry*. 2005;186:121-125. doi:10.1192/bjp.186.2.121

34. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev*. 2011;35(3):804-817. doi:10.1016/j.neubiorev.2010.10.001

35. Ashok AH, Marques TR, Jauhar S, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. *Mol Psychiatry*. 2017;22(5):666-679. doi:10.1038/mp.2017.16

36. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;53:23-34. doi:10.1016/j.pnpbp.2014.01.013

37. Hamdani N, Doukhan R, Kurtlucan O, Tamouza R, Leboyer M. Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. *Curr Psychiatry Rep*. 2013;15(9):387. doi:10.1007/s11920-013-0387-y

38. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet*. 2013;381(9878):1672-1682. doi:10.1016/S0140-6736(13)60857-0

39. Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br J Psychiatry*. 2013;202(3):212-219. doi:10.1192/bjp.bp.112.113548

40. Grande I, Vieta E. Pharmacotherapy of acute mania: monotherapy or combination therapy with mood stabilizers and antipsychotics? *CNS Drugs*. 2015;29(3):221-227. doi:10.1007/s40263-015-0235-1

41. Bobo W V. The Diagnosis and Management of Bipolar I and II Disorders: Clinical Practice Update. *Mayo Clin Proc*. 2017;92(10):1532-1551. doi:10.1016/j.mayocp.2017.06.022

42. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24(2):198-217. doi:10.1038/s41380-018-0044-2

43. Owen MJ, Legge SE, Rees E, Walters JTR, O'Donovan MC. Genomic findings in schizophrenia and their implications. *Mol Psychiatry*. 2023;28(9):3638-3647. doi:10.1038/s41380-023-02293-8

44. Andreasen NC, Carpenter WT. Diagnosis and Classification of Schizophrenia. *Schizophr Bull*. 1993;19(2):199-214. doi:10.1093/schbul/19.2.199

45. Ban TA. Neuropsychopharmacology and the genetics of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(5):753-762. doi:10.1016/j.pnpbp.2004.05.021

46. Tandon R, Gaebel W, Barch DM, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res*. 2013;150(1):3-10. doi:10.1016/j.schres.2013.05.028

47. Kahn RS. On the Origins of Schizophrenia. *American Journal of Psychiatry*. 2020;177(4):291-297. doi:10.1176/appi.ajp.2020.20020147

48. Hoenig J. The Concept of Schizophrenia Kraepelin–Bleuler–Schneider. *British Journal of Psychiatry*. 1983;142(6):547-556. doi:10.1192/bjp.142.6.547

49. Mosolov SN, Yaltonskaya PA. Primary and Secondary Negative Symptoms in Schizophrenia. *Front Psychiatry*. 2022;12. doi:10.3389/fpsyt.2021.766692

50. Moscarelli M. A major flaw in the diagnosis of schizophrenia: what happened to the Schneider's first rank symptoms. *Psychol Med*. 2020;50(9):1409-1417. doi:10.1017/S0033291720001816

51. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *The Lancet*. 2016;388(10039):86-97. doi:10.1016/S0140-6736(15)01121-6

52. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *The Lancet*. 2022;399(10323):473-486. doi:10.1016/S0140-6736(21)01730-X

53. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: A Concise Overview of Incidence, Prevalence, and Mortality. *Epidemiol Rev*. 2008;30(1):67-76. doi:10.1093/epirev/mxn001

54. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295-301. doi:10.1016/S2215-0366(17)30078-0

55. Stilo SA, Murray RM. Non-Genetic Factors in Schizophrenia. *Curr Psychiatry Rep*. 2019;21(10):100. doi:10.1007/s11920-019-1091-3

56. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012;2(11):e190-e190. doi:10.1038/tp.2012.116

57. Haijma S V., Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS. Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophr Bull*. 2013;39(5):1129-1138. doi:10.1093/schbul/sbs118

58. Buck SA, Quincy Erickson-Oberg M, Logan RW, Freyberg Z. Relevance of interactions between dopamine and glutamate neurotransmission in schizophrenia. *Mol Psychiatry*. 2022;27(9):3583-3591. doi:10.1038/s41380-022-01649-w

59. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry*. 2015;2(3):258-270. doi:10.1016/S2215-0366(14)00122-9

60. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. *Br Med Bull*. 2015;114(1):169-179. doi:10.1093/bmb/ldv017

61. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet*. 2009;373(9657):31-41. doi:10.1016/S0140-6736(08)61764-X

62. Bighelli I, Rodolico A, García-Mieres H, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2021;8(11):969-980. doi:10.1016/S2215-0366(21)00243-1

63. Liu CSJ, Bryan RN, Miki A, Woo JH, Liu GT, Elliott MA. Magnocellular and parvocellular visual pathways have different blood oxygen level-dependent signal time courses in human primary visual cortex. *AJNR Am J Neuroradiol*. 2006;27(8):1628-1634.

64. Butler PD, Zemon V, Schechter I, et al. Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry*. 2005;62(5):495-504. doi:10.1001/archpsyc.62.5.495

65. Butler PD, Silverstein SM, Dakin SC. Visual Perception and Its Impairment in Schizophrenia. *Biol Psychiatry*. 2008;64(1):40-47. doi:10.1016/j.biopsych.2008.03.023

66. Bair W. Visual receptive field organization. *Curr Opin Neurobiol*. 2005;15(4):459-464. doi:10.1016/j.conb.2005.07.006

67. Spillmann L, Dresp-Langley B, Tseng C huei. Beyond the classical receptive field: The effect of contextual stimuli. *J Vis*. 2015;15(9):7. doi:10.1167/15.9.7

68. Albright TD, Stoner GR. Contextual Influences on Visual Processing. *Annu Rev Neurosci*. 2002;25(1):339-379. doi:10.1146/annurev.neuro.25.112701.142900

69. Bridgeman B, Dassonville P, Lester BD. The Roelofs and induced Roelofs effects. *Conscious Cogn*. 2018;64:6-12. doi:10.1016/j.concog.2018.05.009

70. de Grave DDJ, Brenner E, Smeets JBJ. Are the original Roelofs effect and the induced Roelofs effect caused by the same shift in straight ahead? *Vision Res*. 2002;42(19):2279-2285. doi:10.1016/s0042-6989(02)00189-x

71. Soechting JF, Engel KC, Flanders M. The Duncker illusion and eye-hand coordination. *J Neurophysiol*. 2001;85(2):843-854. doi:10.1152/jn.2001.85.2.843

72. Brosgole L. An analysis of induced motion. *Acta Psychol (Amst)*. 1968;28:1-44. doi:10.1016/0001-6918(68)90002-4

73. Werner H, Wapner S, Bruell JH. Experiments on sensory-tonic field theory of perception: VI. Effect of position of head, eyes, and of object on position of the apparent median plane. *J Exp Psychol*. 1953;46(4):293-299. doi:10.1037/h0055733

74. BRUELL JH. EFFECT OF ASYMMETRICAL RETINAL STIMULATION ON THE PERCEPTION OF THE MEDIAN PLANE. *Percept Mot Skills*. 1955;5:133. doi:10.2466/PMS.5..133-139

75. Bridgeman B, Gemmer A, Forsman T, Huemer V. Processing spatial information in the sensorimotor branch of the visual system. *Vision Res*. 2000;40(25):3539-3552. doi:10.1016/s0042-6989(00)00193-0

76. Bridgeman B, Peery S, Anand S. Interaction of cognitive and sensorimotor maps of visual space. *Percept Psychophys*. 1997;59(3):456-469. doi:10.3758/BF03211912

77. Li W, Matin L. Two wrongs make a right: linear increase of accuracy of visually-guided manual pointing, reaching, and height-matching with increase in hand-to-body distance. *Vision Res*. 2005;45(5):533-550. doi:10.1016/j.visres.2004.09.026

78. Dassonville P, Bala JK. Perception, action, and Roelofs effect: a mere illusion of dissociation. *PLoS Biol*. 2004;2(11):e364. doi:10.1371/journal.pbio.0020364

79. Lathrop WB, Bridgeman B, Tseng P. Perception in the Absence of Attention: Perceptual Processing in the Roelofs Effect during Inattentional Blindness. *Perception*. 2011;40(9):1104-1119. doi:10.1068/p6859

80. Lester BD, Dassonville P. Attentional control settings modulate susceptibility to the induced Roelofs effect. *Atten Percept Psychophys*. 2011;73(5):1398-1406. doi:10.3758/s13414-011-0123-9

81. Blake R, Turner LM, Smoski MJ, Pozdol SL, Stone WL. Visual Recognition of Biological Motion is Impaired in Children With Autism. *Psychol Sci*. 2003;14(2):151-157. doi:10.1111/1467-9280.01434

82. Walter E, Dassonville P, Bochsler TM. A Specific Autistic Trait that Modulates Visuospatial Illusion Susceptibility. *J Autism Dev Disord*. 2009;39(2):339-349. doi:10.1007/s10803-008-0630-2

83. Fernandes TP, Shoshina II, Oliveira MEC, Andreevna VE, Silva GM, Santos NA. Correlates of clinical variables on early-stage visual processing in schizophrenia and bipolar disorder. *J Psychiatr Res*. 2022;149:323-330. doi:10.1016/j.jpsychires.2022.03.014

84. Chen Y, Levy DL, Sheremata S, Holzman PS. Compromised late-stage motion processing in schizophrenia. *Biol Psychiatry*. 2004;55(8):834-841. doi:10.1016/j.biopsych.2003.12.024

85. Azim E, Seki K. Gain control in the sensorimotor system. *Curr Opin Physiol*. 2019;8:177-187. doi:10.1016/j.cophys.2019.03.005

86. King DJ, Hodgekins J, Chouinard PA, Chouinard VA, Sperandio I. A review of abnormalities in the perception of visual illusions in schizophrenia. *Psychon Bull Rev*. 2017;24(3):734-751. doi:10.3758/s13423-016-1168-5

87. Yang E, Tadin D, Glasser DM, Wook Hong S, Blake R, Park S. Visual context processing in bipolar disorder: a comparison with schizophrenia. *Front Psychol*. 2013;4. doi:10.3389/fpsyg.2013.00569

88. Yoon JH, Rokem AS, Silver MA, et al. Diminished orientation-specific surround suppression of visual processing in schizophrenia. *Schizophr Bull*. 2009;35(6):1078-1084. doi:10.1093/schbul/sbp064

89. Yang E, Tadin D, Glasser DM, Hong SW, Blake R, Park S. Visual Context Processing in Schizophrenia. *Clinical Psychological Science*. 2013;1(1):5-15. doi:10.1177/2167702612464618

90. Chen Y, Norton D, Ongur D. Altered Center-Surround Motion Inhibition in Schizophrenia. *Biol Psychiatry*. 2008;64(1):74-77. doi:10.1016/j.biopsych.2007.11.017

91. Chen Y, McBain R, Norton D, Ongur D. Schizophrenia patients show augmented spatial frame illusion for visual and visuomotor tasks. *Neuroscience*. 2011;172:419-426. doi:10.1016/j.neuroscience.2010.10.039

92. Walter E, Dassonville P. Visuospatial contextual processing in the parietal cortex: An fMRI investigation of the induced Roelofs effect. *Neuroimage*. 2008;42(4):1686-1697. doi:10.1016/j.neuroimage.2008.06.016

93. Lester BD, Dassonville P. The Role of the Right Superior Parietal Lobule in Processing Visual Context for the Establishment of the Egocentric Reference Frame. *J Cogn Neurosci*. 2014;26(10):2201-2209. doi:10.1162/jocn_a_00636

94. Coello Y, Danckert J, Blangero A, Rossetti Y. Do visual illusions probe the visual brain? Illusions in action without a dorsal visual stream. *Neuropsychologia*. 2007;45(8):1849-1858. doi:10.1016/j.neuropsychologia.2006.12.010

95. O'Bryan RA, Brenner CA, Hetrick WP, O'Donnell BF. Disturbances of visual motion perception in bipolar disorder. *Bipolar Disord*. 2014;16(4):354-365. doi:10.1111/bdi.12173

96. Løchen AR, Kolskår KK, de Lange AMG, et al. Visual processing deficits in patients with schizophrenia spectrum and bipolar disorders and associations with psychotic symptoms, and intellectual abilities. *Heliyon*. 2023;9(2):e13354. doi:10.1016/j.heliyon.2023.e13354

97. Chen Y, Levy DL, Sheremata S, Holzman PS. Bipolar and schizophrenic patients differ in patterns of visual motion discrimination. *Schizophr Res*. 2006;88(1-3):208-216. doi:10.1016/j.schres.2006.06.004

98. Paire A, Hillairet de Boisferon A, Paeye C. Empirical validation of QUEST+ in PSE and JND estimations in visual discrimination tasks. *Behav Res Methods*. 2022;55(8):3984-4001. doi:10.3758/s13428-022-02001-4

99. Watson AB, Pelli DG. Quest: A Bayesian adaptive psychometric method. *Percept Psychophys*. 1983;33(2):113-120. doi:10.3758/BF03202828

100. Adelstein BD, Begault DR, Anderson MR, Wenzel EM. Sensitivity to haptic-audio asynchrony. In: *Proceedings of the 5th International Conference on Multimodal Interfaces - ICMI '03*. ACM Press; 2003:73. doi:10.1145/958444.958448

101. Brainard DH. The Psychophysics Toolbox. *Spat Vis*. 1997;10(4):433-436. doi:10.1163/156856897X00357

102. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis*. 1997;10(4):437-442. doi:10.1163/156856897X00366

103. Martz HF. Reliability Theory. In: *Encyclopedia of Physical Science and Technology*. Elsevier; 2003:143-159. doi:10.1016/B0-12-227410-5/00659-1

104. Lynch SM. Bayesian Statistics. In: *Encyclopedia of Social Measurement*. Elsevier; 2005:135-144. doi:10.1016/B0-12-369398-5/00156-0

105. Leek MR. Adaptive procedures in psychophysical research. *Percept Psychophys*. 2001;63(8):1279-1292. doi:10.3758/BF03194543

106. Watson AB. QUEST+: A general multidimensional Bayesian adaptive psychometric method. *J Vis*. 2017;17(3):10. doi:10.1167/17.3.10