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Improving the Diagnosis and Treatment in Major Depressive Disorder and Bipolar Disorder: Novel Psychometric Strategies and the Role of the Network Analysis Model

Doctorate Thesis

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INTRODUCTION

1. Major Depressive Disorder

Major Depressive Disorder (MDD) is a significant psychiatric condition classified as a mood disorder. It is characterized by a persistent and pervasive feeling of sadness or loss of interest and pleasure in most activities, resulting in a range of emotional, cognitive, and physical symptoms (Patel, V., 2010). As one of the most prevalent mental health disorders worldwide, MDD poses a substantial burden on individuals, families, and societies. MDD affects people of all ages, races, and socioeconomic backgrounds. According to the World Health Organization (WHO), depression is estimated to affect more than 264 million people globally. Prevalence of anxiety, depression, and suicidal ideation symptoms among university students: a systematic review (Paula, W. D., 2020). It is more common in women than men, and its onset typically occurs during late adolescence or early adulthood. However, depression can develop at any age, including childhood and later in life. The prevalence of depression exhibits significant regional variations across countries and cultures. Various factors contribute to these disparities, including socioeconomic conditions, access to mental healthcare, cultural norms surrounding mental health, and exposure to adverse life events. Countries with limited mental health resources may struggle to address the growing burden of depression, leading to disparities in prevalence rates (Haroz,E., 2010).

Epidemiological data indicates that individuals with MDD are at a higher risk of suicide compared to the general population. Studies have shown that suicide risk is particularly elevated during acute depressive episodes and early stages of the disorder. According to the World Health Organization (WHO), suicide claims the lives of approximately 800,000 people annually, and a substantial number of these individuals have MDD or other mood disorders (Kim, D.,2022). Moreover, MDD is often a recurrent condition, and scientific research has revealed relatively high rates of relapse. Long-term follow-up studies indicate that about half of those who experience a single episode of depression will encounter at least one more episode in their lifetime, and each subsequent episode increases the risk of further relapses (El-Mallakh, R. S., 2012). Understanding the epidemiological and scientific data related to suicide risk and relapses is essential in implementing effective prevention and intervention

strategies to address these alarming aspects of MDD and reduce the burden of this mental health disorder on individuals and society.

The diagnosis of Major Depressive Disorder requires the presence of specific symptoms that significantly impair an individual's ability to function daily.

The DSM-5 provides specific criteria for diagnosing MDD based on the presence and duration of certain symptoms (Uher, R.,2014). It is essential to remember that only qualified mental health professionals should make a diagnosis. Below are the DSM-5 criteria for Major Depressive Disorder:

Diagnostic Criteria	***Major Depressive Disorder***
A	*Five or more of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure.* 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation by others. 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 3. Significant weight loss when not dieting or weight gain (a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day. 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day. 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day. 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan for committing suicide. *Modest* cognitive decline in one or more cognitive domains, based on:

	1. Concern about *mild* decline, expressed by individual or reliable informant, or observed by clinician. 2. *Modest* impairment, documented by objective cognitive assessment.
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.*
D	*The occurrence of the major depressive episode is not better explained by another mental disorder, such as schizophrenia, schizoaffective disorder, or psychotic disorder.*
Note:	There are several specifiers for Major Depressive Disorder in the DSM-5, which provide additional information about the nature and course of the condition. These specifiers include the presence of psychotic features, atypical features, melancholic features, and more.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013

The symptoms of MDD can have a profound impact on an individual's global functioning and overall quality of life. The persistent feelings of sadness, hopelessness, and lack of interest in previously enjoyed activities can lead to significant impairments in various areas of life. Occupational functioning is often compromised, with difficulties in concentration, decision-making, and decreased productivity. Socially, patients with MDD can cause individuals to withdraw from interactions, leading to strained relationships and feelings of isolation (Vance, D. E.,.2016). The cognitive symptoms, such as poor memory and reduced attention span, can affect academic and professional performance, contributing to decreased self-confidence and self-esteem. MDD's toll extends to physical health, disrupting sleep patterns, appetite, and overall well-being. Financial challenges may arise due to difficulties in maintaining employment, adding to the burden on individuals. In severe cases, suicidal thoughts and behaviors can pose life-threatening risks (Kim, D.,2022). Addressing the impact of MDD on global functioning and quality of life requires comprehensive

interventions, including appropriate treatment, support networks, and a holistic approach to improve the well-being and functioning of affected individuals.

1.1 Pathophysiology of MDD

Major Depressive Disorder (MDD) is a complex condition, and over the past decade, different groups have made significant progress in understanding its pathophysiology (Caraci et al., 2018). Various factors contribute to the development of MDD, and here are some key components that play a role:

1. Genetic Factors: Family and twin studies have provided evidence for a genetic predisposition to MDD. Certain genes and genetic variations have been associated with an increased vulnerability to developing depression. However, it's important to note that genetics is not the sole determinant of depression, and environmental factors also play a significant role (Lohoff, F. W.,2010).
2. Neurobiological Factors: Neurotransmitters, which are chemical messengers in the brain, are crucial for regulating mood and emotions. Imbalances in neurotransmitters, particularly serotonin, norepinephrine, and dopamine, have been implicated in the pathophysiology of depression. Reduced levels of these neurotransmitters in specific brain regions may contribute to the development of depressive symptoms (Khushboo, Siddiqi, N. J.,2022).
3. Psychosocial Factors: Environmental stressors can be significant triggers or exacerbators of depression. Trauma, loss, abuse, neglect, and major life changes are examples of stressors that can contribute to the onset of MDD. Adverse childhood experiences, social isolation, and lack of social support are also linked to an increased risk of developing depression (Carr, C. P.,2013).
4. Cognitive Factors: Cognitive theories propose that negative thought patterns, cognitive biases, and maladaptive coping strategies can contribute to the maintenance and worsening of depressive symptoms. Cognitive distortions and rumination on negative thoughts may play a role in the development of MDD (Lang, T. J.,2012).

Moreover, in addition to the genetic mechanisms and environmental factors mentioned, dysregulation of the monoaminergic system (related to neurotransmitters like serotonin), reduced synaptic plasticity due to chronic stress, impaired neurogenesis of the adult hippocampus, and neurodegeneration of the hippocampus

are also contributing factors in the pathophysiology of MDD Mahar, I., 2014). Epidemiological studies provide compelling evidence for the significant role of chronic stress in MDD (Calabrese, F., 2009). Exposure to stressful life events has been identified as a contributing factor in the development of this debilitating condition (Czéh, B., & Lucassen, P. J. 2007). Chronic stress disrupts the negative feedback mechanism of glucocorticoids (GR) on the activity of the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels (De Kloet, E. R., 2005). The excessive presence of GR can have detrimental effects on the hippocampus, resulting in neuronal death (Yu et al., 2008). Additionally, the prefrontal cortex (PFC), another brain region crucially involved in the cognitive symptoms of depression, can undergo dysfunctional changes under chronic stress (Krishnan E. R., 2008).

Stress also impacts the synthesis of essential factors for neuronal homeostasis, such as Brain-Derived Neurotrophic Factor (BDNF) (Nowacka, M., & Obuchowicz, E. 2013). BDNF is a neurotrophin that plays a fundamental role in maintaining dendritic spines, regulating adult hippocampal neurogenesis, and influencing cognitive and mood-related behaviors and aging (Guerrera, C. S., 2020). Reduced levels of BDNF have been linked to dendritic atrophy, neuronal apoptosis, and inhibition of neurogenesis in MDD (Nowacka, M., & Obuchowicz, E. 2013). Chronic stress has been shown to decrease BDNF concentrations in the hippocampus and PFC of animal models of depression. Moreover, studies in depressed patients have demonstrated reduced expression of BDNF in the cortex, hippocampus, and peripheral tissues (Reinhart, V.,2’15). Furthermore, chronic stress-induced impairment of TGF-β1 (Transforming Growth Factor-beta 1) signaling in various brain regions, including the hippocampus, cortex, and hypothalamus, has been reported (Caraci, F., 2015). This impairment has been associated with the development of depressive-like symptoms in animal models Additionally, recent studies have shown a correlation between reduced TGF-β1 plasma levels, depression severity, and treatment resistance in individuals with MDD Caraci, F., 2018).

Hormonal imbalances, particularly involving the hypothalamic-pituitary-adrenal (HPA) axis, play a crucial role in the body's stress response. Chronic stress can lead to dysregulation of the HPA axis, resulting in elevated levels of the stress hormone cortisol. This can have negative effects on mood regulation and contribute to the development of depression.

In addition to HPA axis hyperactivation, immune system dysregulation and neuroinflammation play also a key role in the pathophysiology of depression (Caraci et al., 2010). The impact of immune system activation on the central nervous system and the overall activity of monoaminergic systems is significant (Caraci et al., 2018). Studies have shown increased levels of pro-inflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor-a (TNF-a), and decreased levels of anti-inflammatory cytokines (e.g., IL-10, IL-4, and TGF-β1) in the hippocampus and cortex of animal models of depression and individuals with MDD (Caruso, G., 2019). Antidepressant drugs, such as sertraline and fluoxetine, exert immunomodulatory effects by reducing the production of proinflammatory cytokines and stimulating the synthesis of TGF-β1 in depressed patients (Sutcigil, L., 2007). Moreover, these drugs have been shown to induce the synthesis and release of BDNF and TGF-β1 in both in vitro and in vivo studies (Caraci et al., 2010). This suggests that the therapeutic latency (2–4 weeks) of antidepressants could, at least in part, be attributed to the time required for BDNF restoration.

Recent studies have highlighted the rapid and long-lasting antidepressant effects of TGF-β1 and its key role in mediating the antidepressant activity of (R)-ketamine, a novel drug under investigation for treatment-resistant MDD patients (Zhang, K., 2020). Interestingly, (R)-ketamine rescued the expression of TGF-β1 and its receptors in the prefrontal cortex (PFC) and hippocampus. Inhibition of TGF-β1 signaling or the use of neutralizing antibodies of TGF-β1 blocked the antidepressant effects of (R)-ketamine, further supporting the essential role of TGF-β1 as an antidepressant.

These findings shed light on the intricate interactions between hormonal, immune, and neurotrophic factors in the pathophysiology of depression. Understanding these mechanisms opens new avenues for the development of novel and more targeted therapeutic approaches aimed at alleviating the symptoms of depression and improving treatment outcomes.

2. Bipolar Disorder

Bipolar Disorder (BD), formerly known as manic depression, is a chronic and severe mental health condition characterized by extreme shifts in mood, energy levels, and activity levels. These shifts, known as mood episodes, oscillate between periods of elevated and expansive mood (mania or hypomania) and periods of intense sadness or depression. Bipolar Disorder significantly impacts a person's daily life, behavior, and emotional well-being. It is estimated that around 1-2% of the global population suffers from Bipolar Disorder (BD) (Pascual-Sanchez, A.,2019). There are several types of Bipolar Disorder, including:

Bipolar I Disorder: Characterized by at least one manic episode, which may be preceded or followed by depressive episodes. Some individuals may experience mixed episodes, where symptoms of mania and depression coexist.

Bipolar II Disorder: Marked by recurrent depressive episodes and at least one hypomanic episode. Hypomania is a milder form of mania and does not cause severe impairment in functioning (McIntyre, R. S.,2020).

Cyclothymic Disorder (Cyclothymia): A milder form of bipolar disorder with chronic mood fluctuations, involving numerous periods of hypomania and mild depression. The symptoms are less severe than those seen in Bipolar I or II (McIntyre, R. S.,2020).

Concerning of clinical features during a manic episode, individuals may experience an elevated or irritable mood, increased energy levels, impulsivity, racing thoughts, decreased need for sleep, grandiosity, excessive involvement in pleasurable activities, and impaired judgment. Manic episodes can be severe and may lead to reckless behavior and potential harm to oneself or others. Hypomanic episodes are like manic episodes but less intense. People with hypomania may feel more energetic, productive, and sociable than usual. However, they can still engage in risky behaviors. Major Depressive Episode: during a depressive episode, individuals experience symptoms such as a persistent sad or empty mood, loss of interest or pleasure in most activities, changes in appetite and weight, sleep disturbances, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and thoughts of death or suicide (Solé, E.,2017).

Bipolar Disorder is characterized by periods of both manic or hypomanic episodes and major depressive episodes. Below are the DSM-5 criteria for Bipolar Disorder:

Diagnostic Criteria	***Bipolar I Disorder***

A	Criteria have been met for at least one manic episode.
B	The occurrence of the manic episode is not better explained by another mental disorder (e.g., schizophrenia, schizoaffective disorder, delusional disorder).
Diagnostic Criteria	**Bipolar II Disorder**
A	Criteria have been met for at least one hypomanic episode and at least one major depressive episode.
B	There has never been a manic episode
C	The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by another mental disorder.
Diagnostic Criteria	**Cyclothymic Disorder (Cyclothymia) (Dsm-5):**
A	For at least 2 years (1 year in children and adolescents), numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet the criteria for a major depressive episode
B	During the 2-year period (1 year in children and adolescents), the hypomanic and depressive periods have been present for at least half the time and the individual has not been without symptoms for more than 2 months at a time.
C	Criteria for a major depressive, manic, or hypomanic episode have never been met.
D	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E	The symptoms are not attributable to the physiological effects of a substance or another medical condition.
F	The symptoms are not better explained by another mental disorder (e.g., schizophrenia, schizoaffective disorder, delusional disorder).

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association; 2013

It is relevant to note that a proper diagnosis of Bipolar Disorder requires a thorough evaluation by a qualified mental health professional. The severity, frequency, and duration of mood episodes are essential factors in determining the specific type of Bipolar Disorder an individual may have (e.g., Bipolar I, Bipolar II, or Cyclothymic Disorder). Additionally, clinicians may also consider any psychotic features or other relevant specifiers to refine the diagnosis further.

Additionally, while the diagnosis of BD primarily revolves around mood episodes, cognitive deficits are among the most persistent and disabling symptoms associated with the illness. These cognitive impairments have a profound effect on the clinical course and functional outcome of individuals with BD. Several cross-sectional studies have indicated a link between the number of affective episodes and cognitive impairment, suggesting a progressive decline in cognitive function, particularly with recurring manic episodes (Van Rheenen, T. E.,2020). This highlights the importance of early interventions to prevent affective recurrences and to address cognitive deficits. Research indicates that cognitive impairment may already be present from the first manic episode. However, episode-free patients might experience improvement in cognitive function during the year following the initial manic episode (Lam, D. H.,2003). This highlights the potential for interventions to reverse cognitive deficits and promote better cognitive functioning in BD patients.

2.1 Pathophysiology of BD

Bipolar disorder (BD) is a challenging and intricate mental health condition characterized by recurrent episodes of mania or hypomania and major depression. As mentioned, its pathogenesis is not straightforward and involves multiple contributing factors. We will now review some of the key elements that contribute to the complexity of clinical phenotypes in BD:

1. Genetic Susceptibility: Family and twin studies have provided compelling evidence that genetics play a significant role in the development of bipolar disorder. Individuals with a family history of BD are at a higher risk of developing the disorder themselves. However, no single gene has been identified as the sole cause of BD. Instead, it appears that multiple genes, each

with a small effect, interact with environmental factors to influence the risk of developing the disorder (Craddock, N.,2013).

2. Neurotransmitter Dysregulation: In bipolar disorder, imbalances in neurotransmitters, such as serotonin, dopamine, and norepinephrine, are thought to contribute to mood fluctuations and the shift between manic and depressive episodes (Sigitova, E.,2017). Abnormalities in the functioning of the brain's reward dopaminergic system and circuits related to emotional regulation also play a role in the disorder's pathogenesis Nestler, E. J., & Carlezon Jr, W. A. (2006)..
3. Neuroplasticity and BDNF: Neuroplasticity refers to the brain's ability to adapt and reorganize in response to experiences and learning. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a critical role in promoting neuroplasticity and supporting the survival and function of neurons (Phillips, C., 2017). Altered BDNF levels have been observed in individuals with BD, and this may contribute to the abnormal neural circuits and cognitive impairments detected in the disorder.
4. Circadian Rhythm Disruptions: The body's internal biological clock, known as the circadian rhythm, regulates various physiological processes, including sleep-wake cycles, hormone secretion, and body temperature. Disruptions in the circadian rhythm have been linked to bipolar disorder, with irregular sleep patterns and disturbances in daily routines potentially triggering mood episodes (Soria, V., & Urretavizcaya, M. (2009)..
5. Stress and Life Events: Stressful life events can act as precipitating factors for the onset of bipolar episodes in individuals who are genetically predisposed to the disorder (Kessler, R. C.,2010). Chronic stress can also exacerbate the severity and frequency of mood episodes, making stress management an essential aspect of bipolar disorder treatment.

In addition, in recent years, emerging research has shed light on the role of inflammation and immune dysregulation in bipolar disorder (Ortega, M. A., 2023). Elevated levels of pro-inflammatory cytokines have been associated with mood episodes, suggesting a link between the immune system and the central nervous system. Understanding these immune-related mechanisms could open up new avenues for targeted treatments in the future (Rosenblat, J. D.,2017).

As the field of bipolar disorder research progresses, efforts are being made to uncover more personalized treatment approaches. A deeper understanding of the underlying molecular and genetic mechanisms may lead to the development of targeted therapies, improving the management and long-term outcomes for individuals with bipolar disorder (Amare, A. T.,2017). Furthermore, this knowledge could help identify early risk factors and allow for more effective early interventions to prevent or delay the onset of the disorder in vulnerable individuals.

In conclusion, the pathogenesis of bipolar disorder is a complex and multifaceted interplay of genetic, neurobiological, environmental, and psychosocial factors. As research continues to advance, a more comprehensive understanding of these factors will likely lead to more individualized and effective approaches to diagnosis and treatment, ultimately improving the quality of life for those living with this challenging condition.

3. Neuropsychological Evaluation in MDD and BD

In the context of neuropsychological evaluation, it is of utmost importance to incorporate a range of psychometric instruments, as we will discuss shortly. Nevertheless, we must not underestimate the significance of conducting a thorough clinical interview with the patient undergoing assessment (Switzer, G. E., 1999). The primary objective of the neuropsychological examination is to achieve a comprehensive evaluation of the patient, encompassing the assessment of affective symptoms, cognitive functions, overall functioning, and, most significantly, preventing misdiagnosis between MDD and BD (Pennington, C.,2015). Differential diagnosis between MDD and BD can be challenging due to the overlap of certain symptoms, creating the potential for misidentification. However, through meticulous evaluation and the use of sensitive psychometric tools, it becomes feasible to distinguish between the two conditions.

Among the main tools of global affective assessment, we should consider:

AFFECTIVE DOMAIN:

The Hamilton Psychiatric Rating Scale for Depression (HDRS), also known as the Hamilton Depression Rating Scale (HDRS), is one of the most widely used and

respected instruments for assessing the severity of depression in individuals. It was developed by Max Hamilton in 1960 and has undergone several revisions since then.

The HDRS is designed to measure the severity of depressive symptoms in patients with mood disorders, including Major Depressive Disorder (MDD) and Bipolar Disorder (BD). It consists of 17 items that cover a range of symptoms commonly associated with depression. The items assess both psychological and physical symptoms, such as feelings of sadness, guilt, insomnia, agitation, loss of interest, and somatic complaints.

Each item is rated on a scale from 0 to 4, with higher scores indicating more severe symptoms. The total score is obtained by summing the individual item scores, with a maximum possible score of 52. The higher the total score, the more severe the depression is considered (Sharp, R., 2015)..

The Beck Depression Inventory (BDI) is a widely used self-report questionnaire designed to assess the severity of depression in individuals. It was developed by Aaron T. Beck in the 1960s and has since been revised multiple times to enhance its validity and reliability.

The BDI consists of 21 items that measure various symptoms commonly associated with depression, such as sadness, pessimism, guilt, irritability, loss of interest in activities, changes in sleep and appetite, and thoughts of self-harm. Each item presents four statements, and the individual is asked to choose the statement that best describes their feelings over the past two weeks, including the day of the assessment.

Each item is scored on a scale from 0 to 3, with higher scores indicating more severe symptoms. The total score is obtained by summing the individual item scores, with a maximum possible score of 63. The higher the total score, the more severe the depression is considered (Beck, A. T.,1987).

NEUROCOGNITIVE DOMAIN:

The Mini-Mental State Examination (MMSE) is a widely used and brief screening test that is commonly employed to assess cognitive function and detect cognitive impairment, especially in the context of dementia and other neurocognitive disorders (Measso, G.,1993).

The MMSE consists of a series of questions and tasks that assess various cognitive domains, including orientation, memory, attention, language, and visuospatial skills. It is typically administered by a healthcare professional, such as a doctor, nurse, or psychologist, and can be completed in about 5 to 10 minutes.

The examination comprises the following components:

1. Orientation: The patient is asked to state the current date (e.g., day, month, year) and the location (e.g., city, state, country).
2. Registration: The examiner gives the patient three unrelated words to remember, such as "apple," "table," and "penny." The patient is then asked to repeat these words back to the examiner.
3. Attention and Calculation: The patient is asked to perform simple arithmetic tasks, such as serial sevens (subtracting 7 from 100 and repeating the process five times) or spelling a word backward.
4. Recall: After a short delay (usually around 5 minutes), the patient is asked to recall the three words mentioned earlier.
5. Language: The patient is asked to follow verbal commands, name common objects, repeat a phrase, and write a sentence dictated by the examiner.
6. Visuospatial Skills: The patient may be asked to copy a simple drawing, such as intersecting pentagons.

Each correct response is assigned a specific score, and the total score is calculated by summing up the individual scores for all the tasks. The maximum score on the MMSE is 30, with higher scores indicating better cognitive function. A score of 24 or higher is considered normal for individuals with 8 or more years of education. However, the interpretation of scores may vary depending on factors such as age, education level, and cultural background.

It is important to note that the MMSE is a screening tool and not a comprehensive assessment of cognitive function. It can help identify cognitive impairment, but it does not provide a definitive diagnosis. If the MMSE indicates potential cognitive deficits, further evaluation and more in-depth neuropsychological testing may be necessary to determine the underlying cause and severity of cognitive impairment.

The Montreal Cognitive Assessment (MoCA) (MoCa: Nasreddine, et al. 2005; Italian version: Santangelo, G., 2015) is a widely used cognitive screening tool designed to detect mild cognitive impairment (MCI) and early signs of dementia.

The MoCA assesses multiple cognitive domains, including attention and concentration, executive functions, memory, language, visuospatial abilities, and orientation. It is designed to provide a more comprehensive evaluation of cognitive function compared to the Mini-Mental State Examination (MMSE) and is particularly

sensitive to detecting mild cognitive deficits. Therefore it has been proposed to evaluate global cognitive function in neuropsychiatric disorders (Rosca, E. C.,2020).

Frontal Assessment Battery (FAB: Dubois, B., 2000; Italian version: Appollonio, I.,2005): It proposes a simple and rapid protocol through six cognitive and behavioral tests including: conceptualization, cognitive flexibility, motor programming, sensitive to interference, control of inhibition, environmental autonomy.

1. Similarities: In this task, the individual is asked to identify similarities between two different objects or concepts. It evaluates abstract reasoning, conceptualization, and cognitive flexibility.
2. Lexical Fluency: This subtest assesses verbal fluency by requiring the individual to generate as many words as possible within a specific category (e.g., animals, fruits) in a given time. It measures semantic fluency and the ability to generate words spontaneously.
3. Motor Series: The individual is asked to mimic a series of hand movements demonstrated by the examiner. It evaluates motor programming and sequencing abilities.
4. Conflicting Instructions: In this task, the individual is asked to perform a specific action while ignoring a conflicting instruction. It assesses response inhibition and resistance to interference.
5. Go-No-Go: The individual is instructed to respond (Go) to certain stimuli but withhold a response (No-Go) to others. It evaluates response inhibition and impulsive tendencies.
6. Prehension Behavior: This subtest assesses the ability to utilize and adapt hand movements appropriately, often involving the use of common objects like scissors. It evaluates motor programming and praxis.

Each subtest in the FAB is scored, and the total possible score is 18. A lower score on the FAB may indicate deficits in frontal lobe functions and executive functions, which can be associated with various neurological and psychiatric conditions, such as traumatic brain injury, stroke, dementia, and certain mental disorders.

The FAB is a valuable tool in clinical settings to assess and monitor cognitive changes related to frontal lobe dysfunction. However, like other neuropsychological assessments, the interpretation of FAB scores should be considered along with other clinical informations and assessments to obtain a more comprehensive understanding of an individual's cognitive abilities and potential areas of impairment.

The Digit Span test is used to evaluate a person's ability to hold and manipulate information temporarily in their memory. It specifically assesses their attention, concentration, and mental processing speed. The forward digit span primarily measures short-term memory, while the backward digit span additionally assesses working memory and the ability to mentally manipulate information (Leung, J. L.,2011).

A typical scoring for Digit Span involves recording the longest sequence of digits that the individual could accurately recall in both forward and backward order. For example, if someone can correctly recall sequences of five digits forward but only three digits backward, their Digit Span scores would be 5 forward and 3 backward.

PSYCHOSOCIAL DOMAIN:

The Functioning Assessment Short Test (FAST) is a brief and user-friendly questionnaire designed to assess the functional impairment of individuals with depression disease (J. Sanchez-Moreno et al., 2009).

The FAST consists of 24 items that cover six areas of functioning, including autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Each item is rated on a 4-point scale, with response options ranging from 0 (no impairment) to 3 (severe impairment). The total FAST score is obtained by summing the scores of all 24 items, with a higher total score indicating greater functional impairment.

The FAST is designed to be completed by the patient or by a clinician who has knowledge of the patient's functioning. It takes about 10 to 15 minutes to administer and is easy to understand and use. This tool has been validated in several studies and has demonstrated good psychometric properties, including high internal consistency and test-retest reliability. It is a valuable tool for assessing the impact of bipolar disorder on an individual's daily life and functioning (Moro, M. F.,2012).

Clinicians often use the FAST to track changes in functional impairment over time, monitor treatment progress, and tailor interventions to address specific areas of dysfunction. It provides valuable information for treatment planning and helps healthcare professionals understand the broader impact of bipolar disorder on the patient's life beyond just symptom severity.

4. Current pharmacological treatment in MDD

Pharmacological treatment for patients with MDD typically involves the use of antidepressant medications. There are several classes of antidepressants available, and the choice of medication may depend on factors such as the patient's specific symptoms, medical history, and individual response to treatment. Here are some common classes of antidepressants used in the treatment of MDD:

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants developed in the 1980s and 1990s. The first SSRI was fluoxetine, followed by five other drugs: citalopram, escitalopram, fluvoxamine, sertraline, and paroxetine. These medications work by increasing the availability of serotonin in the brain, alleviating depressive symptoms. Each SSRI has a different pharmacodynamic and pharmacokinetic profile, with half-lives ranging from a few hours to a week. This aspect is crucial to avoid accumulation in individuals with less efficient metabolism. Some SSRIs may interact with other drugs by inhibiting CYP450 enzymes, leading to potential relevant pharmacological interactions. Although different SSRIs are clinically similar in terms of effectiveness, they may differ in the occurrence of serotonin-related side effects, such as sexual problems and sleep disturbances. Therefore, it is essential to carefully consider the patients' pre-existing symptoms before prescribing an SSRI. Other drugs used in depression treatment include serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NASSAs), norepinephrine and dopamine reuptake inhibitors (NDRIs/DARIs), and serotonin modulators and stimulators (SARIs). Each of these drug classes has specific mechanisms of action and may be indicated for particular depression subtypes or associated symptoms. The choice of medication should be based on the specific needs and responses of the patient, with careful evaluation of potential benefits and side effects. After the 2000s, new antidepressant drugs have been developed that act on sites other than monoaminergic ones. These include agomelatine, glutamatergic agents, and other non-aminergic agents such as CRF1 agonists (Siracusano A., 2014). Research in the field of depression has focused also on alterations in circadian rhythms, sleep-wake cycle, and melatonin secretion. These disturbances have become the primary target for developing new effective drugs for depression treatment. Agomelatine is one of these drugs that can act on these imbalances. It is an antidepressant that acts as an antagonist of 5HT2C receptors and as an agonist of melatonin MT1 and MT2 receptors. Therefore, agomelatine has

antidepressant and anxiolytic properties and regulates sleep without causing sedation. Unlike some available treatments, agomelatine has fewer side effects, especially concerning sexual dysfunction and weight gain (De Bodinat C., 2010). Despite progress in antidepressant research, treatment response and remission rates remain inadequate. Italian studies have shown that only 25.5% of patients treated with monotherapy antidepressants achieved a complete response, while 57.9% only partially responded (Aguglia E, Biggio G., 2014). Many patients have residual symptoms, including cognitive symptoms, which can significantly impact functionality and quality of life (Conradi H.J. Et al., 2011). However, currently available antidepressants have limited efficacy in treating these cognitive symptoms (Conradi H. et al., 2011). Additionally, many patients do not tolerate the side effects associated with antidepressants, such as sexual dysfunction, insomnia, and weight gain, leading to treatment discontinuation (Hunot V.M., Horne R. et al., 2007). Hence, there is a need to develop new antidepressants with a better tolerability profile. Moreover, it has been suggested that antidepressants should act on multiple neurotransmitter systems, such as the glutamatergic, dopaminergic, and cholinergic systems, to overcome the limitations of current monoaminergic therapies (O'Leary O.F., 2014;). Multimodal antidepressants have been developed to interact with multiple pharmacological targets and have multiple mechanisms of action. Some of them aim to enhance all three monoaminergic systems (5-HT, NA, and DA) with triple monoamine reuptake inhibitors like amitifadine, while others include 5-HT1A receptors to reduce clinical onset latency and improve tolerability by reducing sexual disturbances (Rush AJ, Trivedi MH, Stewart JW et., 2011). In summary, the evolution of antidepressants has shifted towards a multimodal approach, aiming to develop drugs that act on multiple neurotransmitter systems and have a better tolerability profile to address the unmet needs in patients with major depression (Rosenzweig-Lipson, S., 2007)

5. Current pharmacological treatment in BD

The choice of pharmacological treatment in bipolar disorder is complex due to its recurrent, episodic, and heterogeneous nature. While some patients may achieve complete remission and experience periods without apparent symptoms, others may have persistent residual symptoms, especially after recurrent manic, hypomanic, or

depressive episodes. This symptom persistence can negatively impact the patient's functioning.

The management of bipolar symptoms includes both pharmacological and non-pharmacological treatments to address the acute phases of manic, hypomanic, and depressive episodes. Additionally, long-term therapy aims to prevent relapses and recurrences of episodes (Treuer, T., & Tohen, M., 2010).

In the past two decades, new therapeutic options with proven efficacy in both acute and chronic phases of bipolar disorder have been identified, expanding treatment possibilities. Therapeutic strategies should focus on better control of acute symptoms, reducing their severity, and preventing relapses and recurrences of manic and depressive episodes.

Mood stabilizers are the preferred drugs prescribed for the treatment of bipolar disorder. However, studies have shown that a significant portion of patients do not respond adequately to monotherapy, necessitating the use of polypharmacotherapy. This type of therapy involves administering two or more psychotropic drugs, which can belong to the same class or different classes such as second-generation antipsychotics and mood stabilizers.

Among the classes of drugs used in the treatment of bipolar disorder, antidepressants, antipsychotics, and benzodiazepines are included, which can be used in combination with mood stabilizers (Fountoulakis, K. N.,2005).

The choice of pharmacological and psychological strategy is influenced by various factors, such as medical and psychiatric comorbidities, previous or concomitant treatments, treatment response, presence of side effects, and the patient's willingness to adhere to therapy. A personalized and collaborative approach is crucial to achieving optimal results in the treatment of bipolar disorder.

In the treatment of bipolar disorder, various drugs are used, including mood stabilizers and anticonvulsants. Mood stabilizers are drugs that act therapeutically during the acute phase of mania and/or depression, and prophylactically against manic and/or depressive episodes without worsening any therapeutic or prophylactic aspect of the disease. Lithium is considered the ideal drug in this category, with proven efficacy in the treatment and prophylaxis of manic and depressive episodes. However, lithium can cause side effects such as gastrointestinal symptoms, renal symptoms, neurological symptoms, endocrine effects, and cardiac effects.

Other mood stabilizers and anticonvulsants used include valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin, and pregabalin. These drugs are employed for the treatment of acute mania and as adjunctive therapy to prevent future manic episodes. However, each drug may present specific side effects, such as sedation, dizziness, gastrointestinal disturbances, and others (Jacob, S., & Nair, A. B., 2016).

The choice of drug depends on various factors, including the severity of bipolar disorder, individual treatment response, contraindications, and patient preferences. Pharmacological therapy can be combined with other forms of treatment, such as psychotherapy, to improve overall outcomes in the management of bipolar disorder (Colom, F., & Lam, D.,2005).

Antipsychotics of the first generation have long been considered the treatment of choice for acute mania, particularly effective in managing positive symptoms such as delusions and hallucinations. Recent data confirms that monotherapy with first-generation antipsychotics in patients with bipolar disorder is more effective than placebo in treating acute and mixed manic episodes (Ketter, T. A. (2008; Gentile, S., 2007). However, if a patient does not respond to therapy after 1-2 weeks, a different treatment should be considered. In such cases, combining a mood stabilizer with an antipsychotic may be a more suitable choice than using either class of drugs alone. However, this treatment can induce severe side effects in patients treated with first generation antipsychotics, including extrapyramidal effects, tardive dyskinesia, weight gain, sexual dysfunction, sedation, hyperprolactinemia, blurred vision, constipation, and cardiotoxicity.

Second-generation antipsychotics approved by the FDA for the treatment of acute mania include aripiprazole, asenapine, clozapine, olanzapine, iloperidone, paliperidone, quetiapine, risperidone, and ziprasidone. Unlike first-generation antipsychotics, these have a broader spectrum of efficacy, extending to negative, depressive, and cognitive symptoms, owing to their antagonist actions on both dopamine and serotonin-2 (5-HT2A) receptors. Second-generation antipsychotics also have a more favorable side effect profile, with reduced tendencies to induce extrapyramidal symptoms and hyperprolactinemia. They have been hypothesized to be effective in treating and preventing both bipolar mania and depression, and therefore, can be considered for any phase of treatment. Numerous studies support their utility in all phases of bipolar disorder, as monotherapy or as adjuncts to

conventional mood stabilizers (Vieta, E., & Goikolea, J. M., 2005; Yatham, L. N.,2018).

Each second-generation antipsychotic has specific indications and side effects. Risperidone, for example, is effective in treating positive, negative, and emotional symptoms of schizophrenia, and it has demonstrated antidepressant properties and efficacy both in manic and mixed states (Cerveri, G., Gesi, C., & Mencacci, C.,2019). Olanzapine, quetiapine, and aripiprazole are indicated for acute mania and depressive phases of bipolar disorder, with olanzapine also approved for maintenance treatment (Perlis, R. H.,2007). Ziprasidone is the only drug approved by the FDA for the treatment of acute manic or mixed episodes in children and adolescents. Clozapine is used for treatment-resistant bipolar patients and has shown anti-suicidal and anti-aggressive properties. Paliperidone, an active metabolite of risperidone, is approved for schizophrenia and schizoaffective disorder and appears to have fewer side effects than risperidone, improving patient compliance.

Antidepressants are commonly used to treat various mood disorders, including depression, bipolar disorder, neuropathic pain, and anxiety disorders. However, recent studies have highlighted the potential risks of administering antidepressants to patients with latent bipolar disorder, as this could lead to a switch to manic or hypomanic episodes, chronicity of the condition, or conversion to rapid cycling. To address these concerns, the International Society for Bipolar Disorders (ISBD) has formed a task force to establish guidelines for the use of antidepressants in bipolar disorder (Pacchiarotti, I.,2013).

Tricyclic antidepressants (TCAs) work by inhibiting the reuptake of serotonin and noradrenaline neurotransmitters, thus improving depressive symptoms. However, TCAs can also affect other neurotransmitter systems, leading to significant side effects such as weight gain, sedation, sexual problems, and cardiac effects. Common TCAs include amitriptyline, clomipramine, desipramine, and nortriptyline.

SSRIs are similarly effective as TCAs, but with reduced toxicity and tolerable side effects. The six SSRIs available are sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, and escitalopram.

Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) like venlafaxine and duloxetine are used to treat major depression, anxiety disorders, panic attacks, and somatic symptoms related to depression.

Serotonin-specific and Noradrenergic Antidepressants (NaSSAs) like mirtazapine enhance serotonin and noradrenaline neurotransmission. Mirtazapine is commonly prescribed for major depression and sometimes for off-label use in anxiety and sleep disorders.

Serotonin Antagonist and Reuptake Inhibitors (SARI), represented by trazodone, act as dual-action antidepressants by inhibiting serotonin reuptake and blocking 5-HT2 receptors. Trazodone is also used to treat insomnia due to its H1 histamine antagonist activity.

Dopamine and Norepinephrine Reuptake Inhibitors (DNRI), such as bupropion, are indicated for depression, obesity, and smoking cessation. Common side effects of bupropion include agitation, dry mouth, constipation, and insomnia.

According to the ISBD guidelines, the use of antidepressants in bipolar disorder should be approached with caution, particularly in patients with bipolar I, mixed states, or rapid cycling (Pacchiarotti, I.,2013). In these cases, a combination of antidepressants with mood stabilizers is often preferred.

6. The role of Network Analysis Model

Network analysis is a mathematical and statistical approach used to study the relationships and interactions between entities within a complex system. In the context of psychology and psychiatry, network analysis has been applied to understand the interconnections between symptoms, behaviors, and variables in mental disorders.

In the network analysis model, entities (e.g., symptoms, behaviors, or variables) are represented as nodes, and the relationships between these entities are depicted as edges. The strength and direction of the connections between nodes in the network provide insights into the associations and dependencies between different components of the system (Galimberti E.,2020).

The main objective of network analysis in psychopathology is to gain a better understanding of how symptoms and variables influence each other, potentially leading to the development and maintenance of a mental disorder. By studying the complex web of interactions between nodes, researchers can identify key symptoms or variables that play a central role in the network and may be critical for the disorder's manifestation (McNally, R. J.,2016).

Network analysis allows researchers to explore the dynamics of the system over time and examine how changes in one node can propagate throughout the network, affecting other nodes. This dynamic perspective can offer valuable insights into the temporal evolution of symptoms and help identify critical intervention points for targeted treatments (Schmittmann, V. D.,2013).

As mentioned earlier, MDD and BD are debilitating psychiatric conditions characterized by a wide range of heterogeneous symptoms of varying severity and pervasiveness. Despite the availability of numerous diagnostic tools, establishing a correct diagnosis between the two disorders can often be complex. A misdiagnosis diagnosis, confusing Major Depressive Disorder with Bipolar Disorder during the depressive phase, could have severe impact on the patient's psychological well-being. In the case of a misdiagnosis of major depression, the prescription of antidepressant medications could trigger a transition to the manic phase in patients with bipolar disorder. This phenomenon, known as "switching," represents a significant risk to the patient's emotional stability and the appropriate management of their condition.

Another critical aspect is the limitation of traditional statistics in capturing the complexity of depressive disorders and understanding the intricate relationships between symptoms. The linear and one-dimensional view often falls short in grasping the entire spectrum of clinical manifestations, necessitating a more advanced and sophisticated approach. In this context, the application of innovative techniques such as network analysis has shown promise as it examines the interconnections between symptoms and the neurobiological and psychosocial aspects of mental disorders (Levinson, C. A.,2018). It provides a systemic perspective, allowing for a more comprehensive view of the complexities of depressive disorders. In recent times, network analysis has emerged as a valuable tool in studying psychopathological conditions, revealing intricate cognitive, emotional, and psychosocial structures. This approach highlights that patients' characteristics are not simply the sum of isolated abilities but the result of complex dynamic interactions.

Integrating network science and dynamic system theory offers a promising avenue for investigating the finely detailed phenotypes of MDD and BD. It enables the integration of data from different levels of analysis and captures the dynamic relationship between symptoms over time, both within patients and in response to different treatment modalities.

Using network analysis and graph theory, researchers can examine the connections between symptoms in MDD and BD, understanding how symptoms may influence, reinforce, sustain, or weaken each other over time. The influence of symptoms on the development of other symptoms may not be the same or equally distributed between these two pathologies. Hence, it is the pattern of connections between symptoms that provides crucial insights into the unique functional impairment of each disorder and the differences and similarities in the underlying factors.

Innovative discoveries from other fields, such as imaging techniques and mathematical modeling, together with graph analysis, have led to new conceptual perspectives, offering more comprehensive and predictive models to understand the psychosocial strengths and needs of patients with MDD and BD. Network analysis has emerged as a promising methodology in contemporary psychopathology research, enabling the analysis of relationships between symptoms and their triggers, challenging the traditional latent disease approach (Smith, K. E.,2018).

In a network model, nodes represent the symptoms of a disorder, while edges denote the relationships between symptoms. Three main measures of centrality - degree, betweenness, and closeness - play a crucial role in identifying the importance of specific symptoms within the network configuration and their impact on neighboring symptoms and functions. This approach provides valuable insights into the symptoms to target with therapeutic interventions and enhances our understanding of the differences between unipolar and bipolar depression for more accurate differential diagnosis.

While network analysis in psychopathology is still in its early stages, it shows promising growth. Some studies have started to use this approach to compare MDD and BD from a cognitive perspective during the depressive phase.

6.1 Network Intervention Analysis

To gain a better understanding of the complexity of clinical phenotypes in MDD and the relationship between symptoms and pharmacological treatment, Network Intervention Analysis (NIA) has been proposed as a novel tool. NIA is an innovative method and an extension of the network analysis model used to study mental disorders, which conceives mental disorders as a result of interactions between different symptoms and variables within a network. In traditional approaches, mental disorders are often considered as distinct entities or categories, with a focus on understanding

individual symptoms or assessing the severity of a disorder. However, the NIA approach takes a more comprehensive view, considering the interconnections and interactions between symptoms and variables within the network. NIA allows researchers to analyze the specific and sequential effects of treatments on symptomatology. It goes beyond merely assessing treatment response or symptom severity and seeks to identify how treatments impact the network of symptoms and variables. This includes examining which symptoms or variables are directly or indirectly influenced by a specific treatment. By applying NIA, researchers can gain a deeper understanding of how a treatment influences different symptoms and domains within a mental disorder. This can be particularly valuable in identifying the most effective treatments for specific individuals and tailoring interventions to target the interconnected aspects of a disorder. Moreover, NIA has potential applications in health psychology, including detecting risky behaviors, supporting primary and secondary prevention efforts, and monitoring the effectiveness of treatments over time (Hunter, R. F., 2019). Its network-based approach provides a more nuanced and detailed perspective on the complex dynamics of mental disorders and treatment outcomes.

Chapter I

Biological and neuropsychological markers of cognitive dysfunction in unipolar vs bipolar Depression: which evidence?

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Abstract

Cognition is a critical aspect of psychopathology. The aim of this review is to evaluate and discuss evidence on neuropsychological and biological markers of cognitive dysfunction in Unipolar and Bipolar Depression, to improve the differential diagnosis and develop personalized pharmacological treatment plans. The different use of biological and neuropsychological markers is reviewed and their use to support the clinical process and differential diagnosis is critically examined. While biological markers can help to reduce the risk of misdiagnosis, neuropsychological markers can be assessed more readily and with less invasive methodology. To this end, additional research on thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on specific psychometric tools proposed in this review. Most importantly, future effort should be directed towards the validation of both types of markers specifically for these two populations. Finally, this review contributes to the field by focusing on the clinical need of a precise differential diagnosis that when put in a translational framework, should combine an integration of research and clinical practice allowing for a better understanding of mental health and for evidence-based clinical practice.

1. Introduction: cognitive dimension in psychopathology

Cognitive functioning has become of growing interest and has been investigated in a variety of contexts and applications, among which neuropsychological assessment, social cognition, and education (Bajaj, 2020; Osborne-Crowley, 2020; Parrales, Palma, Álava, & Campuzano, 2020).

The understanding of psychopathology has been enriched especially, by the focus on human cognitive processes. Nowadays it is well known that mental illness is characterized by significant cognitive impairments that are firmly associated with other affective and behavioral signs and symptoms (Haywood & Raffard, 2017). In schizophrenia, for example, there are alterations in attention, executive functions, language, processing speed, memory and visuospatial ability (Hedges, Farrer, Bigler, & Hopkins, 2019a), while in Obsessive-Compulsive Disorder, specific cognitive

strategies are aimed at the management of a sense of guilt (Mancini & Gangemi, 2018), lower cognitive flexibility/set shifting and higher susceptibility to perseveration (Yazdi-Ravandii, Shamsaei, Matinnia, Shams, Moghimbeigi, Ghaleiha *et al.*, 2018).

Disorders that share a disturbance in mood - defined as *affective disorders* or *mood disorders* (Ellenbroek & Youn, 2016) - show a particular association with cognitive dysfunction, as deficits in cognition often preceed or appear during the early stage of those pathologies and persist after the resolution of emotional symptoms, thereby, contributing to the patient's overall disability (Hedges, Farrer, Bigler, & Hopkins, 2019b). As the category of "affective disorders" mainly refers to the different kinds of Depressive Disorder and Bipolar Disorder, cognitive dysfunction is observed both in unipolar/bipolar depressive as well as in manic/hypomanic states.

According to the World Health Organization, Depression is ranked as the single largest contributor to global disability, is the major cause of suicide deaths and affects about 4.4% of the global population, moreover, this number is set to increase (WHO, 2017).

There are different depressive phenotypes but two of them - unipolar and bipolar - represent the most challenging in terms of differential diagnosis (Hirschfeld, 2014). Indeed, long-term follow-up studies demonstrate that people suffering from Bipolar Disorder spend nearly half of the time (about 40%) in a depressive phase, about 50% of the time in an euthymic phase and only 10% of the time in a manic/hypomanic phase (Judd, Akiskal, Schettler, Endicott, Maser, Solomon *et al.*, 2002). This is particularly true for Bipolar II Disorder (Judd, Akiskal, Schettler, Coryell, Endicott, Maser *et al.*, 2003). Moreover, bipolar patients usually ask for consultation only when they are depressed (Hirshfeld, 2005). Together, these factors together result in late diagnosis or mistreatment, with a negative general outcome regarding the patient's quality of life and a high overall burden of disease (Leyton & Barrera, 2010).

Therefore, differential diagnosis is critical. To this end, research on cognition may significantly help the clinician by describing the cognitive profiles of unipolar and bipolar Depression and efforts should be made to include them as part of the diagnostic process in order to personalize pharmacological treatment. In other terms, collecting and differentiating markers of cognitive dysfunction related to the different depressive phenotypes would increase the specificity of the diagnosis and the appropriateness of adequate treatment.

Starting by acknowledging that unipolar and bipolar Depression are disorders of the brain, and that behavior is the last step of a cascade that started long before problems manifest themselves, we probably should start with the brain, with its wiring and connections, with its metabolism, and with the way it interacts with its surroundings. Much variation exists in how the brain is wired and how it functions, but this variation does not exclude the existence of some possible and predictable set of factors that put bipolar and unipolar depressed patients at a different risk for cognitive problems. When crossing a behavioral, emotional, or cognitive threshold, what underlying different thresholds has each patient crossed that determine their vulnerability? What drives their cognitive dysfunction?

Markers of cognitive dysfunction can be identified either as neuropsychological or as biological, each to be evaluated with their own specific clinical tools.

This review explores the role of neuropsychological and biological markers of cognitive dysfunction in unipolar and bipolar Depression, and collects evidence regarding their potential role in strengthening differential diagnosis. Particular attention will be given to the psychometric tools that we might want to include in the assessment of unipolar and bipolar Depression to improve the quality of clinical decision-making and adequately better plan the treatment.

2. Depression: main phenotypes and cognitive dysfunction

The publication of the DSM-5 (APA, 2013) imposed several important changes in the diagnostic categories compared to the previous DSM-IV-TR (APA, 2000), such as, the abolition of the "Mood Disorders" category (Rodríguez-Testal, Senín-Calderón, & Perona-Garcelán, 2014). In the new Manual, "Bipolar and Related Disorders" and "Depressive Disorders" are two distinct categories. The first includes Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and Disruptive Mood Dysregulation Disorder, while the second includes Major Depressive Disorder (MDD), Persistent Depressive Disorder (Dysthymia), and Premenstrual Dysphoric Disorder.

Given the general aim of this review, it is useful to remind that Bipolar I Disorder must be characterized by a distinct manic episode that may be associated with other periods of Major Depressive Episodes and/or hypomania, whereas Bipolar II Disorder can be diagnosed if there has been at least one episode of hypomania and one

episode of Major Depressive Disorder. Major Depressive Disorder, instead, is characterized by a two-week period showing at least either depressed mood or loss of interest or pleasure, associated with other symptoms like changes in appetite, weight, sleep patterns, diminished energy and feelings of worthlessness and excessive guilt. Specifiers and additional criteria of inclusion and exclusion are thoroughly discussed in the DSM-5.

In depressive phenotypes, two fundamental types of cognitive dysfunction can be distinguished: *cognitive biases* and *cognitive deficits* (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011). The first consist of systematic distortions in the processing of information, in terms of selection, interpretation, encoding and retrieval. They influence the way depressed people view themselves, the world and their future and they are best treated by specific psychotherapeutic approaches (Young, Rygh, Weinberger, & Beck, 2014). Cognitive deficits, instead, can be defined as specific impairments in several domains, among which, attention, executive functions, and memory which represent the main cognitive domains to be considered. They can be detected, measured, and should be taken into consideration to support the diagnosis and the efficacy of treatment. As discussed before, these deficits are expressed in terms of neuropsychological and biological markers. In the next paragraphs, we will present and critically review the markers of cognitive dysfunction in unipolar and bipolar Depression.

3. Markers of cognitive dysfunction in unipolar Depression

3.1. Neuropsychological markers

According to international and Italian psychiatrists, cognitive symptoms rapresent a relevant dimension of MDD and are among the residual symptoms affecting the risk for relapse (Albert, Brugnoli, Caraci, Dell'Osso, Di Sciascio, Tortorella *et al.*, 2016). Indeed, unipolar Depression is characterized by several neuropsychological markers representing a core feature that needs to become a specific target for treatment. For example, SSRI and SNRI medications improve cognitive symptoms independently from their efficacy related to the affective dimension (Castellano, Ventimiglia, Salomone, Ventimiglia, De Vivo, Signorelli, Bellelli *et al.*, 2016). Neuropsychological changes are so obvious, that the term "pseudodementia" has been coined to refer to impaired cognition given the resemblance with neurodegenerative diseases, but instead here it is due to a psychiatric condition

(Brodaty & Connors, 2020). Moreover, the DSM-5 includes the “diminished ability to think or concentrate, as well as indecisiveness” as a criterion for a major Depression episode (APA, 2013).

Moderate deficits in executive functions, memory and attention are altered in depressed patients compared to healthy subjects, and impairment in executive functions and memory persisted even after mood symptoms had remitted (Rock, Roiser, Riedel, & Blackwell, 2014). Also, neurocognitive performance at baseline influenced long-term psychosocial functioning with a specific role played by verbal memory, which predicted the functional outcome after one year in patients who had a partial response to antidepressants (Castellano, Torrent, Petralia, Godos, Cantarella, Ventimiglia *et al.*, 2020).

According to Austin, Mitchell and Goodwin (2001), in MDD there are deficits in attention, verbal and visual memory, executive processes and psychomotor skills which sums up decades of research on this topic. Also, verbal fluency and attentional set-shifting are impaired in depressed elderly patients (Beats, Sahakian, & Levy, 1996) whereas younger out-patients showed similar symptoms with additional deficits in motor speed (Purcell, Maruff, Kyrios, & Pantelis, 1997). Deficits in the Digits backwards task and perseverative responses characterized a sample of patients with endogenous/melancholic Depression (Austin, Mitchell, Wilhelm, Parker, Hickie, Brodaty *et al.*, 1999).

Together, the debate with respect to neuropsychological markers is still wide open and their role in unipolar Depression, either as endophenotypes or as epiphenomena of the pathology (McInerney, Gorwood, & Kennedy, 2016) warrants a more in-depth evaluation.

3.1. Biological markers

Attention towards biological markers of cognitive dysfunction in unipolar Depression is growing fast. The link between Depression and cognitive impairment is so robust, that a lifetime history of Major Depression can be considered as a risk factor for the development of Alzheimer's disease and as a predictor of the conversion from Mild Cognitive Impairment (MCI) to dementia (Steffens, 2012).

Deficits in neurotrophin signaling are observed in Major Depressive Disorder (MDD): reduced plasma levels of BDNF and TGF-β1 - a growth factor and an anti-inflammatory cytokine with key roles in neuroprotection, synaptic plasticity and the

formation of new memories - correlate with Depression severity (Caraci, Spampinato, Morgese, Tascedda, Salluzzo, Giambirtone *et al.*, 2018). Moreover, MDD patients display higher levels of proinflammatory cytokines, such as IL-6 and IL-8, and tumor necrosis factor-α (TNF-α) which correlate with circulating mitochondrial DNA (mtDNA) (Kageyama, Kasahara, Kato, Sakai, Deguchi, Tani *et al.*, 2018). Signs of inflammation and oxidative stress led the hypothesis that the immune system is involved actively in MDD (Maes, Nowak, Caso, Leza, Song, Kubera *et al.*, 2016). Additional data stem from the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to higher levels of cortisol in depressed patients and is often associated with inflammation (Pariante, 2017). Lower levels of neurotrophins and higher levels of glucocorticoids together with heightened inflammation increase Aβ toxicity, hippocampal atrophy and, consequently, cognitive deficits (Caraci, Copani, Nicoletti, & Drago, 2010).

These findings are further strengthened by neuroimaging data. The anterior Cingulate Cortex (ACC) is involved in attention, problem solving, motivation and decision making (Rushforth, Behrens, Rudebeck, & Walton, 2007), while the Dorsolateral Prefrontal Cortex (DLPFC) is considered critical for cognitive functions (Liao, Feng, Zhou, Dai, Xie, Ji *et al.*, 2012). The ACC, DLPFC and Orbitofrontal Cortex (OFC) have been hypothesized to work together to inhibit a negative emotional response and emotional memory thanks to a cognitive control network, within which emotional response and memory originate from regions such as the amygdala and the hippocampus. ACC, DLPFC and OFC appear to be critical biomarkers for cognitive dysfunction in unipolar Depression also when considering data from Electroencephalography (EEG) and Positron Emission Tomography (PET) (Lai, 2019). Furthermore, Magnetic Resonance Imaging (MRI) data indicate the presence of structural changes in recurrent depressed patients with lower grey matter volume in the left hippocampus (Samann, Hohn, Chechko, Kloiber, Lucae, Ising *et al.*, 2013). Also, mean depressive symptom scores are associated with reductions in brain volume in the cingulate gyrus and in the OFC, as well as with the rate of a decline in volume of left frontal white matter (Dotson, Davatzikos, Kraut, & Resnick, 2009).

Taken together, the data regarding biomarkers, do not indicate a clear picture on whether cognitive dysfunction in Depression is part of an underlying and stable neurobiological vulnerability, which would support the neurodevelopmental origins of Depression, or whether cognitive dysfunction occurs only during depressive episodes,

as outlined by McInerney *et al.* (2016), which would support a more immediate environment-related hypothesis with a strong contribute of epigenetics.

4. Markers of cognitive dysfunction in bipolar Depression

4.1 Neuropsychological markers

Cognitive impairment and neuropsychological dysfunction are two fundamental characteristics in Bipolar Disorder patients, especially in the depressive phase, because the resulting deficits compromise the social, relational and professional capacities of these patients, and significantly affect their overall functioning and quality of life (Melloni, Poletti, Vai, Bollettini, Colombo, & Benedetti, 2019).

Much research has highlighted the relationship between the number of episodes related to mood variability and the severity of cognitive deficits, reporting the presence of structural and neuropsychological changes (Hellvin, Sundet, Simonsen, Aminoff, Lagerberg, Andreassen *et al.*, 2012; Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015; Passos, Mwangi, Vieta, Berk, & Kapczinski, 2016). In fact, in bipolar patient anomalies related to white matter (WM), to ventricular enlargement (Birner, Seiler, Lackner, Bengesser, Queissner, Fellendorf *et al.*, 2015), and to the loss of volume and thickness of total gray matter (GM) have been observed (Hallahan, Newell, Soares, Brambilla, Strakowski, Fleck *et al.*, 2011; Gildengers, Chung, Huang, Begley, Aizenstein, & Tsai, 2014).

From a neuropsychological point of view, the most important cognitive impairments of bipolar patients in the depressive phase, are deficits in memory and executive function (Martìnez-Aràn, Vieta, Colom, Reinares, Benabarre, Gastó *et al.*, 2000; Borkowska & Rybakowski, 2001; Bearden, Hoffman, & Cannon, 2001), even after remission. These data have been confirmed by several other studies, which added to the aforementioned dysfunctions, alterations in episodic memory (Sweeney, Kmiec, & Kupfer, 2000), in attention (van der Meere, 2007; Maalouf, Klein, Clark, Sahakian, Labarbara, Versace *et al.*, 2010; Belleau, Phillips, Birmaher, Axelson, & Ladouceur 2013), in verbal appeal and fine motor skills (Malhi, Ivanovski, Hadzi-Pavlovic, Mitchell, Vieta, & Sachdev, 2007), and finally those related to visual-mnemonic skills and verbal fluency (Martìnez-Aràn *et al.*, 2000; Harkavy-Friedman, Keilp, Grunebaum, Sher, Printz, Burke *et al.*, 2006; Xu, Lin, Rao, Dang, Ouyang, Guo *et al.*, 2012), to the aforementioned dysfunctions which worsen based on the progression of mood related episodes (Lee, Hermens, Scott, Redoblado-Hodge, Naismith,

Lagopoulos *et al.*, 2014; Galimberti, Bosi, Caricasole, Zanello, Dell'Osso, & Viganò, 2020). Furthermore, serious damage is observed in functions of the frontal lobe, which involve visuospatial and visuomotor skills, working memory and, most importantly, executive functioning (Borkowska & Rybakowski, 2001).

Recent research has found poor performance in verbal memory, working memory, psychomotor coordination and selective assessment in a sample of bipolar type I depressed patients (Melloni *et al.*, 2019) while marked deficits in episodic memory, in learning and recalling a list of objects, and in encoding information were observed by another study (Dongaonkar, Hupbach, Nadel, & Chattarji, 2019).

As discussed above, the most impaired cognitive function in this phase of Bipolar Disorder, in addition to deficits in memory, seems to be executive functioning: Galimberti and colleagues showed that the centrality of this dysfunction drives the overall cognitive deterioration of the aforementioned patients (Galimberti *et al.*, 2020).

Finally, several authors have explained the relevance of the so-called "suggestive elements" present in the depressive phase of Bipolar Disorder, which involve psychopathological symptoms and clinical variables and refer to, for example, to psychomotor agitation, emotional lability, irritability, insomnia, hyperphagia and rapid thoughts, which although not involved in the cognitive aspects, influence the recognition of the disorder (Ghaemi, Sachs, & Goodwin, 2000; Yatham, 2005).

Taken together, many of the neuropsychological markers belonging to the depressive phase of Bipolar Disorder are similar to those observed in of unipolar depressive disorder, albeit with minimal distinction. Therefore, it is important to further discuss the differences between the two disorders, in order to improve the differential diagnosis and to choose the appropriate therapy most in accordance with the clinical phenotype of the patient.

4.2 Biological markers

A similarity exists between the biological markers of Bipolar Disorder in the depressive phase with those of unipolar Depression which concerns the decrease in levels of brain-derived neurotrophic factor (BDNF) levels (Cunha, Frey, Andreazza, Goi, Rosa, Gonçalves *et al.*, 2006; Bourne, Aydemir, Balanzá-Martínez, Bora, Brissos, Cavanagh *et al.*, 2013). In fact, various mood related episodes negatively affect the homeostatic balance between inflammatory mechanisms, oxidative processes and neuroprotective substances (such as BDNF), and contribute to neuronal apoptosis

(Berk, Kapczinski, Andreazza, Dean, Giorlando, Maes *et al.*, 2011; Fries, Pfaffenseller, Stertz, Paz, Dargél, Kunz *et al.*, 2012; Bauer, Pasco, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014).

Furthermore, in the case of Bipolar Disorder, especially during the depressive phase, the levels of proinflammatory agents are higher, such as for interleukins (IL-6, IL-2R, IL-1beta), tumor necrosis factor (TNF-α), cellular TNF-α receptors (TNFR1), and CXCL10 serum levels (Barbosa, Huguet, Sousa, Abreu, Rocha, Bauer *et al.*, 2011; Bauer *et al.*, 2014; Barbosa, Bauer, Machado-Vieira, & Teixeira 2014a; Barbosa, Machado-Vieira, Soares, & Teixeira, 2014b). In particular, the levels of the pro-inflammatory markers YKL40, sCD40L, and hsCRP are higher, and these alter the function of monoaminergic systems such as dopaminergic and serotoninergic systems, finally affecting cognitive and affective functions (Rosenblat, Brietzke, Mansur, Maruschak, Lee, & McIntyre, 2015). The role of adiponectin is relevant as well, and plays a basic role in metabolic and inflammatory processes: low levels of adiponectin were associated with the depressive state of bipolar subjects (Platzer, Fellendorf, Bengesser, Birner, Dalkner, Hamm *et al.*, 2019).

Additional evidence comes from studies that support the hypothesis that inflammatory diseases, such as, autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), migraine, rheumatoid arthritis (RA), obesity, atherosclerosis, and type II diabetes mellitus, play a significant role in the genesis of Bipolar Disorder (Kupka, Nolen, Post, McElroy, Altshuler, Denicoff *et al.*, 2002; Edwards & Constantinescu, 2004; McIntyre, Konarski, Misener, & Kennedy, 2005; Bachen, Chesney, & Criswell, 2009; Calkin, Van De Velde, Ruzickova, Slaney, Garnham, Hajek *et al.*, 2009; Eaton, Pedersen, Nielsen, & Mortensen 2010; Han, Lofland, Zhao, & Schenkel, 2011; Hsu, Chen, Liu, Lu, Shen, Hu *et al.*, 2014; Perugi, Quaranta, Belletti, Casalini, Mosti, Toni *et. al.*, 2014).

As for unipolar Depression, also for bipolar Depression an involvement of inflammation in metabolic dysfunction has been suggested. In particular, enhanced HPA activity may induce central obesity and insulin resistance (Boutzios & Kaltsas, 2000; Rosenblat *et al.*, 2015).

Research conducted in the field of neuroimaging has contributed greatly to the more accurate analyses of the depressive phase in Bipolar Disorder: bipolar subjects in the depressive phase displayed abnormally high levels of amygdala activity, when

exposed to mostly neutral or sad facial expressions while a reduction was observed in the bilateral amygdala-VMPFC when exposed to happy facial expressions (Almeida, Versace, Mechelli, Hassel, Quevedo, Kupfer *et al.*, 2009).

Other studies, however, observed an increased volume of the lateral and third ventricles (Gulseren, Gurcan, Gulseren, Gelal, & Erol, 2006; Beyer, Young, Kuchibhatla, & Krishnan, 2009; Hallahan *et al.*, 2011; Frey, Andreazza, Houenou, Jamain, Goldstein, Frye *et al.*, 2013; Goldstein & Young, 2013), which became evident only after the occurrence of several mood-related episodes (Strakowski, DelBello, Zimmerman, Getz, Mills, Ret *et al.*, 2002).

Several neurobiological models studying emotional dysregulation have also analyzed the anomalies in fronto-limbic-subcortical structures in bipolar patients, highlighting that they themselves are part of an increase in bottom-up processes and/or a decrease in top-down processes (Savitz & Drevets, 2009; Phillips & Swarts, 2014). These data are supported by functional magnetic resonance imaging (fMRI) studies in which a reduction in activation in the cortical cognitive brain network and increased activation in the ventral limbic brain regions was confirmed in subjects with Bipolar Disorder (Houenou, Frommberger, Carde, Glasbrenner, Diener, Leboyer *et al.*, 2011).

Despite the results achieved, novel studies are needed, including neuroimaging studies, in order to distinguish more clearly the structural and functional differences between unipolar and bipolar Depression, and to identify those biological markers that reflect the pathophysiological processes underlying these two disorders (De Almeida & Philips, 2013).

5. Evidence for differential diagnosis

5.1 Comparing unipolar and bipolar Depression

Carrying out a precise and accurate differential diagnosis between unipolar and bipolar Depression represents a great clinical challenge. The main reason for this concerns not only the higher prevalence of depressive symptoms compared to hypomanic symptoms in bipolar Depression, but also concerns the fact that a significant amount of manic symptoms remain below threshold in both unipolar and bipolar Depression (De Almeida & Phillips, 2014).

Hence, it is easy to understand that the consequences of an incorrect diagnosis could lead to severe problems. For example, if a depressed bipolar patient would be treated only with antidepressants, their effectiveness would be reduced because this

therapy should have been accompanied by mood stabilizers to have the desired effect (Goodwin, 2009; Yatham, Kennedy, Parikh, Schaffer, Beaulieu, Alda *et al.*, 2013). Furthermore, inadequate treatment could result in increased risk of suicide, an easier transition to mania, and an increase in health care costs (Hirschfeld, Lewis, & Vornik, 2003; Perlis, Ostacher, Goldberg, Miklowitz, Friedman, Calabrese *et al.*, 2010; Goodwin, 2012).

Along this line, an accurate screening of the two disorders from a cognitive point of view, would help to avoid an incorrect diagnosis which is of fundamental importance (Hirschfeld, 2014).

Biological markers are certainly one of the key issues in the management of patients with unipolar and bipolar Depression and many are common to both ailments. A difference in this sense can be found in serum BDNF levels, which are lower in bipolar patients and higher in unipolar patients and in control subjects (0.15 ± 0.08, 0.35 ± 0.08 and 0.38 ± 0.12, respectively, $p < 0.001$) (Fernandes, Gama, Kauer-Sant'Anna, Lobato, Belmonte-de-Abreu, & Kapczinski, 2009). The laboratory cut-off, in fact, equal to 0.26 pg/ml, is able to sustain the differential diagnosis of the two disorders with an accuracy equal to 88%. Because of this, BDNF could contribute as a predictive marker, as a marker of the presence of disease or as a surrogate marker (Fernandes, Molendijk, Köhler, Soares, Leite, Machado-Vieira *et al.*, 2015; Polyakova, Stuke, Schuemberg, Mueller, Schoenknecht, & Schroeter, 2015; Sagar & Pattanayak, 2017).

In recent years, the analyses of the neural networks involved in mood disorders, using the neuroimaging data of both structural and functional measures related to the formation of neuronal circuits involved in the processing and regulation of emotions has been very important (De Almeida & Phillips, 2014).

Thanks to structural magnetic resonance imaging irregularities in white matter integrity that characterize Bipolar Disorder with respect to Major Depression have been observed in the corpus callosum and the cingulum (Benedetti, Absinta, Rocca, Radaelli, Poletti, Bernasconi *et al.*, 2011; Cardoso de Almeida & Phillips, 2013; Matsuoka, Yasuno, Kishimoto, Yamamoto, Kiuchi, Kosaka *et al.*, 2017; Repple, Meinert, Grotegerd, Kugel, Redlich, Dohm *et al.*, 2017), and have been associated with alterations in gray matter volume of the prefrontal cortex and hippocampus (Matsuo, Harada, Fujita, Okamoto, Ota, Narita *et al.*, 2019; Niida, Yamagata, Matsuda, Niida, Uechi, Kito *et al.*, 2019). However, a recent study has shown that depressed bipolar

subjects have reduced gray matter volumes in the right hippocampus, in the parahippocampal, in the fusiform gyrus, in the amygdala, in the insula, in the rolandic and frontal operculum, and in the cerebellum (Vai, Parenti, Bollettini, Cara, Verga, Melloni *et al.*, 2020). Similar results have been reported by Liu and colleagues, who have shown that depressed unipolar patients have an increased ReHo in the right parahippocampal gyrus compared to the control subjects. In addition, the ReHo in the right hippocampus of depressed bipolar patients had a larger volume, while the ReHo in the right middle occipital gyrus appeared smaller. Finally, bipolar depressed patients displayed a reduction of ReHo in the right inferior temporal gyrus. This suggests that the latter could be considered as an important biological marker in the differential diagnosis of the two disorders (Liu, Li, Zhang, Liu, Sun, Yang *et al.*, 2020). Still, with regard to regional homogeneity, Liu and colleagues found that subjects with bipolar Depression, compared to unipolar depressed patients, had higher ReHo values in the right dorsal anterior insular, right middle frontal gyrus, right cerebellum posterior gyrus, and the left cerebellum anterior gyrus (Liu, Ma, Wu, Zhang, Zhou, Li *et al.*, 2013). Liang and colleagues, in contrast, emphasized how bipolar depressed patients displayed higher ReHo values in the thalamus than unipolar depressed patients (Liang, Zhou, Yang, Yang, Fang, Chen *et al.*, 2013).

Other studies, concerning structural measures of neuroimaging, have contributed to making differential diagnoses more effective, examining, and comparing healthy subjects, unipolar depressed and bipolar depressed patients. These studies, helped to discover that bipolar depressed patients had a reduction in fractional anisotropy (FA) in the right uncinate fasciculus (Versace, Almeida, Quevedo, Thompson, Terwilliger, Hassel *et al.*, 2010), an increase in periventricular and deep white matter hyperintensities (DWMH) (Silverstone, McPherson, Li, & Doyle 2003), and a volume reduction in the left habenula (Savitz, Nugent, Bogers, Roiser, Bain, Neumeister *et al.*, 2011). In addition, the anterior cingulate cortex appeared to be a biological marker useful for differential diagnosis: in the depressive phase of Bipolar Disorder, the level of glutamate was higher while in unipolar Depression the level dropped considerably (Yüksel & íngür, 2010).

Regarding the functional measures of neuroimaging, several studies examined the functionality of the neuronal circuits involved in emotion. Taylor Tavares and colleagues, for example, conducted research with unipolar, bipolar depressed patients and healthy control subjects, in order to analyze whether a reversed learning paradigm

could measure the ability to modify a behavior when reinforcement (positive or negative) was changed; unipolar depressed patients reversed response after negative reinforcement, unlike bipolar patients who maintained a normal level of neural activity, which appeared to be related to reduced ventrolateral and dorsomedial prefrontal cortical activity of the former. In addition, they displayed reduced activity in the VLPFC during reversal shifting which was associated with a reduction in the activity of the amygdala in the presence of positive reinforcement (Taylor Tavares, 2008). Another study, which employed an executive control model with emotional distractors, and which involved female subjects with bipolar Depression and unipolar Depression, reported that the latter displayed better developed dorsal anterior midcingulate cortical activity compared to the other subjects during the demanding 2-back condition of the model with neutral face distracters (Bertocci, Bebko, Mullin, Langenecker, Ladouceur, Almeida *et al.*, 2012).

Neuropsychological assessment plays a key role in the differential diagnosis between unipolar and bipolar Depression. A number of studies highlights the similarity of neuropsychological functioning that characterizes the two disorders (Sweeney *et al.*, 2000; Gruber, Rathgeber, Bräunig, & Gauggel *et al.*, 2007; Daniel, Montali, Gerra, Innamorati, Girardi, Pompili *et al.*, 2013). For example, research conducted by Liu and colleagues in a sample of healthy controls, depressed unipolar and bipolar patients showed that the latter two groups had similar impairments in psychomotor speed, working memory, visual memory, verbal fluency and switching of attention with respect to the healthy sample (Liu, Zhong, Wang, Liao, Lai, & Jia, 2018). The study conducted by Xu and colleagues showed analogous results. By comparing depressed bipolar I, bipolar II and unipolar patients, a fairly similar cognitive picture emerged regarding dysfunctions in processing speed, visual memory and cognitive functions, although bipolar I patients displayed greater deficits in verbal fluency and executive functions compared to other patients (Xu *et al.*, 2012). Consistent with these studies, others observed similar clinical and cognitive performances between the two disorders, especially with respect to processing speed (Daniel *et al.*, 2013) and verbal memory (Hermens, Naismith, Redoblado Hodge, Scott, & Hickie, 2010).

In fact, these conclusions are consistent with what has been explained in the previous paragraphs, in which we emphasized that the neuropsychological markers of the two disorders clearly overlap and, in some cases, they show the same profile.

In contrast, other studies, support the presence of differences in the type of neuropsychological deficits in unipolar and bipolar Depression. Taylor Tavares discovered that bipolar depressed people displayed more cognitive deficits in than individuals with unipolar Depression (Taylor Tavares, 2007). Similarly, the study of Hori et al. demonstrated that patients with bipolar Depression had greater deficits in verbal memory and executive functions than the patients with unipolar Depression (Hori, Matsuo, Teraishi, Sasayama, Kawamoto, Kinoshita *et al.*, 2012). Furthermore, psycho-motor retardation is a particularly evident factor in defining the difference between the two disorders: numerous studies have observed a more evident psycho-motor slowdown in bipolar as compared to unipolar Depression (Mitchell, Frankland, Hadzi-Pavlovic, Roberts, Corry, Wright *et al.*, 2011; Motovsky & Pecenak, 2013). Similarly, attention deficits appear much more marked in depressive Bipolar Disorder (Benazzi, 2006; Mitchell *et al.*, 2011; Gosek, Heitzman, Stefanowski, Antosik-Wójcińska, & Parnowski, 2019).

Borkowska and Rybakowski, on the other hand, analyzed the differences between the two disorders using tools designed to assess the functionality of the frontal lobe. Depressed bipolar patients displayed a higher level of cognitive dysfunction related to the activity of the frontal lobe (in particular, attention, verbal fluency, spatial planning, and abstract functioning) and had significantly reduced performance in non-verbal intelligence compared to unipolar depressed patients (Borkowska & Rybakowski, 2001). More recent studies (Galimberti *et al.*, 2020) demonstrated enhanced mnemonic impairment in subjects with unipolar Depression compared to bipolar Depression, with marked dysfunctions in executive functions being more evident.

So far, the nature of the neuropsychological differences between bipolar and unipolar depressed patients, are contradictory which leads to important difficulties in the differential diagnosis. However, what is known, is that subjects with bipolar Depression appear to exhibit greater cognitive impairment than subjects with unipolar Depression.

Consequently, the debate regarding the structure and function of the cognitive and neuropsychological profile between unipolar and bipolar Depression is still open. From a clinical point of view, however, the inclusion of cognitive and neuropsychological analyses will provide valid elements to make a more accurate

differential diagnosis between the two nosographic disorders, which up to now have been too often misdiagnosed (Galimberti *et al.*, 2020).

6. Psychometric tools for differential diagnosis

As discussed above, evidence collected so far is ambiguous and therefore hampers the use of cognitive dysfunction in the differential diagnosis using of unipolar and bipolar Depression. While various authors did not find significant differences between unipolar and bipolar depressed patients, others, observed quantitative and non-qualitative discrepancies which suggests that there is concordance in affirming that the cognitive dysfunctions involved in the two types of Depression are the same, but with a different severity of impairment. Indeed, quantitative differences common to both disorders lead to a lower performance in patients with bipolar Depression.

Based on the accumulating empirical evidence, but more importantly because of the paucity in neuropsychological tests that support a scrupulous differential diagnosis between the two disorders, we suggest the following: First we propose to conduct research on the calibration and validation of the psychometric tests presented in the next paragraphs, and define the thresholds differentiating unipolar from bipolar depressive cognitive dysfunction. These (domain specific) cut-off scores, then, will allow us to distinguish the cognitive deficits framed within a unipolar or bipolar Depression from a quantitative point of view.

A large review of the previous literature has helped us understand which tests detect quantitative differences between patients suffering from one or the other disorder. In addition, we suggest adding other psychometric tools to discriminate between the presence or absence of specific neuropsychological deficits. After the suggested calibration mentioned above, these tools should become an essential part of psychometric strategies in support of the differential diagnosis between unipolar and bipolar Depression.

6.1 Memory

Deficits in memory appear to be a neuropsychological dysfunction common to both unipolar and bipolar Depression but is more deficient in bipolar depressed patients (Murphy & Sahakian, 2001; Mansell, Colom, & Scott, 2005).

After a careful review of the literature, we have selected several psychometric tools useful for differential diagnosis.

A first important tool is the California Verbal Learning Test (CVLT), (Delis, Kramer, Kaplan & Ober, 1987). The task is simple: the experimenter reads a list of 16 words (list A), aloud and at intervals of one second, at the end of which the participant will have to repeat the words he remembers in any order. The 16 words, which are part of 4 large semantic clusters (tools, fruit, clothing, spices, and aromatic herbs), are not consecutive in the same category. Subsequently, list B is presented, this is a list of "interferences" that contains two categories of list A and two random categories, not shared by the latter. Neither list contains words common to both. The repetition of the words contained in list A is requested immediately (short delay) as well as after 20 minutes (long delay). The test ends with a recognition exercise, in which 44 words are presented to the subject that must be categorized by him/her as target words or distractors. The CVLT has proved to be highly discriminating not only for mnemonic deficits in general, but specifically for episodic memory, as well as for dysfunctions related to verbal learning, because the test collectively assesses the encoding, the recall and the recognition of the elements presented. Apart from measuring the number of elements that a subject can learn, it also stresses the strategies and techniques that the subject uses to learn new information.

Second, to analyze deficits related to visual-spatial memory the Corsi Test (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000) represents a useful tool. It consists of a wooden tablet on which 9 asymmetrical cubes are glued facing the side of the experimenter. The experimenter first touches the cubes with one finger, forming a standard sequence of increasing length which the subject will have to reproduce later based on what he/she remembers of the path. The test is useful especially for depressed bipolar patients, who have more compromised visual-spatial abilities than unipolar depressed patients.

Regarding deficits involving working memory, the Mini Mental State Examination (MMSE) is a very useful test (Folstein, Folstein, & McHugh, 1975). The MMSE is composed of 30 questions which, in addition to verifying the dysfunctions in working memory, also analyze problems related to space-time orientation, attention, language and constructive praxis. The MMSE represents an excellent tool for differential diagnosis because once calibrated for unipolar and bipolar Depression, it would offer a wider range of cognitive areas to be evaluated, allowing to assess the differences between the two Depressions more accurately.

Finally, the Rey Auditory Verbal Learning Test (RAVLT) is an excellent tool to discriminate mnemonic disorders, especially those related to verbal memory (Rey, 1958; Taylor, 1959). The RAVLT consists of 7 tests. In the first, the examiner reads a list of 15 words that the subject must immediately repeat, and this is repeated 4 times. In the sixth, the administrator distracts the subject with visuo-spatial tasks for 15 minutes, to then make him repeat the words read previously. If the subject cannot remember them all, another 45 words will be presented to him (30 distractors together with 15 of the first test) and he/she will be asked to list them again. The test is very useful not only because it discriminates deficits in verbal memory, but also because it analyzes verbal learning, which is strongly compromised in subjects with bipolar Depression and, therefore, useful in a differential diagnosis.

6.2 Executive functions

Executive functions, like memory, seem to be particularly deficient in bipolar Depression (Hori, Matsuo, Teraishi, Sasayama, Kawamoto, Kinoshita *et al.*, 2012).

The Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000) is a sophisticated test that we suggest being included in the neuropsychological evaluation of patients with bipolar and unipolar Depression. The test battery is divided into 6 cognitive and behavioral tasks: conceptualization of similarities, phonemic lexical fluency, motor programming, response to conflicting instructions, task on inhibitory control (go-no-go), and prehension behavior. The FAB is recommended because it discriminates the overall functioning of all executive functions, thanks to its 6 cognitive tasks.

Next, an important battery to be included to test executive function, is the Behavioral Assessment of the Dysexecutive Syndrome (BADS) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). The BADS is an excellent tool because it is composed of various tests that globally evaluate many aspects of executive functions, using an ecological approach that reproduces contexts and problems similar to those encountered in everyday life. The 6 cognitive tasks to be performed include: test of the rule change of cards; action planning test; key search test; test of cognitive estimates; zoo map test; modified test of the 6 elements.

Finally, an important practical test to be included for the evaluation of the aforementioned functions, is the Tower of London Test (Allamanno, Della Sala, Laiacona, Pasetti, & Spinnler, 1987). It consists of a tablet with three vertical rods

positioned in ascending order, on which 3 balls of different colors are inserted in a specific order. The rods are long enough to accommodate one, two or three balls. The subject will have to move the balls, one at a time, in order to reach an arrangement previously established by the administrator. This test helps to understand the subjects' abilities regarding strategic decision-making processes, and the planning of effective solutions as well as the capacity to inhibit impulsiveness as it has the objective of solving a specific task while being constraint by specific rules

6.3 Attention

We carefully reviewed the literature, and attention has emerged to be markedly involved in both unipolar and bipolar Depression. To test attention and attention-related functions, it is essential to carefully choose specific neuropsychological tests that are able to discriminate the presence or absence of any attention related deficits.

To this end, we propose the following two tests for the assessment of attention in bipolar and unipolar depressed patients.

The first is the Trail Making Test A-B (Reitan, 1958), which can be performed on paper or on computer. In version A of the test, the 25 stimuli are numbers that the subject must connect with a line in an increasing manner, in the shortest possible time. Version B, on the other hand, is characterized by stimuli which are both numbers and letters; in this case the subject, starting from number 1, alternates his ability to connect, in an increasing way, a number and a letter. This test not only discriminates deficits related to attention, but it is also sensitive to the detection of dysfunctions related to spatial planning skills. Several studies have used the Trail Making Test to make a differential diagnosis. For example, Xu and colleagues highlighted that bipolar depressed patients had poorer attention and visual-motor performance than unipolar depressed patients (Xu, Lin, Rao, Dang, Ouyang, Guo *et al.*, 2012). Borkowska and Rybakowski, on the other hand, noticed a tendency in depressed bipolar patients to obtain poorer results on theTMT-B than unipolar patients (Borkowska & Rybakowski, 2001).

The second test we propose is the Stroop Color Word Interference Test (Golden, 1978). It is a test in which the subject must name the ink color with which the names of different contrasting colors are written. To do this, it is necessary to inhibit the automatic tendency to read the color name rather than focusing on the color of the ink itself. Borkowska and Rybakowski used the Stroop test to analyze

differences between the two types of depression regarding attention, and observed that here also, the scores of depressed bipolar patients were lower than those of unipolar patients (Borkowska & Rybakowski, 2001).

6.4 Abstract reasoning

Abstract reasoning, which represents one of the most important cognitive abilities in carrying out activities related to daily life, is compromised in both unipolar and bipolar Depression.

One of the most valid and reliable tests that assesses this neuropsychological function is the Wisconsin Card Sorting Test (WCST) (Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The WCST uses a deck of cards called "response" cards which must be combined to the "stimulus" cards, according to an entirely personal criterion that changes from subject to subject. During the test, the administrator is allowed to give (minimal) feedback regarding the strategies used by the patient, thanks to the feedback, will identify the most correct classification criteria. Between the criteria for one type of classification, the experimenter changes to another criterion without informing the subject. The subject's task now is to develop a new classification strategy. The WCST is an excellent test not only because it is able to discriminate deficits related to abstract reasoning, but also because it specifically examines the frontal functions of the subject, is more compromised in bipolar depressed patients (Borkowska & Rybakowski, 2001). In addition, the WCST helps to evaluate the degree of flexibility of patients towards problem solving and the strategies used in everyday life to cope with difficulties. From this point of view, it would be important to analyze the problem solving skills of unipolar and bipolar depressed people, and include the WCST to help the differential diagnosis of the two disorders: Borkowska and Rybakowski indicated worse performance on the WCST in depressed bipolar patients as compared to unipolar depressed patients (Borkowska & Rybakowski, 2001).

6.5 Verbal fluency and processing speed

Finally, to evaluate dysfunctions in verbal fluidity and processing speed, the Wechsler Adult Intelligence Scale (WAIS-IV) could be used. The WAIS is made up of 15 subtests, divided into 4 dimensions: visual-perceptual reasoning, working memory, verbal comprehension, and processing speed. For our purpose, the last two dimensions are those that interest us in particular.

Verbal comprehension is characterized by the Subtests Similarities, Vocabulary, Information and Understanding. The index of this dimension predicts the results regarding crystallized intelligence (connected to the knowledge acquired in the educational and the school context) and concerns contextualized learning within the social environment.

Processing speed, on the other hand, is characterized by the subtests Search for symbols, Cipher and Cancellation, whose index mainly measures the speed with which the visual stimuli and the manual motive responses are performed by the subject.

This test offers important advantages because it helps not only to assess the dysfunctions related to verbal fluency and speed of processing, both severely compromised in the two types of Depression, but also because the test helps to give a general judgment concerning the patient's intellectual functioning and allows for the analyses of other possible deficits related to cognitive and intellectual abilities. In the end the results from all the different domains will provide us with the necessary insight into the patients strengths and needs that will lead to the development and planning of individually tailored interventions for the recovery or enhancement of the patient’s skills.

7. Conclusion

Depression is a complex disorder causing long-term disability, when not treated adequately. In this review, evidence related to the difference between unipolar and bipolar Depression was collected and presented, with a specific focus on cognitive dysfunction. Biological markers can help to reduce the risk of misdiagnosis, but neuropsychological markers can be assessed more quickly, more easily and with less invasive methodology. To this end, additional research on thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on the psychometric tools proposed in this review.

As stated by Cammisuli and Pruneti (2018), the psychopathology of cognition is now focused on how cognitive dysfunction is related to the origin and the development of psychiatric conditions, as cognitive processes are intrinsically linked to emotional and relational functioning. The scope of this review was to contribute to the field focusing on the clinical need of a precise differential diagnosis that when put in a translational framework, should combine an integration of research and clinical

practice allowing for a better understanding of mental health and for evidence-based clinical practice.

Including biomarkers is not going to give us a definite answer, but may help to identify risk, not the cause of the cognitive dysfunction. Furthermore, given the extreme complexity of the problem, most biological risk factors will contribute a small amount of risk but together with other risk factors (pertaining to other dimensions) they may help to explain and predict a substantial part of present and future cognitive disability. By using a combination of neurocognitive and biological markers, we may be able to redefine how to think about cognitive dysfunction in unipolar and bipolar Depression.

Patients diagnosed with Depression often develop clinically meaningful deficits in attention, information processing speed, executive functions such as working memory, and emotional and psychosocial functioning. These deficits can have a detrimental impact on their quality of life. Failure to comprehensively assess and closely monitor the specific cognitive signs and symptoms of unipolar and bipolar depressed patients may lead to confusion or misattribution surrounding their day to day struggles. Therefore, early detection combining biomarkers with appropriate neuropsychological indicators and cutoffs for cognitive dysfunction may help us to intervene in a timely and appropriate manner using the right treatment for each individual patient. To that end, this review contributes to an empirically founded use of psychodiagnostic tools in a field yet to be fully investigated.

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Chapter 2

New psychometric strategies for the evaluation of affective, cognitive, and psychosocial functioning in unipolar versus bipolar depression: impact of drug treatment

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Keywords: Unipolar Depression; Bipolar Depression; antidepressants; second-generation antipsychotic; mood stabilizers; cognitive functioning; affective functioning; psychosocial functioning.

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Abstract

Background: Different studies have been conducted to understand how patients with unipolar and bipolar depression differ in terms of cognitive and affective symptoms as well as in psychosocial function. Furthermore, the impact of antidepressants, second-generation antipsychotics, and mood stabilizers on these dimensions needs to be characterized, as well as the best psychometric approach to measure changes after pharmacological treatment.

Objectives: to analyze the impact of psychotropic drugs on cognitive, affective, and psychosocial functioning in MDD and BD patients; to test the sensitivity of psychometric tools for measuring those changes; to understand how psychosocial abilities are associated with affective and cognitive dimensions in patients with MDD and BD.

Methods: 22 patients with MDD and 21 patients with BD in the depressive phase were recruited. Several psychometric tests were administered to assess affective, cognitive, and psychosocial symptoms before and after 12 weeks of drug treatment (T0 and T1) with different psychotropic drugs including second-generation antidepressants, second-generation antipsychotics and mood stabilizers (lamotrigine).

Results: MDD patients showed significant improvement in MoCA, Delayed Recall of Rey's 15 Words and HDRS, while a significant worsening was detected on Digit Span Backwards and on FAST scores. Instead, patients with BD showed significant improvements in the MoCA as well as on the BDI-II. A positive correlation was detected in both groups between FAST HDRS and BDI-II scores.

Conclusions: Our results demonstrate that drug treatment with psychotropic drugs can improve cognitive and affective symptoms, but not all psychometric tools are equally sensitive to detect those changes. Moreover, we found that affective and cognitive dimensions can be considered as different psychopathological dimensions both in unipolar and bipolar depression.

1. INTRODUCTION

Cognitive dysfunction is a clinically relevant dimension of affective disorders, such as Major Depressive Disorder (MDD) and Bipolar Disorder (BD) [1–3]. Cognitive symptoms are constitutive symptoms, to the extent that the DSM-5 considers difficulty in thinking, concentrating, and remembering as relevant criteria for diagnosis [4,5]. Several meta-analyses have shown that cognitive symptoms occur both in the acute

and in the remission phase of affective disorders with a prevalence of 39-44% and the persistence of residual cognitive symptoms correlates with an increased risk of recurrence [6,7]. Interestingly, cognitive dysfunction does not necessarily correlate with the severity of affective symptoms and their overall duration [8,9]. Indeed, approximately 40% to 60% of euthymic patients with BD and 70% of patients with MDD reported cognitive dysfunction that persisted even during remission of affective symptoms [5,10,11]. As a consequence, affective and cognitive symptoms seem to represent two distinct psychopathological dimensions [12,13]. Focusing on MDD and BD patients during depressive episodes, current evidence suggests that the same cognitive functions are impaired (attention, speed of information processing, working memory, verbal fluency, sustained attention, and more in general executive functions), but it is not clear how the two groups differ in terms of overall cognitive performance and across single domains [14,15]. According to several studies, there is an increased severity of cognitive dysfunction in bipolar compared to unipolar patients, especially in the case of the BP-I subtype [16–18]. A recent study found that patients with BD had widespread deficits when compared to MDD patients, mainly on sustained attention and inhibitory control [19]. Cognitive deficits are also associated with impaired psychosocial functioning, compromising the individual's coping abilities, academic and occupational achievement, interpersonal relationships, independent living, and community participation, which, in turn, exerts a large impact on functional recovery [20,21]. Despite the great clinical relevance of cognitive dysfunction in affective disorders, the cognitive profiles of unipolar versus bipolar depression still need further characterization. It is also still unclear what the impact of cognitive symptoms is on overall psychosocial functioning both in MDD and BD patients. Moreover, the effect of antidepressants, second-generation antipsychotics, and mood stabilizers on cognitive deficits in these patients is not yet clearly understood. A recent 12 week prospective observational study conducted in MDD patients with a recent history of partial response to antidepressants indicated that Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) improve cognitive symptoms independently from their efficacy on affective symptoms. Importantly, cognitive symptoms were also associated with an incomplete response to antidepressants [12,22]. The presence of residual cognitive symptoms also increases the risk of relapse [23]. The evidence on the efficacy of mood stabilizers on cognitive functions in BD are still heterogenous [24,25]. Moreover, these studies are

preliminary and will need further validation by multiple and more advanced psychometric tools in larger samples of patients. Therefore, it is clinically crucial to examine the effects of these different psychotropic drugs on cognitive deficits, using the MoCA and MMSE. Moreover, the differential diagnosis between Type-I BD and MDD (both with a depressive episode) might be improved by analyzing the impact of antidepressants and/or antipsychotics and mood stabilizers such as lamotrigine on cognitive symptoms. Along this line of reasoning, here we adopted the same psychometric approach in MDD and Type-I BD patients and analyzed: 1) the different impact of drug treatment (i.e., antidepressants, antipsychotics, and mood stabilizers) on affective, cognitive, and psychosocial functioning in Type-I BD and MDD both with a depressive episode; 2) the sensitivity of psychometric tools to assess affective and cognitive symptoms of MDD and Type-I BD; 3) How psychosocial functioning correlates with affective and cognitive dimensions in MDD and BD.

2. MATERIALS AND METHODS

2.1 Study sample

All MDD and Type-I BD patients recruited in the study were admitted and hospitalized at Villa dei Gerani Psychiatry Clinic, Catania, Italy. Forty-three subjects were preliminarily screened during the twelve weeks of the study. All patients (mean age 51.3 ± 9.4 SD years; 26 women and 17 men; mean education 10.4 ± 3.74 SD) met the inclusion/exclusion criteria and were then recruited for their inclusion in the different cohorts of the study. The DSM-5 [26] was used for clinical diagnosis of depressive episodes both in MDD and BD. All recruited MDD patients (N=22) were recurrent depressive patients with an ongoing depressive episode at the beginning of the study and a recent history – in the last 4 weeks – of partial response to a previous treatment with an antidepressant drug. All 22 partial responder MDD patients (mean age 54.14± 8.7 SD years) were then switched to second-generation antidepressants (SSRI or SNRI Group 1 cohort n=14) or second-generation antidepressants (SSRI or SNRI) + low dose of a second-generation antipsychotics (Group 2 cohort n=8) for 12 weeks of treatment (Table 1). The following drugs were used: escitalopram (10 mg/day), paroxetine (20 mg/day), sertraline (100 mg/day), citalopram (40 mg/day); duloxetine (60 mg/day), venlafaxine (150-225 mg/day); risperidone (2-3 mg/day), olanzapine (2,5-5 mg/day), aripiprazole (2,5-5 mg/day). All 21 Bipolar I Disorder patients with a depressive episode (mean age 48.33± 9,35 SD years) were all switched to the same

treatment: second-generation antipsychotics + lamotrigine for the 12 week treatment period (Table 1). The following drugs were used: Olanzapine (20 mg/day), Aripiprazole (100 mg/day); lamotrigine (100-200 mg/day).

Table 1. Sociodemographic and clinical characteristics of MDD and BD patients.

	Total n = 43,	**MDD cohort, n = 22,**	**BD cohort, n = 21.**
Gender n (%) Male Female	 17 (39,5) 26 (60,5)	 8 (36,4) 14 (63,6)	 9 (42,9) 12 (57,1)
Age Mean (SD)	51,3 (9,37)	54,14 (8,67)	48,33 (9,35)
Education Mean (SD)	10,4 (3,74)	9, 82 (4,17)	11 (3,22)
Pharmacological drugs prescribed during the 12 weeks of the study,	Escitalopram, Paroxetine, Sertraline, Citalopram, Duloxetine, Venlafaxine, Risperidone, Olanzapine, Aripiprazole, Lamotrigine.	*Group 1* Citatopram, Escitalopram, Paroxetine, Duloxetine, Venlafaxine. *Group 2* Paroxetine, Sertraline, Risperidone, Olanzapine, Aripiprazole.	Olanzapine, Aripiprazole, Lamotrigine.

Patients were recruited according to the following inclusion criteria: 1) A diagnosis of acute episodes of recurrent (1-4 episodes) MDD according to DSM-5; or a diagnosis

of Bipolar I Disorder according to DSM-5 with a current depressive episode; 3) A recent history in MDD patients (in the last 4 weeks) of partial response to a previous treatment with an antidepressant drug or a recent history (in the last 4 weeks) of partial response to antidepressant in Type-I BD patients; 5) Aged at least 18 years (without upper limit of age); 6) Not participating in another study simultaneously; 7) Having signed an informed consent according to the Declaration of Helsinki principles; 8) Accepting to give a personal reference contact. According to the exclusion criteria, patients were not included in these cohorts if they fulfilled at least one of the following criteria: 1) their ability to consent was impaired or questionable (e.g., patients suffering from psychotic depression); 2) they had to stop an ongoing antidepressant that was effective for their depression; 3) they were already treated with another antidepressant that they wished to continue in addition to the new prescribed antidepressants drug. Contra-indication and precautionary measures mentioned in the Summary of Product Characteristics were respected. Physicians had to refer to local and/or national available prescribing guidelines for MDD and Type-I BD. All recruited MDD and Type-I BD patients signed an informed consent prepared according to the Declaration of Helsinki principles.

2.2 Study procedures and psychometric assessment

Patients who met the inclusion criteria were subdivided in two different groups according to their diagnosis (MDD or Type-I BD with a current depressive episode). The MDD cohort was then divided into two subgroups based on their treatment: the first subgroup treated with antidepressants (SSRI or SNRI) and the second one with SSRI + second-generation antipsychotics. Type-I BD patients were all treated with lamotrigine in combination with antipsychotics. MDD and Type-I BD patients were monitored for 12 weeks. They underwent neuropsychological assessment, carried out before the switch of the pharmacological treatment (T0) and after 12 weeks (T1).

2.3 Neuropsychological Assessment

MDD and Type-I BD patients were assessed with multiple psychometric tools, related to the cognitive, affective, and psychosocial dimensions, both before (T0) and after 12 weeks of treatment (T1). The following psychometric tools were used: 1) For the assessment of affective changes: the Hamilton Depression Rating Scale (HDRS) [27,28] and the Beck Depression Inventory (BDI-II) [29]; 2) For the assessment of

psychosocial skills: The Functioning Assessment Short Test (FAST) was considered the primary outcome at the study endpoint and identifies predictors for specific functional domains, such as: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. For this study, we only analyzed the score of overall functioning and the score of four specific FAST scale domains. It is important to note that the higher the score, the lower the psychosocial functioning is. 3) For the assessment of global cognitive functions: Mini Mental State Examination (MMSE) [30], which evaluates different areas of cognitive domains, such as memory, orientation, and language, and the Montreal Cognitive Assessment (MoCA) [31], is a shorter tool that instead evaluates a large range of cognitive abilities such as executive functions, attention and visuospatial functions. Furthermore, the MoCA is more sensitive than the MMSE in detecting mild cognitive impairment (MCI) [32,33]; 4) For the assessment of specific cognitive functions: Rey's 15 Words Test [34], which analyzes abilities related to verbal memory, quantifying immediate (Rey_I) and delayed recall skills (Rey_D), Verbal Memory Span (Digit Span) was used to measure the short-term memory of participants.

2.4 Statistical analysis

Changes in affective (HDRS, BDI-II), cognitive (MMSE, MoCA, Rey, Digit Span), and psychosocial (FAST) functioning into and between MDD and Type-I BD groups and relationship between variables, were analyzed at the end of the observation study (12 weeks) using two sample t-test and t-test for repeated measures.

In addition, the two-sample t-test was used to analyze changes in psychometric instrument scores, combining patients by both diagnosis and pharmacological treatment.

T-test for repeated measure was used to assess difference in psychometric tools scores between T0 and T1 in each sample group.

Pearson Correlation coefficient was used to analyze the correlation between psychosocial functioning on FAST score and psychometric tools useful to assess cognitive and affective symptoms.

The level of statistical significance was defined as $p<0.05$.

All analyses were performed by software SYSTAT 12.0.

3. RESULTS

Results showed that the overall sample of MDD patients presents a statistically significant improvement on the MoCa when comparing the scores collected at T0 with those at T1 (Table 2). However, the same outcome was not observed for the MMSE (MoCA from 20,18 to 22, $p < 0,01$; MMSE from 23,49 to 24,48, $p < 0,30$), which assesses global cognitive functioning such as memory, orientation, and language, but not executive function evaluated by the MoCA. Furthermore, a significant improvement was observed for the delayed Rey's 15 Word (Rey_D, from 6,19 to 7,38, $p < 0,05$), but not for immediate recall (Rey_I, from 31,03 to 34,05, $p < 0,12$). Moreover, we found a significant worsening of working memory as assessed by the Digit Span Backwards (Span B, from 3,45 to 2,95, $p < 0,02$). Focusing on affective symptoms, HDRS scores significantly improvement at T1 (from 22,5 to 18, 95, $p < 0,03$), whereas BDI-II did not (from 32,27 to 28,45, $p < 0,12$). With respect to psychosocial functioning in MDD, we found that, after twelve weeks of treatment, there was a significant worsening of the FAST scores (from 29,05 to 35,55, $p < 0,05$). However, this significant negative change was found in the occupational subdomain only (from 5,55 to 9,45, $p < 0,01$). Indeed, this reflects the fact that patients were hospitalized and therefore they were not able to keep their job activities. Interestingly, patients taking antidepressants in combination with antipsychotics showed a greater improvement on Rey_D and MMSE scores when compared to MDD patients taking antidepressants only. who, instead, showed a major improvement in HDRS and MoCA scores. Next, we analyzed cognitive, affective, and psychosocial functioning in Type-I BD patients with a depressive episode. Type-I BD patients showed a significant improvement in MoCA (from 21,38 to 23,52, $p < 0,001$) after 12 weeks of pharmacological treatment. However, BDI-II (from 22,14 to 15,48, $p < 0,10$) and HDRS did not significantly improve (from 19,38 to 15,62, $p < 0,11$). Moreover, delayed Rey's 15 Words Test (Rey_D, from 5,73 to 6,85, $p < 0,17$), and immediate recall (Rey_I, from 31,45 to 31,55, $p < 0,96$) did not improve. Regarding psychosocial functioning, and we found that, after twelve weeks of treatment, FAST scores did not change (from 24,05 to 25,62, $p < 0,75$). Furthermore, we analyzed the correlations among FAST and other psychometric tools (Table 3). Considering the sample as a whole, a positive relationship between FAST - considered in all its subdomains - and HDRS was observed (Pearson $r = 0,48$; $p < 0,05$) and BDI-II ($r = 0,67$; $p < 0,05$). In contrast, the correlations between the FAST and other cognitive tools showed a negative correlation with MMSE ($r = - 0,36$; $p < 0,05$) and the Forward Digit Span (r

= - 0,35; p < 0,05). In particular, the subdomains of autonomy (r = - 0,29; p < 0,05), financial (r = - 0,31; p < 0,05), and interpersonal (r = - 0,34; p < 0,05) negatively correlated with MMSE, whereas occupational (r = - 0,41; p < 0,05) and cognitive subdomains (r = - 0,46; p < 0,05) negatively correlated with the Forward Digit Span.

Table 2. Comparison between baseline and 12 weeks of treatment using psychometric tools

	MDD cohort, n=22 Mean			**BD cohort, n=21 Mean**		
	Baseline	**12 weeks**	***t* (*p*)**	**Baseline**	**12 weeks**	***t* (*p*)**
HDRS	22.50	18.95	2.29 **(0.03)**	19.38	15.62	1.66 (0.11)
BDI-II	32.27	28.45	1.62 (0.12)	22.14	15.48	1.94 (0.07)
MMSE	23.49	24.48	- 1.05 (0.30)	25.13	25.75	- 0.75 (0.46)
MoCA	20.18	22	- 2.97 **(0.01)**	21.38	23.52	- 3.95 **(0.00)**
Immediate Rey test	31.03	34.05	- 1.64 (0.12)	31.42	31.55	- 0.06 (0.96)
Delayed Rey test	6.19	7.38	- 2.09 **(0.05)**	5.73	6.85	- 1.44 (0.17)
FAST total	29.05	35.55	- 1.99 **(0.05)**	24.05	25.62	- 0.35 (0.73)
FAST		5.27	0.78	3.00	3.86	

Autonomy	4.82		(0.44)			-0.92 (0.37)
Occupational	5.55	9.45	-3.00 **(0.01)**	3.67	4.57	-0.68 (0.51)
Cognitive	6.86	7.55	-0.75 (0.46)	5.86	5.62	0.27 (0.79)
Financial	1.50	1.82	-0.70 (0.49)	2.38	2.27	-0.63 (0.54)
Interpersonal	6.59	7.55	-0.77 (0.45)	5.86	5.57	0.19 (0.85)
Leisure	3.68	3.91	-0.58 (0.57)	3.48	3.43	0.09 (0.93)

* In bold: significant difference between groups. Significance considered at p <.05.

Abbreviations: HDRS= Hamilton Psychiatric Rating scale for Depression; BDI-II= Beck Depression Inventory; MMSE= Mini Mental State Examination; MoCA= Montreal Cognitive Assessment; FAST = Functional Assessment Short Test; t= Two-sample t-test.

Table 3. (n=43) Pearson correlations between FAST and other psychometric tools

Delta:	**MMSE**	**MoCA**	**Rey_I**	**Rey_D**	**HDRS**	**BDI-II**
FAST (total)	-0,36 *	-0,28	-0,18	-0,22	0,48 *	0,67 *
Autonomy	-0,29	-0,22	-0,03	-0,23	0,44 *	0,41 *
Occupational	-0,24	0,00	-0,12	-0,15	0,33 *	0,52 *
Cognitiv	-	-	-	-	0,40	0,61

e	0,27	0,30	0,14	0,15	*	*
Financial	-0,31*	-0,23	-0,29	-0,28	0,41*	0,55*
Interpersonal	-0,34*	-0,40*	-0,19	-0,11	0,29	0,47*
Leisure	0,02	-0,40	-0,11	-0,14	0,37*	0,35

* p<.05 se r > .29

4. DISCUSSION

Unipolar and bipolar depression are multifactorial mental illnesses characterized by affective, cognitive, and psychosocial symptoms. Cognitive deficits represent a key dimension of depression which strongly affect psychosocial functioning [35,36]. In the present study, we adopted the same psychometric strategy both in unipolar and bipolar depressive patients to analyze the different impact of psychotropic drug treatment (antidepressants, antipsychotics, and mood stabilizers (lamotrigine)) on affective, cognitive, and psychosocial functioning. Moreover, we analyzed the correlation between affective and cognitive symptoms and psychosocial functioning in both groups of depressive patients.

Significant differences were detected after pharmacological treatment when data collected at T0 and T1 were compared in MDD and Type-I BD (Table 2). However, psychometric tools demonstrated a different sensitivity in assessing the effects of drug treatment.

In particular, despite both MoCA and MMSE are instruments to assess global cognitive functioning, a statistically significant improvement was observed only with respect to the MoCA both in MDD and Type-I BD patients. In contrast, no differences were observed in MMSE scores from T0 to T1. Therefore, the MoCA seems more sensitive in detecting improvements in global cognitive functioning in relation to pharmacological treatment, probably because, in addition to the domains assessed by the MMSE itself, it also evaluates executive functions. Moreover, considering the structure of the MoCA, this psychometric tool might be more sensitive in evaluating memory, as confirmed by the results of the Rey results, which showed an improvement in delayed recall after 12 weeks of treatment in all MDD patients. Those findings

confirm those in the literature, where the MoCA has demonstrated cases, its accuracy and major sensitivity in many when compared to the MMSE, especially when prodromal and slight clinical changes are considered [32,37–39]. Therefore, when assessing the effectiveness of pharmacological treatment, multiple tools for the evaluation of global cognitive functioning should be used to better evaluate the impact of psychotropic drugs on global cognitive function. This approach is further sustained by the uneven cognitive profile observed in the MDD sample, as demonstrated by the significant worsening of the Backwards Digit Span. This could be due to attention difficulties, given that memory had improved. Only a psychometric battery composed of different types of tests will be able to detect those complex and independent variations of cognitive domains.

Focusing on the affective symptoms, the HDRS showed significant better scores at T1, but the same result was not using the BDI-II. HDRS has already proved its capacity to identify patients with MDD and to discriminate them from other groups of patients, like bipolar patients [40,41]. On the other hand, the BDI-II has been criticized for self-report bias and underreporting in unipolar depressed patients [42]. This evidence leads us to hypothesize that clinician-administered tests and interviews, such as the HDRS, are more sensitive in measuring improvement in affective symptoms in MDD patients when compared to self-report tools, such as the BDI-II.

MDD patients showed a significant worsening in psychosocial functioning after treatment. This result, which could seem counterintuitive, can be explained by analyzing the different subdomains of the FAST: the occupational area was the only one negatively affected after treatment, probably because the patients were hospitalized during the entire twelve weeks of the study, with a clear impact on their professional autonomy and functioning.

Focusing on the different drug treatments in the two subgroups of MDD, a very interesting finding is that those who were treated with antidepressants showed greater improvement in HDRS and MoCA. A possible explanation for this result is that MDD patients who did not receive add-on antipsychotic treatment, suffered from a less severe clinical phenotype of depressive episodes.

Antipsychotics treatment, on the other hand, was prescribed to more severe cases, known to be more difficult to treat. In the latter subgroup of MDD patients, where antipsychotic drugs were used, we found an important improvement in global

cognitive function, as assessed by the MMSE and Delayed Recall of 15 Rey's words scores when compared to subgroup with antidepressants only.

The limited changes observed using the MoCA could be explained again by being more complete. In contrast to the MoCA, the MMSE did not detect a change given its additional subdomains focused, for instance, on executive functions known to be more impaired in severe MDD cases .Summarizing, patients treated with antidepressants and antipsychotics improved in the domains assessed by MMSE only, while these improvements were not detected with the MoCA.

Regarding Type-I BD patients, the results had shown that the MoCA tool was more sensitive than MMSE to assess cognitive changes after drug treatment. To assess the improvement of affective symptoms, indeed, the BDI-II has proven to be more sensitive than HDRS. This finding has been confirmed by different studies, which showed that BDI-II is a psychometric tool that is useful for measuring self-reported depression in patients with Bipolar I disorder [43], while HDRS may be less indicated to recognize bipolar depression due to the different presentation of affective symptoms when compared to MDD [44]. Moreover, bipolar depressive patients show a better insight of the disease, so they can be diagnosed effectively even with self-report psychometric tools, like the BDI-II [45]. Taking into account those and previous considerations, we hypothesize that the appropriate use of BDI-II and HDRS in the differential diagnosis distinguishing depressive symptoms in Bipolar Disorder and Major Depressive Disorder patients is still difficult and that larger and long-term observational studies are needed to validate this hypothesis.

Focusing on the impact of drug treatment with the addition of lamotrigine in Type-I BD patients, we hypothesize that the assessed improvement in cognitive function after 12 weeks of treatment is due to the efficacy of this drug on this particular clinical dimension. Our data are in agreement with recent evidence; for instance, Dias et al. (2012) demonstrated that lamotrigine was the least neurotoxic in tests of memory and executive functions, compared to valproate, carbamazepine, and topiramate [24]. In addition, other studies have found that lamotrigine improves cognitive functions, in particular executive functions and working memory [25]. In summary, treatment with lamotrigine as add-on therapy in BD patients has been associated with improved cognitive functioning, reduced neurocognitive side effects, and alleviated clinical symptoms.

No significant changes were recorded in the FAST, so the pharmacological treatment did not seem to affect psychosocial functioning. This finding might be related to the euthymic phases experienced by bipolar patients, which positively affect their perception of overall social adjustment.

When psychosocial functioning was analyzed in the whole sample using the overall FAST scores, a downward trend (worsening) was observed. A positive relationship was observed between the FAST - considered in all its subdomains - and the HDRS and BDI-II, whereas a negative correlation was observed with the MMSE and Forward Digit Span. Therefore, we can infer that the improvement in affective symptoms is linked to the improvement of functional skills, but not to improvement in cognitive functioning. Our study, in line with the literature, confirms that affective and cognitive domains are different dimensions and seem to follow independent paths; therefore, both of them must be appropriately and independently evaluated to assess the efficacy of drug treatment [12,13].

5. CONCLUSION

Depression is a condition affecting millions of people and causes long-term disability. Our data suggest that drug treatment can improve cognitive and affective symptoms, while psychosocial functioning should be addressed by other types of interventions, like behavioral procedures and psychoeducational programs. Moreover, affective and cognitive symptoms seem to be not associated with each other. Different and specific psychometric tools should be used in MDD and Type-I BD with a depressive episode as their sensitivity is not the same for the two psychiatric conditions. In this way, differentiating the approach according to each specific condition, we will be able to make the differential diagnosis more efficient and evaluate the effectiveness of interventional plans more appropriately. With the combination of adequate assessment and treatment, therefore, the quality of life of patients can be improved more successfully.

LIST OF ABBREVIATIONSS

MDD = Major Depression Disorder

BD = Bipolar Disorder

SSRIs = Selective Serotonin Reuptake Inhibitors

SNRIs = Serotonin and Noradrenaline Reuptake Inhibitors

HDRS = Hamilton Depression Rating Scale

BDI-II = Beck Depression Inventory

FAST = Functioning Assessment Short Test

MMSE = Mini Mental State Examination

MoCA = Montreal Cognitive Assessment

REY I = Rey's 15 Words Test – Immediate recall

REY D = Rey's 15 Words Test – Delayed recall

Digit Span = Verbal Memory Span

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethical committee of the coordinating center 1) ASP3 Catania-Villa dei Gerani Clinic (July 24 2012). The study met the ethical administrative Italian legislation in force when the study administrative process started (03.06.2012) according to CM 6 02.09.2002, GU 214 12.09.2002, and D 29.03.2008 of the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) and GU 76 31.03.2008, Art 10 (Procedures for Observational Studies). The study design was a prospective, observational (non-interventional), multicenter cohort study conducted in two different clinical centers in Sicily (Italy). The study complied with the definition of "observational" (i.e., "non-interventional") study provided in Article 2(c) of Directive 2001/20/EC, meaning that the investigator who carries out the study does not interfere with the physician's decision regarding which drug is clinically pertinent to be prescribed to each individual patient. Therefore, the prescription of medication solely resulted from an independent clinical evaluation, according to the physician's clinical judgment, and based on each patient's clinical profile. Moreover, the decision to include a patient in the study, following his/her agreement, was taken independently of the clinical decision to prescribe medications. Finally, the study did not affect the medical practice of the participating physicians and did not trigger additional medical visits.

HUMAN AND ANIMAL RIGHTS

Research Involving Humans

All clinical investigations should be conducted according to the Declaration of Helsinki principles.

AVAILABILITY OF DATAS AND MATERIALS

The data supporting the findings of the article are available in the medical records of ASP3 Catania-Villa dei Gerani Clinic and can be shared according to the policy's of this institution and the Italian Law on privacy 679/2016.

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CONFLICT OF INTEREST

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Chapter 3

Predictors of functional outcome in patients with major depression and bipolar disorder: A dynamic network approach to identify distinct patterns of interacting symptoms.

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Abstract

The purpose of this study is to use a dynamic network approach as an innovative way to identify distinct patterns of interacting symptoms in patients with Major Depressive Disorder (MDD) and patients with Bipolar Type I Disorder (BD). More precisely, the hypothesis will be testing that the phenotype of patients is driven by disease specific

connectivity and interdependencies among various domains of functioning even in the presence of underlying common mechanisms. In a prospective observational cohort study, hundred-forty-three patients were recruited at the Psychiatric Clinic "Villa dei Gerani" (Catania, Italy), 87 patients with MDD and 56 with BD with a depressive episode. Two nested sub-groups were treated for a twelve-week period, which allowed us to explore differences in the pattern of symptom distribution (central vs. peripheral) and their connectedness (strong vs weak) before (T0) and after (T1) treatment. All patients underwent a complete neuropsychological evaluation at baseline (T0) and at T1. A network structure was computed for MDD and BD patients at T0 and T1 from a covariance matrix of 17 items belonging to three domains–neurocognitive, psychosocial, and mood-related (affective) to identify what symptoms were driving the net- works. Clinically relevant differences were observed between MDD and BD, at T0 and after 12 weeks of pharmacological treatment. At time T0, MDD patients displayed an affective domain strongly connected with the nodes of psychosocial functioning, while direct connectivity of the affective domain with the neurocognitive cluster was absent. The network of patients with BD, in contrast, revealed a cluster of highly interconnected psychosocial nodes but was guided by neurocognitive functions. The nodes related to the affective domain in MDD are less connected and placed in the periphery of the networks, whereas in BD they are more connected with psychosocial and neurocognitive nodes. Noteworthy is that, from T0 to T1 the "Betweenness" centrality measure was lower in both disorders which means that fewer "shortest paths" between nodes pass through the affective domain. Moreover, fewer edges were connected directly with the nodes in this domain. In MDD patients, pharmacological treatment primarily affected executive functions which seem to improve with treatment. In contrast, in patients with BD, treatment resulted in improvement of overall connectivity and centrality of the affective domain, which seems then to affect and direct the overall network. Though different network structures were observed for MDD and BD patients, data suggest that treatment should include tailored cognitive therapy, because improvement in this central domain appeared to be fundamental for better outcomes in other domains. In sum, the advantage of network analysis is that it helps to predict the trajectory of future phenotype related disease manifestations. In turn, this allows new insights in how to balance therapeutic interventions, involving different fields of function and combining pharmacological and non-pharmacological treatment modalities.

Introduction

Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are among the most debilitating and prevalent mental disorders, often leading to substantial functional impairment [1–3].

Patients with MDD or BD represent an enormously heterogenous group while identified risk factors lack the capacity to distinguish individual trajectories. Also, no single treatment modal- ity has proved to be truly effective in preventing relapse or the worsening of symptoms. At present, research indicates that the profoundly engrained traditional categorical approach linking just one or a few individual mediators (often molecular or biological) to an illness related phenotype, has provided limited understanding of the complex underlying pathologic conditions. More importantly, this traditional approach has often hampered progress in the development of personalized and more efficacious treatments.

Consequently, a paradigm shift is necessary that invests in the detection of trajectories of disease which allow to better understand the specific evolution of the clinical pattern of differ- ent patient populations over time. Innovative discoveries from other fields, such as, imaging techniques and mathematical modeling together with graph analysis have led to new concep- tual thinking resulting in increasingly explanatory and predictive models which may offer a more realistic image representation of the psychosocial strengths and needs of patients. A dynamic network approach, able to model interacting neurocognitive, psychosocial, and mood-related determinants of MDD and BD, represents such an approach and allows to explain the individual behavioral variances of different patient groups. Based on a multimodal approach [4], it gathers evidence from different realms of function such as subtle neurocogni- tive disfunction and uses them (together with biomarkers) as clinical predictors of risk [5].

The network analysis model is of growing interest in the study of contemporary psychopa- thology. Network analysis studies the relationships between symptoms and their triggers [6] and has challenged the traditional latent disease approach [7, 8]. Recent studies highlight that many clinically meaningful findings emerge from the study of the correlations between symp- toms using a network approach [9, 10] and suggest the presence of underlying relationships common to multiple psychiatric disorders but different at the phenotypic level. In fact, several studies have introduced network analysis and found that different cognitive, emotional, and psychosocial

patterns are present in different psychopathological conditions, accentuating that patients' characteristics are not simply the sum of separate abilities but the result of complex dynamic interactions [8, 11].

Based on these premises, here we used network analysis to study the fine-grained phenotypes of MDD and BD hypothesizing that the integration of data across diverse levels of analysis will capture the nature of their dynamic relationship over time, both among patients and between treatment modalities. Furthermore, using network analysis and graph theory, we tested the hypothesis that patients with MDD and BD display different connections among symptoms, which may change, strengthen, sustain, or weaken each other over time [12].

Also, the influence of symptoms on the development of other symptoms might not be the same or distributed equally in the two pathologies. What is ultimately important, is the pattern of connections between symptoms in relation to the functional impairment observed in each pathology. Additionally, network analysis will help to understand what factors are driving the network and what are the differences and similarities between the driving factors. Lastly, this type of analysis may provide new insights regarding the choice of pharmacological treatment to more effectively treat MDD and BD [10, 13].

Few studies have used this methodology to study affective disorders, especially when com- paring unipolar and bipolar Depression [14]. Galimberti and colleagues [15] conducted a study using network analysis to examine possible differences between MDD and BD from a cognitive perspective. Results showed that the BD network was less connected when compared to the MDD network. Also, in BD, executive dysfunction was more central, while in MDD, memory impairment played a key role with a strong impact on functional impairment [15].

Given that unipolar and bipolar Depression are often misdiagnosed [16], network analysis could represent a new and useful tool and improve both the diagnosis and treatment of these diverse affective disorders. The dynamic organization of different functions in networks of interdependent factors Willemstad underscore the differences between unipolar and bipolar Depression and, thus, enhance the accuracy of the differential diagnosis. Moreover, network analysis provides an important tool to verify the impact of treatment by monitoring changes in interdependencies as well as the configuration of symptoms and their connections and devel- opment over time.

A large body of evidence demonstrates that MDD and BD display mainly cognitive deficits, affective symptoms, and psychosocial impairment. In MDD, for instance, cognitive deficits consist of executive dysfunction, verbal and visual memory impairment, reduction of motor speed and attention, which persist long after affective symptoms have subsided [17–19]. Also, baseline cognitive performance still influenced the performance of subjects one-year into fol- low-up. In a recent study, Castellano et al. demonstrated a critical role for verbal memory in relation to psychosocial functioning after one year of treatment in MDD patients, partially responding to treatment [20].

Diversely, in BD, cognitive deficits influenced social and professional skills, with an overall negative impact on quality of life [19, 21], episodic memory [22], attention [23], fine motor skills [24], reduced psychosocial functioning (negatively affected by memory and depressed mood [25], and executive functions [26, 27]). Psychosocial health of BD patients was also impaired by psychomotor agitation, irritability, insomnia, and emotional lability [19, 28, 29].

In light of this, network analysis provides a way to visualize and understand how cognitive, affective, and psychosocial symptoms and capacities interact with and depend on each other before and after treatment with psychotropic drugs. While a psychotherapeutic approach helps patients to manage the cognitive biases underlying their way of thinking [30] and often effec- tively reduces the severity of symptoms, pharmacological treatment improves cognitive and affective symptoms [31]. Recently, a prospective observational study was conducted on the effectiveness of SSRIs and SNRIs in a sample of 33 MDD patients. Cognitive and affective assessment, performed at baseline and at 4 and 12 weeks into treatment, showed that SSRIs and SNRIs improved cognitive symptoms in MDD independently of their efficacy on affective symptoms [32].

Ultimately, the purpose of our study is to use network analysis to clarify the structure of the relationships between affective, cognitive, and psychosocial symptoms and capacities in a sam- ple of 87 MDD and 56 BD patients. Moreover, two nested sub-groups of patients underwent a twelve-week period of pharmacological treatment, allowing to explore differences in the pat- tern of symptom distribution (central vs. peripheral) and their connectedness (strong vs weak) before (T0) and after (T1) treatment. Finally, the overall aim is to better understand the inter- action between neurocognition, psychosocial functioning and affective symptoms, to identify which

symptoms are driving the network of patients with MDD compared to BD and consequently guide the implementation of individualized effective treatment plans aimed to pro- mote functional recovery.

Material and methods

Subjects

Patients were recruited at the Psychiatric Clinic "Villa dei Gerani" (Catania, Italy). All patients received oral and written information on the planned use of the data and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The study was approved by the ethical committee of the "Azienda Sanitaria Provinciale 3 (ASP3) of Catania of which the "Villa dei Gerani Clinic" (clinical coordinator of the study), is part (Approval date of the extended study July 24, 2012). The study met the ethical administra- tive requirements under Italian legislation in force when the study's administrative process started (03.06.2012) according to CM 6 02.09.2002, GU 214 12.09.2002 and D 29.03.2008 of the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) and GU 76 31.03.2008, Art 10 (Procedures for Observational Studies).

The study design was a prospective, observational (non-interventional), cohort study. The study complied with the definition of "observational" study (i.e., "non-interventional") pro- vided in Article 2(c) of Directive 2001/20/EC, meaning that the investigator who carries out the study does not interfere with the physician's decision regarding which drug is to be pre- scribed to each individual patient. Therefore, prescription of antidepressants, antipsychotics, or mood stabilizers resulted solely from an independent clinical evaluation, according to the physician's clinical judgment, and based on each patient's clinical profile (presence of a depres- sive episode). Moreover, the decision to include a patient in the study, following his/her con- sent, was taken independently of the clinical decision to prescribe psychotropic drugs. Finally, the study did not affect the medical practice of participating physicians and did not trigger additional medical visits.

One hundred-forty-three patients (97 females and 46 males, mean age 50.78 ± 10.18) were recruited for this study, and 45 of them (20 males and 25 females, mean age 50.68 ± 10.25) completed the 12 weeks of treatment (Table 1). Among the 143 patients at T0, 87 were diag- nosed with Major Depressive Disorder (29 males, 58 females, mean

age 52.38), and 56 with Bipolar I Disorder with a depressive episode (19 males, 37 females, mean age 53). Among the 45 patients at T1, who completed the study after 12 weeks of treatment, 16 were diagnosed with Major Depressive Disorder (5 males, 11 females, mean age 53.62) and 29 with Bipolar I Disorder with a depressive episode (12 males, 17 females, mean age 50.86).

Table 1. Demographic and clinical characteristics of the studied population with their relative percentages.

	ALL		Major Depressive Disorder		Bipolar Disorder	
DEMOGRAPHICS	**SAMPLE**	**PERCENTAGE**	**SAMPLE**	**PERCENTAGE**	**SAMPLE**	**PERCENTAGE**
Sample size	143	100	87	100	56	100
Gender			**Gender**			
Male	46	29.9	29	33.3	17	30.4
Female	97	70.1	58	66.7	39	69.6
Mean Age	50.78	\	52.38	\	53	\
Marital status			**Marital status**			
Unmarried	34	24.3	18	20.7	16	28.6
Married	68	47.2	45	51.7	23	41.1
Divorced	29	20.1	17	19.5	12	21.4
Widow	12	8.3	7	8.0	5	8.9
Education			**Education**			
Primary school	13	9	11	12.6	2	3.6
Secondary school	54	37.5	34	39.1	20	35.7
High school	58	40.4	29	33.3	29	51.8
University and more	18	13.1	13	14.9	5	8.9
Employment status			**Employment status**			
Student	1	0.7	0	0.0	1	1.8
Employed	87	60.4	51	58.6	36	64.3
unemployed/Retired/Housewife	55	38.9	36	41.4	19	33.9
Age at onset			**Age at onset**			

Before 20 years old	33	22.9	20	23.0	13	23.2
After 20 years included	110	77.1	67	77.0	43	76.8
Previous depressive episodes			**Previous depressive episodes**			
0	11	7.6	4	4.6	7	12.5
1	57	39.6	39	44.8	18	32.1
2	64	45.2	38	43.7	26	46.4
3	11	7.6	6	6.9	5	8.9

The criteria for inclusion in the study were:

1) A diagnosis of MDD or BD (Type I) according to DSM-V criteria.
2) Age between 18–65 years old.

Criteria for exclusion from the study were:

1) A history of mental retardation or any clinical condition that could affect cognitive performance.
2) Axis I comorbidity.
3) Electroconvulsive therapy 1 year prior to neuropsychological assessment

Pharmacological treatment

Between T0 (first neuropsychological evaluation) and T1 (second evaluation) forty-five [33] patients followed a twelve-week treatment tailored to the needs of the individual patient. Treat- ments can be summarized as follows:

1. Sixteen patients with Major Depressive Disorder were treated exclusively with ANTIDEPRESSIVE drugs (SSRIs, SNRIs and tricyclics).
2. Eight of the patients with Type I Bipolar Disorder were given GENERATION I and II ANTIPSICOTICS (Treatment 1).
3. The remaining twenty-one patients with Bipolar Disorder Type I were treated with GENERATION II ANTIPSICOTICS and MOOD STABILIZERS (Treatment 2).

In terms of constructing the networks, the two treatment subgroups of patients with bipolar I disorder were combined which allowed us to make observations about the change itself and not the specific treatment.

Neuropsychological assessment

Patients underwent a complete neuropsychological evaluation carried out at baseline and at the end of 12-weeks of pharmacological treatment. At baseline depressive symptoms were assessed by the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI–II). Patients were also assessed using a comprehensive neuropsychological battery consisting of: 1) Tools for the assessment of global cognitive function: Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), and 2) Tools for the assessment of specific cognitive functions: Rey 15 Words Test and Verbal Memory Span (Digit Span), the Phonetic Verbal Fluency test (FAS), the "Vocabulary" test from the WAIS-IV, and finally, the Frontal Assessment Battery to measure executive functions (FAB). More specifically, with executive functions we intend functions controlled primarily by the frontal lobes like short- term memory, working memory, planning, inhibition, and attention in all its declination (sustained, alternating, and divided). All these functions were explored with some subtests contained in the MoCA, MMSE, and FAB (all considered neuropsychological tests for global screening of cognitive functions) and more specific tests:

- SPAN-A (forward) for short verbal memory
- SPAN-I (backward) for working memory
- REY (15 Rey's words–Immediate recall) for short-term verbal memory for unstructured material
- FAS (Test of Phonemic Fluency) for evaluating vocabulary and lexical organization on phonemic cue (this means not accessing the semantic level). In this test people have to produce words not accessing the semantic warehouse and, at the same time, trying not to say words already said, proper names and with the same root. This means using inhibition, short-term memory, planning, and self-monitoring; all executive functions (frontal).

In addition, FAB also contains a subtest of Phonemic Fluency giving the patient the letter "S" and 1 minute to say all the words that start with that letter.

In the article we talked about executive functions because FAS also investigate them.

Functional assessment

The Functioning Assessment Short Test (FAST) 25 was used as a primary outcome of psycho- social risk at the study endpoints to identify predictors for specific domains of function, such as: autonomy (Atn), occupational functioning (Occ), cognitive

functioning (Cog), financial issues (Fnn), interpersonal relationships (Int), and leisure time (Lsr). The FAST was assessed after 12 weeks from the start of the pharmacological treatment. For this study, we only included the score of the overall functioning and the score of six specific FAST scale domains.

Statistical analyses

A network structure was computed for MDD and type I bipolar adult patients at the onset of the study (T0) and after twelve weeks of treatment (T1). A covariance matrix of 17 items belonging to three domains–the neurocognitive, social, and mood-related domains–was used to analyze the interaction between neurocognition, psychosocial functioning and affective symptoms, and to identify what symptoms were driving the network and could be targets for effective treatment plans to promote functional recovery.

The structure of a network model is characterized by two main elements: nodes and edges. Usually, nodes are depicted with circles and represent, in the psychopathological scenario, the symptoms of a disorder [11]; the edges are depicted with lines connecting nodes to each other, and represent, the relationships between symptoms [12, 34].

Generally, three main measures of centrality are considered: strength/degree, betweenness and closeness centrality.

- **DEGREE CENTRALITY (STRENGTH/DEGREE):** the number of connections of a node: the more connections it has, the more important it is.

Clinically speaking, if a symptom (e.g., depressed mood) has many connections within a psychopathological system, it may be considered as a risk factor for the development of a variety of other symptoms. If, on the other hand, it has a low number of connections, it is considered peripheral with a scarce risk of fostering or influencing other symptoms [35]. The strength of a node in a weighted network is given by the product of the number of nodes to which a node is connected and the average of the weights of these nodes, adjusted for a tuning parameter:

$$C_{\mathrm{D}}^{w\alpha}(i) = k_i \times \left(\frac{s_i}{k_i}\right)^{\alpha} = k_i^{(1-\alpha)} \times s_i^{\alpha}$$

where α is the positive tuning parameter that is chosen based on the data and ki and si are the Degree and Strength of the nodes, respectively:

$$k_i = C_{\mathrm{D}}(i) = \sum_{j}^{N} x_{ij} \qquad s_i = C_{\mathrm{D}}^{w}(i) = \sum_{j}^{N} w_{ij}$$

where i is the reference node, j are all other nodes, N is the total number of nodes, and x is the adjacency matrix in which the cell xij is defined 1 if node i is connected to node j, and 0 otherwise. W is the weighted adjacency matrix.

- **BETWEENNESS:** measures how a node is involved in the shortest path between other nodes [15]. It is used to determine which nodes are most likely to connect other nodes to each other and, therefore, which are most likely to facilitate connections in the network. For example, through this measure it is possible to determine the most important doins affecting the connectivity between problems and symptoms [36]. The algorithm for calcu- lating "shortest paths" is that of Dijkstra (1959) [37], implemented in R and repurposed by Opsahl, Agneessens and Skvoretz (2010) [38]. The length of the shortest path between two nodes is defined as follows:

$$d^{w\alpha}(i,j) = \min\left(\frac{1}{(w_{ih})^{\alpha}} + \ldots + \frac{1}{(w_{hj})^{\alpha}}\right)$$

This algorithm can be used directly for the Closeness measure (described below) and con- siders both the number of intermediate nodes and the weight of connections.
The combination of the formula of Freeman (1978) [39] and the above formula of Dijkstra leads to a final formulation of the Betweenness parameter formula:

$$C_B^{w\alpha}(i) = \frac{g_{jk}^{w\alpha}(i)}{g_{jk}^{w\alpha}}$$

Where gjk is the number of shortest paths between two nodes, gjk(i) is the number of those paths passing through node i, and α is the positive tuning parameter.

- **CLOSENESS:** is used to understand the importance of a symptom and its immediate impact on neighboring symptoms or functions. The nodes with the highest closeness quickly affect other nodes and, in turn, they are more likely to be influenced. The combination of these three different measures, strength/degree, betweenness, and closeness identifies the domains that are most important in the configuration of a network and improves our understanding regarding the symptoms to target with precise individualized therapeutic interventions.

Network construction was based on Spearman correlations by defining negative/positive relationships between nodes, so that weighted undirected networks could be built. The thick- ness and color of a connection represent the strength and the sign–positive (in black) or negative (in red)–of significant correlations ($p<0.05$): the more accentuated the line, the stronger the association. In the absence of an edge, the relationship was 0. The correlations were assessed through various psychometric tools: HDRS and BDI-II for affective symptoms, FAST for psychosocial functioning, MoCA and MMSE for global neurocognition, FAS (phonetic verbal fluency), Vocabulary, backward/forward Span, Rey Memory Test and FAB for specific cognitive functions. The resulting networks were analyzed considering three measures of centrality: Strength, Betweenness and Closeness. Networks were estimated using the package "qgraph" in the R software by the Fruchterman-Reingold algorithm which is based on an iterative procedure that places the most crucial nodes in the center of the network, whereas the weakest nodes are placed in the periphery. This algorithm is automatically calculated using the command "layout = spring". The Fruchterman & Reingold (FR) algorithm transforms the network into a system of particles with mass. The nodes are interpreted as particles, and the edges as the pushes they give each other through attractive forces (calculated between adjacent vertices) and repulsive forces (between pairs of vertices). Furthermore, to reduce the quadratic complexity of the repulsive forces, the algorithm ignores these forces between distant vertices.

Also, we added another feature to the networks: a predictability ring around each node using the package "mgm" in R software. It shows the degree to which a given node

can be predicted by all other nodes in the network with which it has connections. Predictability is an important measure when considering psychopathology because it tells us on an interpretable absolute scale how much a node is determined by other nodes in the network allowing for increasingly explanatory parameters of risk (importance of a node). Because this measure gives us an idea of how clinically relevant connections are, it is useful to estimate the potential success of clinical interventions which could thereby effectively guide treatment selection. As predictability measures, we selected, for continuous variables, the root mean square error (RMSE) as a proportion of the explained variance [40].

The labels of each node are summarized as follows.

Neurocognitive domain (pink color in the images): MCA = Montreal Cognitive Assessment, MMS = Mini Mental State Examination, FAB = Frontal Assessment Battery, FAS = Phonetic verbal Fluency, Vcb = Vocabulary, REY = Rey 15 Words immediate recall, RDC = Rey 15 Words deferred recall, SPAN_A = digit span forward, SPAN_I = digit span backward.

Depression related domain (blue color in the images): BDI = Beck depression inventory II, HDR = Hamilton depression rating scale.

Psychosocial domain (green color in the images): Cgn = Cognitive functioning,

Occ = occupational functioning, Atn = Autonomy, Lsr = Leisure time, Int = interpersonal relationships, Fnn = financial issues.

Results

Differences between major depressive disorder and type I bipolar depression at the onset of the study (Time 0)

As shown in Fig 1A, the affective cluster in patients with MDD is placed in the periphery and the two nodes represented by HDRS and BDI do not occupy a central role in driving the net- work. Although the affective domain is highly connected with the nodes of psychosocial functioning, direct connectivity with the neurocognitive cluster is absent. The central domain of affective appraisal served as a bridge between the psychosocial domain and the neurocognitive domain. No direct connectivity was observed among specific frontal related executive functions and the psychosocial domain. With frontal related functions we intend functions con- trolled primarily by the frontal lobes like short-term memory, working memory, planning, inhibition, and attention in all its declination (sustained, alternating, and divided). Moreover,

psychosocial ability and depressive symptoms seem to form one separate system. while frontal related functions compose another world. The latter is represented by diffusely connected nodes, with MoCA and MMSE driving the neurocognitive cluster, assuming a bridge function to the more emotional psychosocial area (Figs 1 and 2). In fact, the majority of connections start from the MoCA and MMSE nodes and go to the Psychosocial and Affective nodes. In addition, Centrality measures show that these two nodes, of all others, have higher values of "Betweenness". This means that many "shortest paths" go through the MoCA and MMSE nodes. In addition, clusters are internally hyperconnected, demonstrating low resilience to change induced by external positive or negative factors [41].

The network of Bipolar I patients at T0 is characterized by a main division in two dimensions–a neurocognitive and a psychosocial one–and displays a different pattern of connectivity among nodes (Fig 1B). The cluster of neurocognition is scarcely connected and heavily driven by functions tested with the MoCA (Fig 2). Furthermore, the Affective nodes of patients with BD are diffusely related to the domain of psychosocial functioning. Psychosocial impairment especially related to interpersonal (Int) and occupational (Occ). Interpersonal (Int) and Occupational (Occ) nodes drive the area of psychosocial functioning because they have the highest "Betweenness" and "Strength" values (centrality measures) and are only second to the Cognitive (Cgn) node. Now because this last node is the one that has the majority of edges connecting the psychosocial and neurocognitive clusters, its centrality measures are affected by the dual influence of these two domains. In addition, the "Cognitive" node has much more in common with the neurocognitive node than "Int" and "Occ". For these reasons, "Int" and "Occ" are more segregated and better reflect the influence of the psychosocial domain.

The network of patients with MDD displayed a central role for cognitive-emotional control which proved highly significant in driving the psychosocial and depression-related clusters of symptoms. Cognitive-emotional control provides a bridge to the neurocognitive cluster, as evidenced by an elevated level of betweenness centrality (Fig 2). In contrast, in patients with BD the executive function cluster was the most influential and likely drives the neurocognitive domain overall. Though the psychosocial domain is characterized by substantial closeness centrality, only the nodes "Cognitive" (Cgn) and "Interpersonal" (Int) display the highest number of connections in this cluster.

Predictability measures expose an additional difference between unipolar and bipolar depression. Values tend to be higher in unipolar depression than in bipolar depression; this means that nodes in the unipolar network "better" explain the variance among themselves than from external factors. In contrast, the backbone of bipolar disorder is a higher genetic imprint that determines aspects of functional brain organization. This is further supported by the fact that in the BD network the nodes representing frontal functions are placed in the outer part of the neurocognitive cluster (Fig 1B).

In sum, at the onset of the study (baseline), the network of MDD patients is driven by three well connected clusters, with cognitive-emotional ability or disability driving the psychosocial domain and providing a bridge connecting depression-related symptoms to the neurocognitive cluster. The network of depressed patients with type I bipolar disorder, on the other hand, is characterized by a highly interconnected cluster of psychosocial nodes but driven by neuro- cognitive functions. Neurocognitive functions in BD are less connected among each other (fewer edges among the nodes) than in MDD where the neurocognitive world displays a num- ber of edges connecting nodes among each other. Noteworthy, in patients with MDD, the indexes related to the affective domain are less connected and placed in the periphery of the network, whereas in BD patients they are more connected with psychosocial and neurocognitive nodes. Lastly, predictability measures show additional differences between unipolar and bipolar depression and could be used to better understand the relationships between symptomatology and the functions investigated.

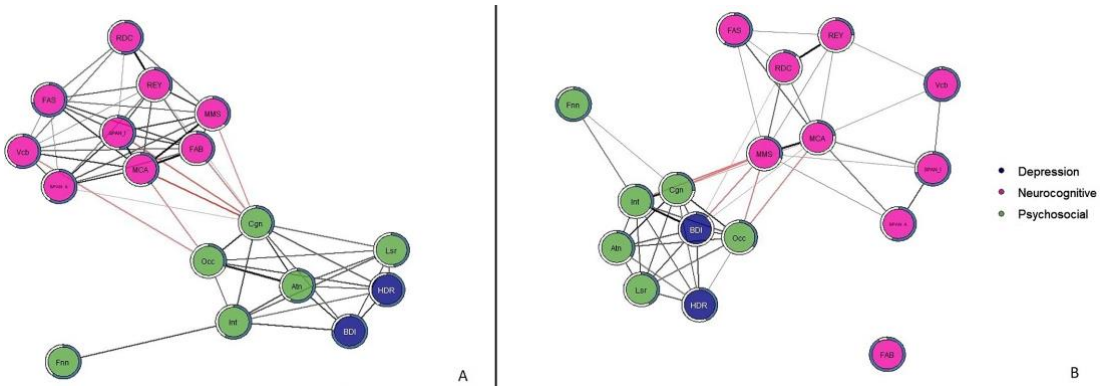

Fig 1. Resulting networks at the onset of the study (T0). Part A represents the network of patients with MDD. Part B represents the network of Type I BD patients. Pink color groups the neurocognitive domain, green color the psychosocial domain and blue color the depression-related nodes. Black edges represent positive Spearman

correlations, red edges negative Spearman correlations. The blue ring around each node represents its predictability and the fuller the bar is, the higher the RMSE value is. Cognitive domain: MoCA = Montreal Cognitive Assessment, MMS = Mini Mental State Examination, FAB = Frontal Assessment Battery, FAS = Phonetic verbal Fluency, Vcb = Vocabulary, REY = Rey 15 Words immediate recall, RDC = Rey 15 Words deferred recall, SPAN_A = digit span forward, SPAN_I = digit span backward. Depression related domain (blue color in the images): BDI = Beck depression inventory II, HDR = Hamilton depression rating scale. Psychosocial domain (green color in the images): Cgn = Cognitive functioning, Occ = occupational functioning, Atn = Autonomy, Lsr = Leisure time, Int = interpersonal relationships, Fnn = financial issues.

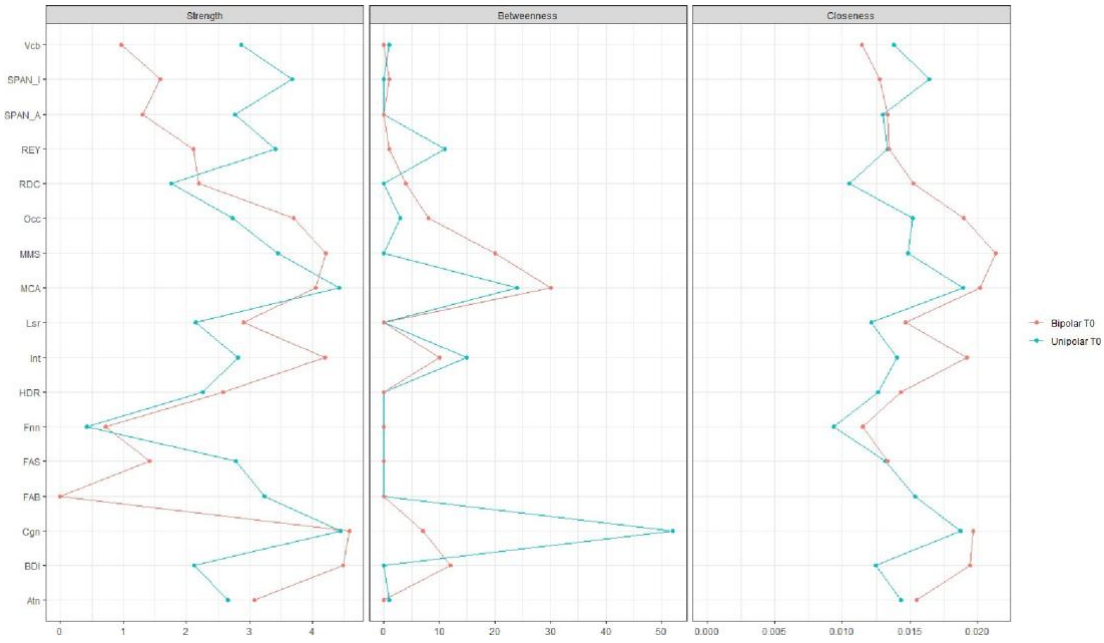

Fig 2. Centrality measures (strength, betweenness, closeness) of MDD and BD patients at baseline (T0). Red color represents Bipolar Patients and Blue Color MDD patients. MoCA = Montreal Cognitive Assessment, MMS = Mini Mental State Examination, FAB = Frontal Assessment Battery, FAS = Phonetic verbal Fluency, Vcb = Vocabulary, REY = Rey 15 Words immediate recall, RDC = Rey 15 Words deferred recall, SPAN_A = digit span forward, SPAN_I = digit span backward, BDI = Beck depression inventory II, HDR = Hamilton depression rating scale, Cgn = Cognitive functioning, Occ = occupational functioning, Atn = Autonomy, Lsr = Leisure time,

Int = interpersonal relationships, Fnn = financial issues.

Differences between MDD and BD after twelve weeks of treatment (Time 1)

At Time 1, after twelve weeks of treatment, a dynamic change was observed in the networks of the two groups of patients. The network of MDD patients displayed a rather different structure from the onset of the study. As for T0, at T1, the same three separate clusters of psychosocial, affective, and neurocognitive domains were observed (Figs 3A and 4). How- ever, at T1, the neurocognitive cluster (the ensemble of nodes that represent entirely or in part the executive functions, assessed by SPAN-A; SPAN-I; REY; FAS; MoCA, MMSE, and FAB), although less connected internally, was more centrally positioned, with executive functions related to the frontal cortex driving the network and providing a link to the other two domains. More precisely, executive functions seem to drive the neurocognitive domain because they have the highest values of centrality measures. In particular the "Strength" value is indicative because it indicates how many connections start from that node. These executive function nodes provide a link to the psychosocial and affective domains because they are the only nodes to have "inter-domain" connections (neurocognitive to psychosocial and neurocognitive to affective.

Similarly, in patients with BD, twelve weeks of treatment resulted in a shift in the centrality of symptoms. In the new post-treatment scenario, depression-related indexes were more cen- trally placed in the network of BD. From T0 to T1, both the BDI and HDRS nodes assume a bridge function connecting the psychosocial domain and the neurocognitive domain. More- over, the neurocognitive cluster displayed a significant loss in connectivity among its nodes (Figs 3B and 4). This indicates that from the high number of connections (correlations) among the nodes at T0, very few were conserved at T1, both within the cluster itself and among the two clusters. Thus, the network of patients with BD is less influential and, therefore, more resilient to factors that may cause it to change.

A dynamic pattern of change emerged in the network of BD with respect to what were the driving forces of the network before and after treatment. A large positive change was observed from time 0 to time 1, especially with respect to neurocognitive functions related to the frontal cortex. At time 1, these functions are more central in the communication within the network, reciprocally connecting many nodes (symptoms). Little or no change was observed in depres- sion related parameters. In BD functions tested by the MMSE and MoCA were central in the network at time 0. AT T1 MoCA

assumes a primary role connecting the neurocognitive cluster of nodes with the psychosocial cluster indicating that MoCA is the only node that has connec- tions that link the two clusters.

In both groups MDD and BD, the predictability values of each node decreased at T1 with respect to T0. In particular, the Predictability (calculated with the RMSE: root mean squared error) Mean in MDD was 0.51 at T0 and 0.22 at T1; in BD, values diminished from 0.41 at T0 to 0.05 at T1.

The external inclusion of a "drug treatment variable", not reported within the network but having a primary impact on network reorganization, seems to be the reason why nodes can no longer account for the influence they had on each other at T0.

In sum, in MDD patients, pharmacological treatment primarily affected executive functions which seem to improve with treatment and drive the network. In contrast, in patients with BD, twelve weeks of treatment resulted in an improvement in the overall connectivity and cen- trality of the affective domain, which seems then to affect and direct the network. More specifi- cally an improvement in Connectivity was observed in relation to the number of edges connected from one-time point to the other which is further supported by the increasing val- ues of "Strength" and "Betweenness". In particular, the "Affective" Nodes (HDRS and BDI) show an increase in these two measures. This suggests that at T1 the two nodes have a greater impact in redistributing information in the network than they did before and that the connec- tions with the other nodes are much stronger. In fact, Figs 2 and 3B show that there is a change in the scores of these two centrality measures (red line represents Bipolar Disorder).

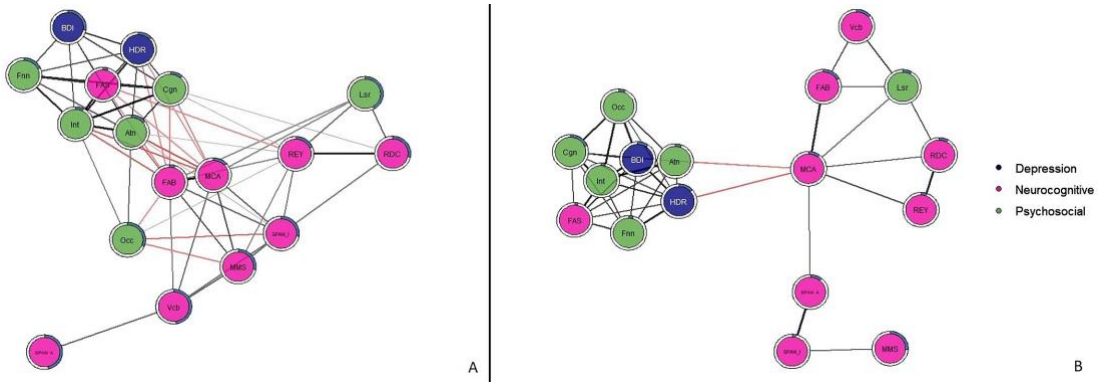

Fig 3. Resulting networks at first endpoint (T1). Time 1 of the study (T1). Part A represents the cluster of MDD. Part B represents the network of type I BDs. Pink color groups the neurocognitive domain, green color the psychosocial domain and blue the depression-related nodes. Black edges represent positive Spearman correlations, red

edges negative Spearman correlations. The blue ring around each node represents its predictability and the fuller the bar is, the higher the RMSE value is. Cognitive domain: MCA = Montreal Cognitive Assessment, MMS = Mini Mental State Examination, FAB = Frontal Assessment Battery, FAS = Phonetic verbal Fluency, Vcb = Vocabulary, REY = Rey 15 Words immediate recall, RDC = Rey 15 Words deferred recall, SPAN_A = digit span forward, SPAN_I = digit span backward. Depression related domain (blue color in the images): BDI = Beck depression inventory II, HDR = Hamilton depression rating scale. Psychosocial domain (green color in the images): Cgn = Cognitive functioning, Occ = occupational functioning, Atn = Autonomy, Lsr = Leisure time, Int = interpersonal relationships, Fnn = financial issues.

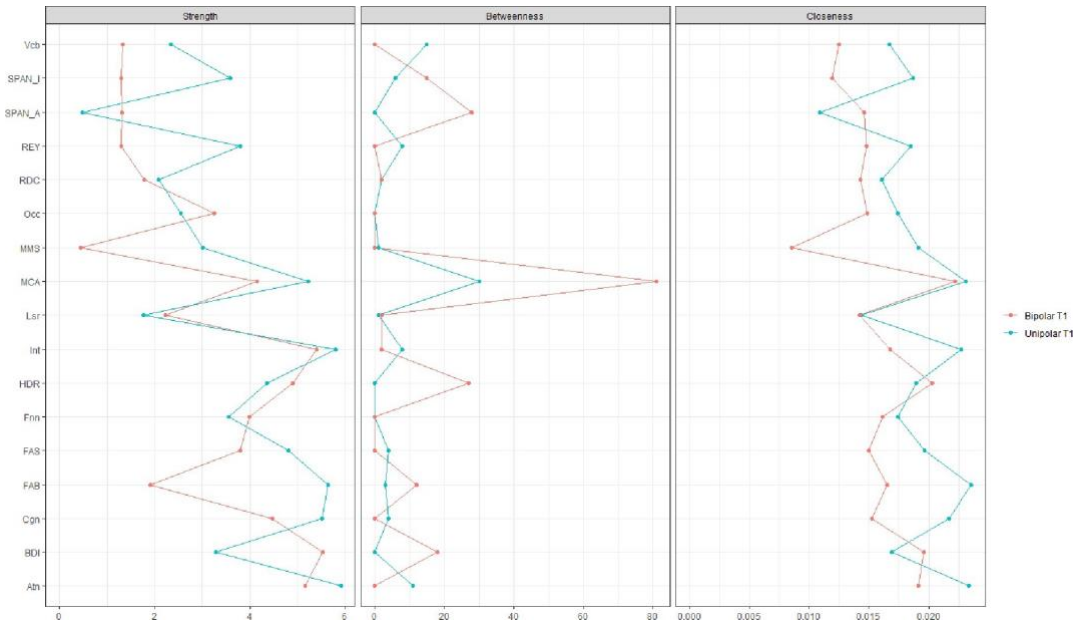

Fig 4. Centrality measures (strength, betweenness, closeness) of MDD and BD patients at first endpoint (T1). Red color represents BD and Blue Color MDD. MCA = Montreal Cognitive Assessment, MMS = Mini Mental State Examination, FAB = Frontal Assessment Battery, FAS = Phonetic verbal Fluency, Vcb = Vocabulary, REY = Rey 15 Words immediate recall, RDC = Rey 15 Words deferred recall, SPAN_A = digit span forward, SPAN_I = digit span backward, BDI = Beck depression inventory II, HDR = Hamilton depression rating scale, Cgn = Cognitive functioning, Occ =

occupational functioning, Atn = Autonomy, Lsr = Leisure time, Int = interpersonal relationships, Fnn = financial issues.

Discussion

The results of the study highlight clinically relevant differences between unipolar depression and bipolar depression at T0 and after 12 weeks of pharmacological treatment (T1). In both unipolar depression and bipolar disorder, the data indicate that treatment should be more focused on cognitive symptoms, as improvement in this domain appears to be crucial for better results in other domains, and of outcome overall.

Patients with MDD, displayed strong connectivity between psychosocial function and the affective domain while no direct connectivity with the neurocognitive domain was observed. The two realms of function were connected by the central domain of cognitive-affective evaluation, which acts as a bridge between the psychosocial domain and the neurocognitive domain. No direct connection was observed between the affective and cognitive realm of function. Our data agree with evidence coming from many recent studies suggesting that cognitive dysfunction represents a distinct biological and clinical dimension in MDD, independent from affective symptoms [3, 20, 32, 42].

Furthermore, psychosocial competence and depressive symptoms appear to form a separate world in patients with MDD, while cognitive functions with frontal affinity constitute another neighborhood/world.

The network of patients with BD, on the other hand, was characterized by a cluster of highly interconnected psychosocial nodes but guided by neurocognitive functions. However, these functions were less correlated to each other. Noteworthy, in both MDD and BD, the indices related to the affective domain were less connected and placed at the periphery of the networks which suggests that they do not play a central role.

The results of our study concur with other studies using the same methodology. Weintraub et al. (2020) [43], for example, carried out a network analysis in adolescents with bipolar disor- der, which highlights the prominent role played by fatigue, depression, mood lability and irri- tability in the clinical symptomatology. Moreover, data presented by Chavez-Baldini et al. (2021) [44], are in line with our results, and demonstrate the crucial influence of cognition on psychopathology, cognitive functioning seems to be an independent dimension related to psy- chiatric clusters

which interact in a transdiagnostic manner. Besides, the results from our study add a longitudinal aspect to the evidence already available: indeed, at time 1, twelve weeks after starting treatment, a dynamic change was observed in the networks of the two patient groups.

As for patients with MDD, the networks of patients with bipolar disorder display a division between the affective and cognitive domains of function, with the latter being more central.

Previously, Vieta and colleagues [45] showed that euthymic bipolar patients, even after drug treatment, displayed significant impairments in executive functions [46]. These results are in accordance with a study by Godard and colleagues (2012) [47]: after a follow-up of 12 months, both unipolar and bipolar patients presented significant impairment in the cognitive realm of function, especially in executive functions (Godard et al., 2012) [47]. Moreover, Galimberti and colleagues (2020) [15], suggested that the network of patients with bipolar depression display greater executive dysfunction than that of patients with MDD. Data from Kapczinski (2016) [1] are also aligned with these results. As in bipolar patients, severe depression has been associated with lower scores in the domain of executive functioning, examined using the FAST [1].

In addition, in patients with bipolar disorder, connections were stronger within the cogni- tive domain. Therefore, we can assert that for these patients, pharmacological treatment is more effective in producing a change in cognitive functioning than for patients with MDD. This is coherent with the literature sustaining that treating cognitive symptoms is a critical step in the clinical approach to depression, and will help to improve psychosocial functioning, enhance the quality of life and avoid relapses [25, 33, 48].

The differences observed in network structure and connections lead to think that in MDD, the psychosocial area is primarily affected. The increase in severity of symptoms results in rap- idly enhanced impairment in various areas of social life and autonomy of the individual because of the high density of connections. In turn, this leads to decreased performance on the global cognitive scales (negative connections between the two clusters) which, then, diminish the performance in the remaining cognitive nodes. As a result, patients lack the mental capac- ity to cope with the situation they find themselves in.

Given that the connection between each pair of nodes in the network is not directed, and therefore not absolute, a mechanism is triggered that self-feeds the symptoms which leads patients to experience extreme difficulty in finding alternative ways to cope with the situation (Fig 5A). In addition, a hyperconnected network will take much longer to stabilize after the trigger has disappeared which might lead to or favor chronicity or recurrence of depressive episodes.

The predictability index gives additional information about the structure of the network at T0. The results show that the valence loops are on average full in MDD. This suggests that much of the variance of those variables is explained by the neighboring nodes with which they have direct connections. At the qualitative level, predictability introduces the possibility to consider change by working both on the variable itself as well as on neighboring nodes.

Predictability, together with hyper-connectivity, suggests that in MDD, the psychosocial, neu- rocognitive, and affective variables influence each other and, to a large extent, explain their variability. Consequently, treating the depressive symptomatology and providing cognitive strategies at the same time is likely the most appropriate way to cope with this pathology.

The structure that emerges from the analysis of BD networks displays a different pattern. A breakdown of cognitive aspects, especially frontal ones, is evident from an early stage, and does not seem to have a direct impact on depressive symptoms and psychosocial impairment. In addition, agitation, manic episodes, irritability, insomnia, and other specific symptoms of bipolar disorder primarily involved the psychosocial sphere which represents the weaker clus- ter (greater number of connections). Combining these two aspects, the data suggest e that cog- nitive dysfunction and psychosocial dysfunction both contribute to the development and worsening of depressive symptoms. In turn, this may centrally direct and increase psychosocial impairment (Fig 5B). In contrast, frontal functions lack a primary role in the network and are unable to control or mitigate depressive symptoms.

Finally, predictability proved to be an important additional parameter to diversify the dynamics within a network and provided new insights for differential diagnosis at baseline. RMSE values, on average, were lower in BD than in MDD.

Therefore, we can postulate that in MDD the variability of each node is better explained among the nodes/variables analyzed. On the contrary, values are lower in networks of patients with BD. This may be attributed to the fact that intrinsic factors,

such as, genetic predisposition play a more significant role in BD than in MDD. Also, the patients in this study all had rather severe forms of both disorders and were often hospitalized during the treatment period. Creat- ing networks including predictability might be even more important for patients with less severe symptomatology. Here, prediction of risk might allow us to work preventively and con- sider the strengths and needs resulting from the patients' network to develop preventive treat- ment strategies, among which cognitive therapy. Taken together, our findings suggest that treatment of MDD should include tailored cogni- tive therapy, because improvement in this central domain appears to be fundamental for better outcomes in other domains. Likewise, in BD, treatment should include both pharmacological and non-pharmacological interventions, which, in turn, may lead to possible improvements in the other domains due to their pivotal role in driving change.

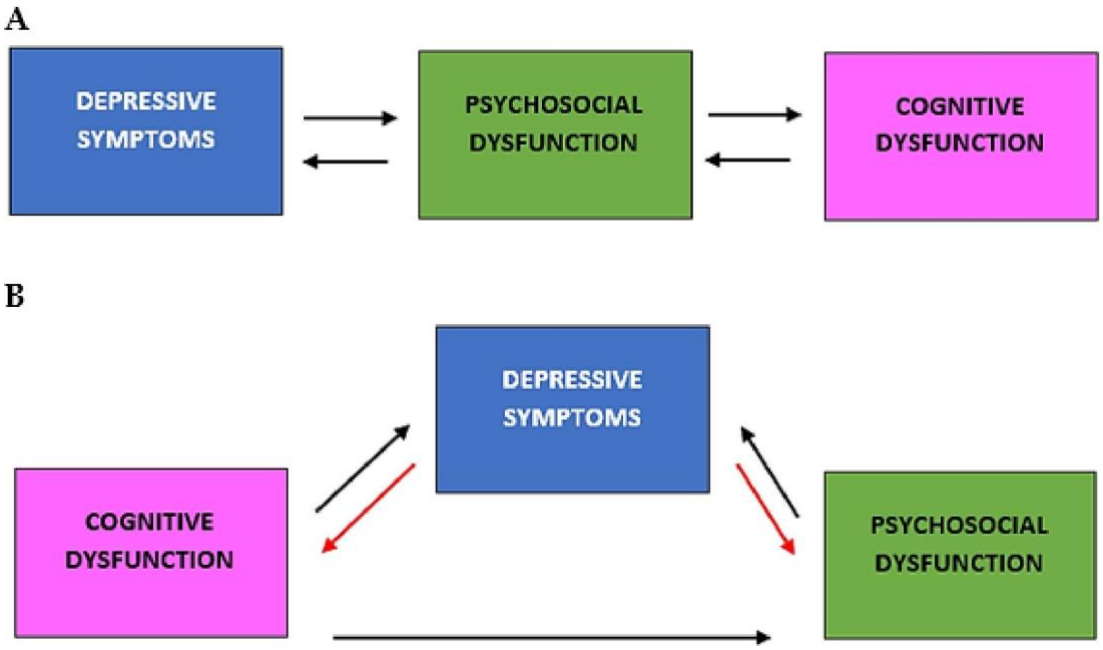

Fig 5. Domains and their possible interaction in MDD and BD. Part A: Possible interactions among domains for MDD by analyzing patients' test performance and resulting networks. Part B: Possible interactions among domains for BD by analyzing patients' test performance and resulting networks. Color coding is consistent with network images. Black arrows represent the main path of interactions between studied functions. Red arrows should be interpreted as a secondary effect due to black arrows.

Conclusions

As suggested from recent studies [49], a dynamic network approach represents a novel tool to identify distinct patterns of interacting symptoms in neuropsychiatric disorders. The dynamic network approach that combines the relationships between risk and protective factors from different realms of functions has the advantage that it is:

1. Personalized: it offers insight in therapy options focused on the clinical trajectory of individual patients with MDD or BD. In addition, it provides alternative targets to take into consideration when making treatment and follow-up care decisions.
2. Collaborative: it engages the patient in the process of care offering individual guidance regarding their strengths and needs.
3. Efficient: assist in finding the best treatment for the patient and reach the right balance based on an integrated process involving different fields of function.
4. Predictive: predicts the trajectory of future disease manifestations of patients diagnosed with MDD or BD and assists in defining risk while offering a highly useful approach in planning and surveilling a combination of pharmacological treatment and psychotherapy.

In conclusion, our network analysis established unique patterns of interconnected domains of function and for each disorder this "depressive disorder connectome" will help to recognize interrelated behaviors allowing to isolate the domain(s) most central to the overall risk and dis- tinguish different trajectories thus improving successful programs fundamental for the surveil- lance and monitoring of personalized interventions.

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Chapter 4

The Dynamic Interaction Between Symptoms and Pharmacological Treatment In Patients With Major Depressive Disorder: The Role Of Network Intervention Analysis.

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Abstract

Introduction. The Major Depressive Disorder (MDD) is a mental health disorder that affects millions of people worldwide. It is characterized by persistent feelings of sadness, hopelessness, and a loss of interest in activities that were once enjoyable. MDD is a major public health concern and is the leading cause of disability, morbidity, institutionalization, and excess mortality, conferring high suicide risk. Pharmacological treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) is often the first choice for their efficacy and tolerability profile. However, a significant percentage of depressive individuals do not achieve remission even after an adequate trial of pharmacotherapy, a condition known as treatment-resistant depression (TRD). **Methods**. To better understand the complexity of clinical phenotypes in MDD we propose Network Intervention Analysis (NIA) that can help health psychology in the detection of risky behaviors, in the primary and/or secondary prevention, as well as to monitor the treatment and verify its effectiveness. The paper aims to identify the interaction and changes in network nodes and connections of 14 continuous variables with nodes identified as "Treatment" in a cohort of MDD patients recruited for their recent history of partial response to antidepressant drugs. The study analyzed the network of MDD patients at baseline and after 12 weeks of drug treatment. **Results.** At baseline, the network showed separate dimensions for cognitive and psychosocial-affective symptoms, with cognitive symptoms strongly affecting psychosocial functioning. The MoCA tool was identified as a potential psychometric tool for evaluating cognitive deficits and monitoring treatment response. After drug treatment, the network showed less interconnection between nodes, indicating greater stability, with antidepressants taking a central role in driving the network. Affective symptoms improved at follow-up, with the highest predictability for HDRS and BDI-II nodes being connected to the Antidepressants node. **Conclusion.** NIA can help identify specific symptoms that may be targeted for intervention, as well as potential pathways for intervention that may have the greatest impact on overall symptom severity.

Keywords: Depression, Major Depressive Disorder, Network Analysis, Antidepressants, pharmacological treatment

Background

Major Depressive Disorder (MDD) is a mental health disorder characterized by persistent feelings of sadness, hopelessness, and a loss of interest in activities that were once enjoyable, [1] often in comorbidity with several disorders such as cardiovascular disease, dementia, and cancer [2]. In addition, a lifetime history of depression has been considered as a risk factor for later Alzheimer's disease (AD) development and the presence of depressive symptoms can increase the conversion from mild cognitive impairment (MCI) to AD [3].

Although the prevention programs aiming at increasing awareness about potential risk factors for depression, including physical inactivity [4] and unbalanced diet [5,6] have been proven effective, according to the Institute for Health Metrics and Evaluation (IHME), MDD affects about 3.28 % of adults globally, with a peak of 4 % among women, and about 4 % of adults older than 60 years [7]. It has been estimated that worldwide approximately 280 million people develop depression [8].

This disorder constitute a major public health concern and is the leading cause in the global burden of disease in terms of disability, morbidity, institutionalization, especially in late-onset depression, and excess mortality, conferring high suicide risk [1,9–12]. Depression is now widely recognised as a complex and multifactorial illness characterized by affective, cognitive and psychosocial symptoms [13,14]. The heterogeneous nature of MDD, therefore, poses challenges to understanding the relationship linking these three different dimensions [15–17]. This highlights the need of a multimodal approach for management and treatment taking into account the complex interplay between affective, cognitive and psychosocial domains.

When considering pharmacological treatment, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Noradrenaline Reuptake Inhibitors (SNRI) are the most commonly used antidepressants in MDD, often emerging as the first-choice for their efficacy and tolerability profile and ease of use [18].

The majority of antidepressant drugs have been developed according to the monoaminergic hypothesis of depression, representing a useful therapeutic tool on affective symptoms of depression, but it is unclear whether they can improve cognitive symptoms [19]. According to clinical practice guidelines, antipsychotic agents are recommended in combination with antidepressant drugs for treating depression with psychotic features or major depression with a partial response to SSRIs or SNRIs [20]. In this context, also non-pharmacological approaches such as psychotherapy [21] and

physical activity were considered as add-on treatment strategies to improve cognitive deficits and affective symptoms of depression [22].

Despite the availability of multiple FDA-approved medications, including SSRIs and SNRIs, a significant percentage of depressive individuals do not achieve remission even after an adequate trial of pharmacotherapy. This condition is known as treatment-resistant depression (TRD), and its prevalence is estimated to be around 30% among MDD patients [22], probably because emerging additional factors involved in MDD pathophysiology such as the role of chronic stress and neuroinflammation, should be considered [3]. Second-generation antipsychotics (e.g. quetiapine, aripiprazole, risperidone, brexpiprazole) have been proposed in combination with SSRI/SNRIs to improve the treatment of MDD with a partial response to antidepressants (PRD) or TRD [23].

To better explain the complexity of clinical phenotypes in MDD, and the relationship between symptoms and pharmacological treatment in these patients, we propose Network Intervention Analysis, an extension of the network analysis model, which conceptualizes mental disorders as the product of interplay between symptoms. Several authors have extended the Network Analysis approach with the purpose of analyzing the specific and sequential effects of treatments on symptomatology, proposing this innovative method in the context of different psychiatric disorders [24–27]. This method, in fact, allows us both to assess the relationship between emerging symptomatology, and to consider the variable of treatment, in order to identify on which symptoms and/or variables it acts with greater effects.

More in detail, NIA analyzes the sequence of changes that the treatment induces on the symptoms and/or variables, taking into account not only the interactions among all those that are part of the network, but also specifying which among them are affected directly or indirectly by that specific treatment [28]. This method differs, hence, from traditional analyses that usually provide us only scores on severity of a disorder or dichotomous aspects, such as response or non-response to treatment [25].

The strength of NIA, therefore, is that this approach can clearly explain how a treatment is effective to improve the different symptoms and/or domains and how this effect can spread throughout the network. For all these reasons, NIA could help health psychology in the detection of risky behaviors, in the primary and/or secondary prevention, as well as to monitor the treatment and verify its effectiveness [29].

In light of the current state-of-art, this paper aims to identify the interaction and changes in network nodes and connections of 14 continuous variables with nodes identified as “Treatment” in a cohort of MDD patients recruited for their recent history of partial response to antidepressant drugs.

Material and Methods

Setting and recruitment

Patients were recruited at the Psychiatric Clinic “Villa dei Gerani” (Catania, Italy). All patients received oral and written information on the planned use of the data and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The study design was a prospective, observational (non-interventional), cohort study conducted in a clinical center in Sicily (Italy). The study complied with the definition of “observational” study (i.e., “non-interventional”) provided in Article 2(c) of Directive 2001/20/EC, meaning that the investigator who carries out the study does not interfere with the physician's decision regarding which drug is clinically pertinent to be prescribed to each individual patient. Therefore, prescription of pharmacological treatments resulted solely from an independent clinical evaluation, according to the physician's clinical judgment, and based on each patient's clinical profile (presence of a depressive episode).

Moreover, the decision to include a patient in the study, following his/her consent, was taken independently of the clinical decision to prescribe psychotropic drugs. Finally, the study did not affect the medical practice of participating physicians and did not trigger additional medical visits.

Participants

Eighty-one MDD patients were recruited for this study, and twenty-eight of them completed a 12 weeks of treatment (Table 1).

Table 1 - Demographic characteristics of the overall sample at T0 and T1

The criteria for inclusion in the study were:

1) A diagnosis of MDD according to DSM-5 criteria.

2) Age between 18-65 years old.
3) A recent history in MDD patients (in the last 4 weeks) of partial response to a previous treatment with an antidepressant drug
4) Not participating in another study simultaneously;
5) Having signed an informed consent

Criteria for exclusion from the study were:
1) A history of mental retardation or any clinical condition that could affect cognitive performance.
2) Comorbidiy with psychotic disorder.
3) Electroconvulsive therapy 1 year prior to neuropsychological assessment.

Pharmacological treatment

Between T0 (first neuropsychological evaluation) and T1 (second evaluation) twenty-eight (28) patients followed a twelve-week treatment tailored to the needs of the individual patient. Because the patients selected for T1 were partial responders, all 28 patients with MDD were treated with Antidepressants and adjunctive Second Generation Antipsychotics.
The following drugs were used: escitalopram (10 mg/day), paroxetine (20 mg/day), sertraline (100 mg/day), citalopram (40 mg/day); duloxetine (60 mg/day), venlafaxine (150-225 mg/day); risperidone (2-3 mg/day), olanzapine (2,5-5 mg/day), aripiprazole (2,5-5 mg/day).

Neuropsychological assessment

During the observational study, patients underwent a complete neuropsychological evaluation carried out at baseline and at the end of 12-weeks of pharmacological treatment.

AFFECTIVE DOMAIN

- Hamilton Depression Rating Scale (HDRS) [30]: it is a 21-item hetero-administered scale in which determinant areas are explored in assessing the subject's depressive state. A score <7 indicates no depression; between 8 and 17 indicates mild depression; between 18 and 24 moderate depression; >24 severe depression.
- Beck Depression Inventory (BDI–II) [31]: it is a 21-item self-administered instrument to detect the severity of depression in adults and adolescents from age 13 onward. Scores 0-13 indicate no depressive content; scores between 14-19: mild depression; scores 20-29 moderate depression; scores 30-63: severe depression.

For both instruments, the higher the score, the worse the depressive symptomatology.

NEUROCOGNITIVE DOMAIN:

Global cognitive functions assessment

- Montreal Cognitive Assessment (MoCA) [32]: it is a rapid screening tool for global cognitive functions, and executive functions. It assesses several cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructive skills, abstraction, computation, and orientation. The maximum possible score is 30 points; a score of 26 or higher is considered normal.

*Specific cognitive functions assessmen*t

- Rey 15 Words Test [33]: it assesses immediate and delayed memory span and provides an assessment on learning. The test consists of 5 presentations, with recall after 30 minutes, of a list of 15 words.
- Forward and Backward Digit Span [34]: it assesses verbal memory span.
- Phonetic Verbal Fluency test (FAS)[35]: it is a measure of phonemic word fluency, which is a type of verbal fluency. It assesses phonemic fluency by requesting an individual to orally produce as many words as possible that begin with the letters F, A, and S within a prescribed time frame, usually 1 min.
- the “Vocabulary” test from the WAIS-IV [36]:

- Frontal Assessment Battery (FAB) [37]: it is a hetero-administered tool useful for assessing certain frontal functions: conceptualization (analogies), lexical fluency, motor series, interference sensitivity, inhibitory control, and environmental dependence. Scores from 0 (test failure) to 3 (no errors) are given. Once the scores are summed, an adjustment is made for age and schooling.

PSYCHOSOCIAL DOMAIN

- Functioning Assessment Short Test (FAST) [38]: it was used as a primary outcome of psychosocial risk at the study endpoints to identify predictors for specific domains of function, such as: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, leisure. For this study, we only included the score of four sub-domains (autonomy, cognitive functionic, financial issues, interpersonal relationship).

Statistical analyses

Descriptive and Inferential statistics:

The collected data were initially analyzed qualitatively through the estimates of mean, standard deviations, and percentages to obtain general demographic information about the sample. The corrected scores (by age and schooling) of individual tests were treated as variables in the statistical and network analysis. Traditional independent t-test and parametric unidirectional analysis of variance (ANOVA) were performed to determine the difference among groups (T0 and T1) for continuous variables. Normal distribution was established by the Shapiro-Wilk test ($p > .05$ for normal intake). In addition, the homogeneity of variances within each group was established by Levene's test for equal variation ($p > .05$ for assumption of equal variance), and when violated, Welch' correction for unequal variances was applied. All analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R software (version 4.0.3 / 2020-10-10).

Network Analysis

Network analysis was performed on 81 MDD patients at T0 and on 28 patients that completed a 12-week treatment (T1).

Networks were computed with the package “qgraph” [39] in the R software using the Fruchterman-Reingold algorithm, which transforms the network into a system of massive particles. Nodes are interpreted as particles and edges as mutual pushes. The algorithm attempts to minimize the used energy of the physical system. Fruchterman and Reingold's (1991) algorithm [40] adds "uniform vertex distribution" compared to earlier versions.

Introducing drug treatment as a dichotomous variable (presence/absence), a Mixed Graphical Model (MGM) implemented through the R-package mgm [41] was used to compute the NIA. Networks are composed of nodes (circle nodes: test scores; square node: treatment) and edges. The edges represent the conditional dependence relations between variables. Thus, they indicate the association between two nodes controlled for associations with all the other nodes of the network. Green edges indicate positive associations, red edges negative associations, and gray edges partial correlations between dichotomous and continuous variables.

The thickness of an edge represents the strength of the association (thicker the edge, greater the correlation value). All the relationships represented in our model are pairwise interactions (k = 2, interactions). In addition, the resulting network consists of the estimates of the relationships between the variables taken two by two, and these relationships are controlled for by all other variables. This means that the absence of a relationship between two variables indicates that those two variables are conditionally independent given all the other variables. The difference size of nodes between T0 and T1 is explained as follows: if the test score increases, the node will be larger, vice versa if the score decreases, the node will be smaller.

The predictability of each node in the network was also calculated (i.e., nodewise predictability). This measure represents how much variance of the variable is explained by all the other variables with which it is connected. High values of predictability indicate that most of the variance of that variable can be predicted by the variables with which it has direct links. For all these reasons, predictability is an important measure when working in psychopathology. Because this measure gives us an idea of how clinically relevant connections are, it is useful to estimate the potential success of clinical interventions which could thereby effectively guide treatment selection.

For continuous variables, the proportion of explained variance (i.e., R2) was chosen as the measure of predictability: a value of 0 means that the node is not predicted by all neighboring nodes (i.e. all the nodes with which it has connections) in the network, while a value of 1 means that the node can be perfectly predicted by its neighboring nodes.

We analyzed two main measures of centrality: strength centrality and betweenness.

Strength centrality refers to the number of connections a node has: more connections indicate greater importance of the node in the network. In a clinical context, a symptom with many connections in a psychopathological system may be considered a risk factor for the development of other symptoms, while a symptom with fewer connections may be considered more peripheral and less likely to promote worsening of other symptoms. In weighted networks, as in this study, links connecting nodes are no longer treated as binary interactions but are weighted in proportion to the strength of the correlations.

Betweenness is a parameter that measures the involvement of a node in the shortest path between two other nodes. It helps to identify which nodes are more likely to facilitate connections in the network. For example, this measure can be used to identify important domains by examining the connectivity between a patient's problems and symptoms.

The algorithm for calculating "shortest paths" is that of Dijkstra (1959) [42], implemented in R and repurposed by Opsahl, Agneessens and Skvoretz (2010) [43].

In interpreting these indices, bootstrap tests were done to analyze their stability (bootstrapped strength centrality and bootstrapped betweenness). It was done to make sure that central nodes were also so among all the subsamples of the data and whether the centrality of a node remained so in 95% of the bootstrapped subsamples.

Lastly, a cluster holding algorithm was computed in order to explore the differences in connectivity

structure among the three groups from an additional perspective. Clusters of nodes represent more connected subnetworks in a larger network. The cluster identifies a group of nodes that can be affected more rapidly when a node that is part of it changes its state. The walktrap algorithm was used to provide a measure of similarities between vertices based on random walks across the network connections (igraph package) [44] which can capture the community/cluster structure in the graph [45].

The number of clusters identified equals the number of latent factors in each dataset.

Results

Descriptive and Inferential Results

Descriptive analyses are reported for demographic data in the table above (Table 1). Regarding the results at the psychometric tools, there are few significant differences between T0 and T1. Despite an improving trend in almost all psychological tests, only HDRS shows a significant enhancement after the 12-weeks treatment (T1) (from 23,37 to 17,92, p = .001). Regarding homogeneity of variance, Levene's Test showed significance only for HDRS (p = .014), remaining significant also after Welch's correction (p = .007).

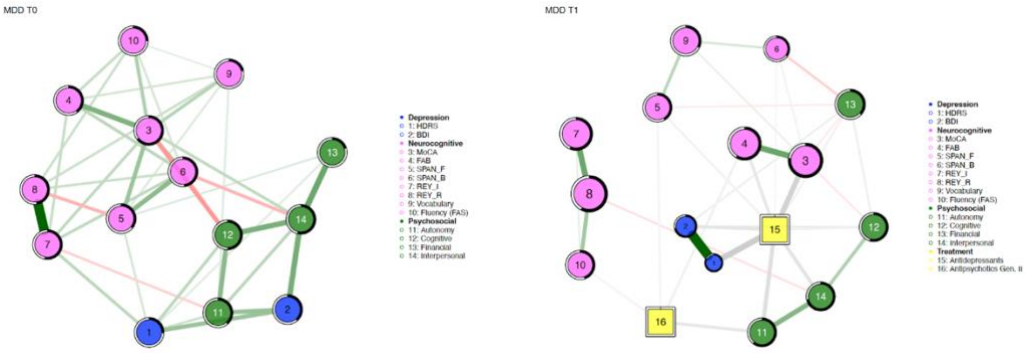

Fig 1: Resulting Networks in MDD sample, at baseline (T0), and after 12 weeks of treatment (T1).

Left side - round nodes: continuous variables; lines between nodes: partial correlations between variables (thicker the edge, greater the correlation value); green edges: positive correlations; red edges: negative correlations; Around each node the predictability value was represented by a ring, the blacker the ring, the more predictable the variable by all connected nodes.

Right side - in addition to above, square node: categorical variables; gray edge: partial correlations between dichotomous and continuous variables

Network Analysis results

At the baseline, the network of MDD (Fig. 1 - left side) patients show neurocognitive and psychosocial as separated 'dimensions' [46]. The latter also includes the two nodes assessing depression, HDRS (1) and BDI-II (2).

Moreover, the network is well interconnected (number of edges = 39; density index = 0,42). This suggests that there is suboptimal stability because modification of a single node results in changes that easily spread to the rest of the network [47].

As for the centrality analysis, considering particularly "Betweenness" (Fig. 2 - blue line), the two nodes with the highest values and thus being the main conduit of information passing within the network are MoCA (3) (1.00) and Interpersonal (14) (0.69). Regarding, indeed, "Strength centrality", MoCA (3) (1.00) is the node with the highest number of connections, representing the most important node driving the whole network.

Interestingly, nodes assessing affective symptoms such as depression (BDI-II and HDRS) do not have a great influence on the network per se.

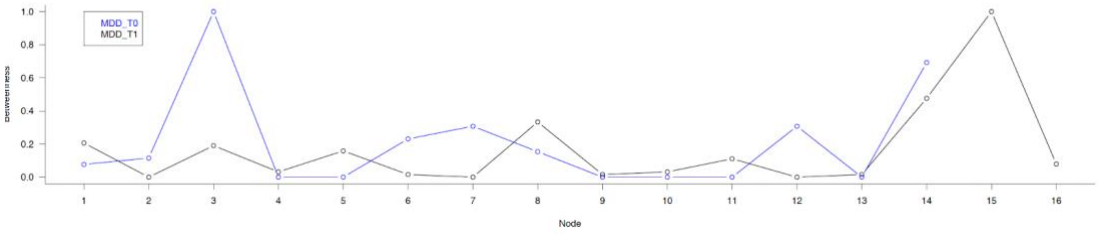

Fig 2: Betweenness index in MDD sample at T0 and T1

At follow up (T1) (Fig. 1 - right side), after 12 weeks of pharmacological treatment, the network of MDD patients significantly changes. The network shows less interconnection between nodes (number of edges = 34; density index = 0,28) than T0, providing us with feedback of greater stability (and less tendency to change) once drug treatment is introduced.

Analyzing the measures of centrality, and considering once again the betweenness (Fig 2 - black line), the node with highest value and, hence, the main information transmission pathway within the network is Antidepressants (15) (1.00).

Furthermore, Antidepressants (15) is also the node with the major strength centrality index (1.00) (Fig 3 - black line), representing the node with the highest numbers of connections and, hence, the one that drives the network.

Moreover, it is possible to highlight the change in size of the two depressive assessment nodes (1) and (2). This means that the scores have decreased at T1 with the treatment introduction. A decrease of HDRS (1) and BDI-II (2) scoring denotes an improvement in affective symptoms. Despite this, only variance between T0 and T1

for HDRS is statistically significant (T0: *mean* = 23,37; *sd* = 6,90; T1: *mean* = 17,93; *sd* = 9,20; *ANOVA:* p = .001).

Additionally, taking into account predictability, HDRS (1) has a percentage of variance explained by the other variables with which it has connections (BDI-II (2) and Antidepressants (15)) equal to 83,2% (R2 = 0.832), while BDI-II (2) has it at 71,5% (R2 = 0.715).

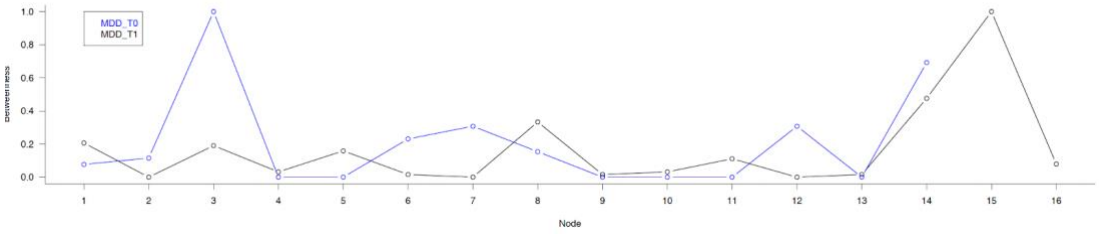

Fig 3: Strength centrality index in MDD sample at T0 and T1

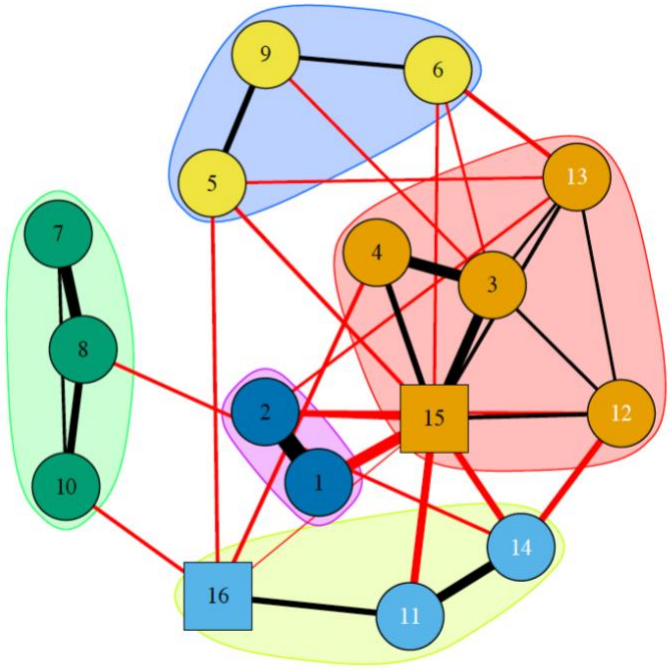

Fig 4: Clusters in MDD sample at T1

Analyzing clusters, the walktrap algorithm used reports the presence of 5 distinct clusters (Fig. 4).

The first, dark blue, includes some neurocognitive variables (5: SPAN_F; 6: SPAN_B; 9: Vocabulary), particularly which involve specifically memory and language. The second, in green, includes other neurocognitive variables (7: REY_I; 8: REY_R; 10:

Fluency (FAS)) which also involve memory and language. A third cluster became evident, in purple, including all affective variables. Fourth, an orange cluster is evident, including two neurocognitive variables, in particular global cognitive node (3: MoCA) and executive functioning node (4: FAB), two psychosocial variables, especially cognitive (12) and financial (13), and Antidepressants node (15). Finally, a last cluster has been identified in yellow, including remaining psychosocial variables, such as Autonomy (11) and Interpersonal (14), and Second Generation Antipsychotics (16).

Discussion

MDD is a complex and heterogeneous mental illness characterized by affective, cognitive, and psychosocial symptoms.

In clinical practice, antidepressant drugs such as SSRIs and SNRIs are effective for most depressed patients, even if in accordance with scientific evidence, 10%-30% of patients with MDD show a partial response to pharmacological treatments and an increased risk of relapse. Recommendations from clinical practice guidelines suggest several strategies to improve the treatment for partial or no responders such as adjusting the drugs dosage considering age of patients, concomitant pathological conditions and side effects induced by the antidepressant drug used, or drug replacement and/or augmentation strategies with antipsychotics [20].

In order to grasp the multifactoriality of MDD, several psychometric tools are available and used in clinical practice as can be evident from the psychometric protocol employed in the present study. Therefore, the introduction of a new statistical method as NIA can help to identify how symptoms interplay, which of them may be targeted for selective intervention and have the greatest impact on overall symptom severity, overcoming the limit of low significance that traditional statistical analyses have provided us.

The purpose of this observational study is to highlight the strengths of the NIA, in order to identify the interaction and changes in network nodes and connections of 14 continuous variables with nodes identified as “Treatment” in MDD.

Analyzing the network of MDD at baseline, neurocognitive and psychosocial domains appear as separated ‘dimensions’ [46]. Despite the whole network is well interlinked, the affective cluster is highly connected with the psychosocial one, it has very few and weak connections with the cognitive domain. Our data agree with evidence coming from many recent studies suggesting that cognitive dysfunction represents a distinct

biological and clinical dimension in MDD, independent from affective symptoms, which strongly affects psychosocial functioning [48–51].

It is also well known that cognitive symptoms could be considered among the most relevant residual symptoms in MDD patients compromising patients working and might predict the low rate of response to antidepressant drugs [52].

In the network at baseline, the key role of cognitive symptoms in MDD is further highlighted by the high strength centrality index of MoCA. It represents the node with the highest number of connections, driving, hence, the whole network. In addition to this, MoCA is the node with the highest betweenness index, that is it is the main conduit and facilitator of information passing within the network. Our results suggest that MoCA might represent a novel and interesting psychometric tool for a better evaluation of cognitive deficits in MDD and to monitor the clinical response to pharmacological and non-pharmacological treatments [14,53].

When considering the strengths of the NIA method, it is interesting to observe how the network changes after including a 12-week drug treatment as a categorical variable.

At follow up, the network of MDD patients significantly changes. First of all, there is no longer a marked distinction between the cognitive and psychosocial-affective clusters. Additionally, the network shows less interconnection between nodes than T0. According to Cramer et al. (2016) [47] a lower interconnected network is more stable and less vulnerable to change. So greater stability results once drug treatment is introduced with antidepressant drugs.

Pharmacological treatment, especially Antidepressants, take a central role in driving the network. Antidepressants node is, in fact, the one with the highest betweenness and strength centrality indexes, representing the main information transmission pathway within the network and the most connected node.

Moreover, at follow up (T1) it is evident an improvement of affective symptoms, demonstrated by reduction size of HDRS and BDI-II nodes. Along this line, it is interesting to observe that affective nodes are just those with higher levels of predictability. These data suggest that most of the variance of HDRS and BDI-II nodes can be predicted by the variables with which they have direct connections, in this case Antidepressants node.

Limitations

This study has some limitations: the first limitation concerns the number of patients that completed the follow-up. Given the observational nature of the present study, it was problematic to recruit a larger sample, but in future studies it would be essential to enroll a larger number of MDD patients with a recent history of partial response to antidepressants to achieve more relevant results. The last limitation certainly concerns the sampling method, which in this case is non-probabilistic. The patients were all recruited within the same psychiatric clinic unit, which is why the variability of the sample is not so high. Multicentric observational studies might be essential to increase clinical variability.

Conclusion

To conclude, NIA allows us to understand not only what symptoms enhance after pharmacological treatment, but especially the role it plays within the network and with which nodes it has stronger connections. Moreover, NIA can help identify specific symptoms that may be targeted for intervention, as well as potential pathways for intervention that may have the greatest impact on overall symptom severity. Some scientific papers have found out that NIA could also help to better understand how effective psychotherapy interventions enhance mental disorders symptomatology [24,25].

NIA represents a promising new approach to understanding and treating complex mental disorders like MDD.

Declarations

Ethics approval and consent to participate

Patients were recruited at the Psychiatric Clinic "Villa dei Gerani" (Catania, Italy). All patients received oral and written information on the planned use of the data and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The study was approved by the ethical committee of the "Azienda Sanitaria Provinciale 3 (ASP3) of Catania of which the "Villa dei Gerani Clinic" (clinical coordinator of the study) is part (Approval date of the extended study July 24, 2012). The study met the ethical administrative requirements under Italian legislation in force when the study's administrative process started (03.06.2012) according to CM 6 02.09.2002, GU 214 12.09.2002 and D 29.03.2008 of the Italian Medicine Agency

(Agenzia Italiana del Farmaco, AIFA) and GU 76 31.03.2008, Art 10 (Procedures for Observational Studies).

Consent for publication

Not applicable

Availability of data and materials

The data supporting the findings of the article are available in the medical records of ASP3 Catania-Villa dei Gerani Clinic and can be shared according to the policy's of this institution and the Italian Law on privacy 679/2016.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors contributed to the study design. C. S. Guerrera, G.A. Platania, P. Sarti and J.M.C. Blom, performed the data analysis; F.M. Boccaccio helped with the interpretations of the results and all authors contributed to the writing of the manuscript. S. Castellano and F. Caraci supervised the study. All authors approved the final version of the paper for submission.

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General discussion

MDD and BD are among the most debilitating and prevalent mental disorders, often leading to significant functional impairment.

Patients with MDD or BD constitute an extremely heterogeneous disease, and the identified risk factors lack the capacity to distinguish individual trajectories. Additionally, no single treatment modality has proven to be truly effective in preventing relapses or worsening of symptoms. Currently, research indicates that the deeply ingrained traditional categorical approach, which links only one or a few individual mediators (often molecular or biological) to an illness-related phenotype, has provided limited understanding of the complex underlying pathological conditions. Moreover, this traditional approach has frequently hindered progress in the development of personalized and more effective treatments.

Based on this, a paradigm shift is needed to better understand the specific evolution of the clinical pattern of different patient populations over time. The dynamic network approach, incorporating various realms of function such as neurocognitive dysfunction and biomarkers, offers a more realistic representation of patients' psychosocial strengths and needs. Network analysis has gained interest in contemporary psychopathology as it studies relationships between symptoms and their triggers, revealing underlying relationships common to multiple psychiatric disorders.

Considering that Major Depressive Disorder and Bipolar Disorder are often misdiagnosed, network analysis can be a valuable tool to improve diagnosis and treatment. The dynamic organization of different functions in interdependent networks highlights the differences between Major Depressive Disorder and Bipolar Disorder, enhancing the accuracy of the differential diagnosis. There are still few studies in the literature that have used this methodology to compare Major Depressive Disorder with Bipolar Disorder. Among them, the study by A. et al. investigated the cognitive dimension, demonstrating that BD patients had a less connected network compared to MDD patients, with a more central role of executive dysfunction in BD and a key role of memory impairment in MDD.

In the present PhD thesis, I have applied the innovative statistical method of network analysis to examine the detailed phenotypes of MDD and BD, revealing their dynamic relational patterns over time and differences in symptom connections. This analysis allowed for the identification of key factors and provided insights for a more effective

pharmacological treatment in MDD and BD. Specifically, the study results revealed significant clinical differences between unipolar depression and bipolar depression at both baseline (T0) and after twelve weeks of pharmacological treatment (T1). In both MDD and BD, the findings emphasize the importance of prioritizing treatment targeting cognitive symptoms, as improving this domain appears crucial for overall better outcomes and advancements in other areas.

In patients with MDD, we observed a strong connectivity between psychosocial function and the affective domain, while direct connectivity with the neurocognitive domain was absent. The cognitive-affective evaluation acted as a bridge between the psychosocial and neurocognitive domains, with no direct connection observed between the affective and cognitive realms. These findings align with recent evidence suggesting that cognitive dysfunction represents a distinct biological and clinical dimension in MDD, independent of affective symptoms. Psychosocial competence and depressive symptoms appeared as separate entities in MDD, whereas cognitive functions with frontal affinity constituted another distinct dominion with specific clinical phenotypes.

On the contrary, the network of patients with BD showed a highly interconnected cluster of psychosocial nodes driven by neurocognitive functions. However, the correlations among these neurocognitive functions were weaker. In both MDD and BD, the affective domain demonstrated lower connectivity and was positioned at the periphery of the networks, indicating a less central role in the overall network.

In conclusion, our study findings suggest that tailored cognitive therapy should be an integral part of the treatment plan for MDD, as improvement in this central domain appears fundamental for better outcomes in other domains. For BD, a comprehensive treatment approach involving both pharmacological and non-pharmacological interventions may lead to improvements in other areas due to their pivotal role in driving positive change.

Additionally, through the Network Intervention Analysis (NIA), it was possible to monitor changes in interdependencies and symptom configuration over time, following pharmacological treatment on various symptoms of the disorder. This second study investigated the alteration of the network structure in patients with Major Depressive Disorder (MDD) and Bipolar Disorder (BD) separately, at baseline and at follow-up after a 12-week pharmacological treatment. The baseline MDD network revealed separate "dimensions" for neurocognitive and psychosocial domains, with the

affective cluster showing strong connections with the psychosocial domain, but weak connections with the cognitive domain. Cognitive dysfunction in MDD was identified as a distinct dimension, independent of affective symptoms, significantly impacting psychosocial functioning and predicting poor response to antidepressant drugs. The MoCA node, representing cognitive deficits, played a central role in the baseline MDD network. After the 12-week pharmacological treatment, the MDD network at follow-up showed significant changes, with fewer interconnections and no clear distinctions between cognitive and psychosocial-affective clusters. Antidepressants played a central role in driving the network at follow-up, with the antidepressant's node being the primary pathway for information transmission. The BD network at baseline exhibited distinct "worlds" for neurocognitive and psychosocial domains, suggesting potential resistance to change in the neurocognitive domain. Global cognitive functions assessed by MoCA and frontal executive capacities assessed by FAB acted as bridges between the neurocognitive domain and psychosocial-affective domains. The nodes with the highest betweenness, MoCA and FAB, played critical roles in information transmission, with FAB standing out as the primary node driving the network. At follow-up, the BD network underwent significant changes, with mood stabilizers playing a central role in driving the network. Global cognitive functions (MoCA) and affective symptoms (HDRS) also played key roles. The improvement in affective symptoms was supported by the decrease in HDRS and BDI-II scores, confirmed by ANOVA analysis. MoCA mediated the change in HDRS, while the variance in BDI-II score was partially explained by weak direct connections with mood stabilizers and Second-Generation Antipsychotics. The study findings provide insights into the network structures of MDD and BD, shedding light on potential therapeutic targets and the effects of pharmacological treatments on symptom improvement. Further research in this area could enhance our understanding of these complex mental illnesses and aid in the development of more targeted and effective interventions.

Concluding remarks

In the present PhD thesis, I have conducted a comprehensive overview of the current understanding of Major Depressive Disorder (MDD) and Bipolar Disorder (BD) and emphasized the need for a paradigm shift in their diagnosis and treatment with novel psychometric strategies and novel tools. The traditional categorical approach has limitations in capturing the heterogeneity and complexity of these disorders, making it challenging to identify individual trajectories and effective treatment modalities.

In the present PhD thesis, I have demonstrated that the dynamic network approach, using network analysis, emerges as a promising method to study the relationships between symptoms and their triggers, offering a more realistic representation of the complex dynamic interaction between the different symptoms characterizing depressive disorders. By incorporating various realms of function such as neurocognitive dysfunction and biomarkers, this approach helps to better understand the specific evolution of clinical patterns in different patient populations over time.

The research conducted during my Ph.D. was based on the application of the innovative statistical method of network analysis to examine the specific clinical phenotypes of MDD and BD, revealing their dynamic relational patterns and differences in symptom connections. Our findings suggest that cognitive dysfunction plays a distinctive and key role in MDD, independent from affective symptoms, and should be a focal point in personalized cognitive therapy. On the other hand, BD patients showed a highly interconnected cluster of psychosocial nodes driven by neurocognitive functions, with the affective domain playing a less central role.

Finally, the Network Intervention Analysis (NIA) allowed monitoring changes in interdependencies and symptom configuration over time following a 12-week pharmacological treatment. This analysis provided insights into new potential therapeutic targets and the effects of pharmacological treatments on symptom improvement both in MDD and BD.

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