Università degli Studi di Genova
Genoa University

Scuola di Scienze sociali
School of Social Sciences

DISFOR Dipartimento di Scienze della Formazione

CORSO DI LAUREA IN

PSICOLOGIA

TITOLO DELLA TESI

RELATIONSHIP BETWEEN AUTOIMMUNE THYROIDITIS AND BIPOLAR DISORDER: A SYSTEMATIC LITERATURE REVIEW

Relatore: Prof. Gianluca Serafini

Correlatore: Andrea Brugnolo

Candidato: Beatrice Bilucaglia

ANNO ACCADEMICO

2023/20

Table of contents

Introduction

This work focuses on the analysis of the relationship between Hashimoto's thyroiditis, a specific type of autoimmune thyroiditis, and bipolar disorder, a severe psychiatric disorder characterized by alternating depressive and manic or hypomanic phases (episodes of excessively elevated, expansive, or irritable mood). The connection between bipolar disorder and one of the possible complications of thyroiditis, Hashimoto's encephalopathy, a severe condition characterized by acute, sub-acute, or chronic brain distress, likely of autoimmune origin with extremely high levels of antithyroid antibodies, is also significant. These clinical conditions are distinct, but recent studies suggest a potential link between them.

The decision to delve into this interconnection between the two disorders stems from the growing awareness of the significant impact autoimmune diseases can have on the psyche of each individual (and viceversa), due to specific mechanisms involved in the development of these conditions, such as chronic inflammation.

Furthermore, an important motivation for this thesis concerns the clinical need to improve the understanding of this relationship, as many patients with mood disorders have undiagnosed or improperly recognized thyroid dysfunctions. Awareness of this interaction could ensure early interventions and better, more personalized treatments for each patient.

The aim of this thesis is, therefore, to analyze the available literature with a critical and systematic approach to firstly assess the presence of an association between bipolar disorder and Hashimoto's thyroiditis, considering various pathophysiological aspects, such as the interaction between the immune system and the nervous system, genetic components that may increase the risk of developing these conditions, and the body

inflammation generated by thyroid autoantibodies in cases of autoimmune disease. Once the presence of such a relationship between the conditions is established, this thesis seeks to promote greater awareness among healthcare professionals, such as psychologists, about the significance of the comorbidity between autoimmune and psychiatric disorders on patient health. This approach could offer new therapeutic perspectives, enhancing the well-being and clinical management of patients affected by both conditions.

The thesis was conducted as a systematic review of the literature available on the main search engines of the University of Genoa, such as PubMed and Web of Science. The research was conducted by entering a string into the databases; it required that only articles simultaneously citing autoimmune thyroiditis (with particular reference to Hashimoto's thyroiditis and encephalopathy) and bipolar disorder were considered, excluding all reviews and meta-analyses. Once this work was completed, the most significant studies were included in a table analyzing the sample size, the type of antithyroid antibodies or markers for hypothyroidism used by the authors, the thyroid issue found in the sample, and the type of study used.

One of the main strengths of the work lies in the methodological approach used for the selection and study of the literature, which allowed for a critical and precise analysis of the available information. This thesis aims to provide the practical relevance of the clinical implications derived from the results.

The conclusions drawn from the review will be presented in detail in the final chapter.

1. Bipolar disorder

Bipolar disorder (BD) is a psychiatric disorder that causes a wide variety of symptoms, particularly alternating between depressive and manic manifestations. The emotions experienced by the patient are very intense and exaggerated, as well as being largely unpredictable. Usually, it manifests itself in late adolescence or early adulthood (from about 18 to 30 years of age) and recurs throughout life; generally, however, it intensifies with advancing age (Johnson, S. L. et al, 2013). It is estimated that about 1-4% of the population may suffer from this disorder. BD is present almost equally between men and women, but with slight differences: for example, in female subjects, the age of onset of the disease would be older and there would be a greater number of depressive episodes than manic ones (Pillai, M., Munoli, R. N., Praharaj, S. K., & Bhat, S. M., 2021).

The patient may experience periods of high or highly irritated mood, high energy, hypertrophic self-esteem, excessive involvement in potentially risky activities, psychomotor agitation, flight of ideas, more talkativeness and decreased need for sleep (in this case, we speak of mania, or hypomania), alternating with periods of extremely low mood, lack of energy, suicidal thoughts and low self-esteem.

There are differences between mania and hypomania: in particular, we speak of mania when the symptoms last at least a week and are very serious, so much so that they significantly hinder the patient's life, both from a social and work point of view. In addition, if mania is present, it is much more likely that the subject may resort to self-harm or behavior that is dangerous to himself and others. The manic episode could be very intense, so much so that it causes psychotic episodes, pantoclastic crises or conditions that require hospitalization of the patient himself. On the contrary,

hypomania is defined as a condition in which the subject has a high mood and an increase in his activity that lasts at least four days, but with less severe symptoms than manic episodes. The social functioning of the individual, therefore, is not so compromised. Finally, dangerous behaviors are less frequent than those of manic patients and delusions or other psychotic symptoms are not usually present. (Parker G., Graham R. et al, 2013)

Depending on the clinical manifestation, two different types of bipolar disorders can be found, bipolar I disorder (BD-I) and bipolar II disorder (BD-II).

The diagnosis of BD-I is confirmed with at least one manic episode, alternating with a depressive or hypomanic episode. The diagnosis of BD-II requires at least one major depressive episode and one hypomanic episode, but no manic or mixed episodes have ever been present. In this type of disorder, depression prevails, so patients have more depressive symptoms than hypomanic ones: because of this, hypomanic patients are more likely to have a misdiagnosis and be treated as patients with major depression (about 12% of BD-IIs) (Datto, Pottorf, Feeley, et al., 2016). It is more frequent in women.

It is also necessary to analyze depressive and manic episodes with mixed characteristics, in which counter polar symptoms occur simultaneously.

The first to describe mixed states in bipolar patients was Emil Kraepelin (1989), speaking of "manic-depressive psychosis", which was initially distinguished from Schizophrenia for a more favorable prognosis, but which was later taken into consideration as a different psychopathological entity.

Currently, five types of mixed bipolar disorder are distinguished:

1. Agitated depression: it is characterized by depressed mood and great restlessness, which causes greater suicidal ideation;
2. Logorrheic depression: the subjects are verbose and with an anxious mood and the ideational contents take place on a melancholic theme.
3. Auto sarcastic depression: the mood is a mixture of sadness and euphoria, of fear and arrogance, with auto sarcasm (gallows mood);
4. Manic stupor: the mimicry is euphoric, but the subject remains motionless;
5. Oligoid mania: the mood is euphoric, but ideic overproduction is not present, so subjects often repeat the same phrases (this denotes unproductivity of thought) (Maina, G., Bertetto, N., DOMENE BOCCOLINI, F., DI SALVO, G., Rosso, G., & Bogetto, F., 2013).

	Mood	Motor activity	Ideation
1. Depressive mania	-	+	+
2. Excited depression	-	+	-
3. Unproductive mania	+	+	-
4. Manic stupor	+	-	-
5. Depression with flight of ideas	-	-	+
6. Inhibited mania	+	-	+

Figure 1: the table shows the mixed states as they were identified by Kraepelin, emphasizing the typical characteristics of each disorder, highlighting mood, motor and ideic activity. Maina, G., Bertetto, N., DOMENE BOCCOLINI, F., DI SALVO, G., Rosso, G., & Bogetto, F. (2013). The concept of mixed state in bipolar disorder: from Kraepelin to DSM-5. Journal of Psychopathology, 19, p.288.

In the updated Diagnostic and Statistical Manual of Mental Disorders (DSM-5- TR), the definition of "mixed episode" has been removed and a "mixed-characteristic" specifier applied to manic episodes and major depressive episodes (MDEs) presenting with subthreshold symptoms of the opposite pole is used in their place.

Mixed bipolar disorders would also be more frequent in women and would be associated with a worse prognosis as well as a greater risk of suicide. (Solè E., Garriga M. et al., 2016).

Bipolar disorder is placed, within the DSM-5-TR, as a "bridge" category between schizophrenia and other psychotic disorders and depressive disorders due to its symptomatology and genetic component. To speak of a manic episode, the DSM imposes the presence of persistently elevated, expanded or irritable mood with at least four (three if irritable mood) of the following symptoms.

1. Increased self-esteem;
2. Reduced need for sleep;
3. Logorrhea;
4. Accelerated thinking and a flight of ideas;
5. High distractibility;
6. Increase in purposeful activities or psychomotor agitation (which has no purpose, especially at inappropriate times, such as during the night);
7. Excessive involvement in potentially risky activities, such as spending a large amount of money, having promiscuous sexuality, etc.

To differentiate the manic episode from the hypomanic one, criteria are used for time (the former lasts at least seven days, the latter at least four days) and severity (the manic episode is more severe and often requires hospitalization, while the hypomanic one can also be managed without hospitalization).

In addition to manic or hypomanic episodes, bipolar disorder is also characterized by depressive episodes. The DSM-5-TR defines them for the presence for at least fifteen days of at least five of these criteria:

1. Depressed mood most of the time;
2. Anhedonia;
3. Significant weight loss (or gain);
4. Insomnia or hypersomnia;
5. Agitation or psychomotor retardation;
6. Lack of energy;
7. Guilt or ineffectiveness;
8. Lack of concentration;
9. Suicide attempt/suicide.

Specifiers of the disorder can be combined with the diagnosis to provide details about the severity and manifestation of the disease. It should be noted:

1. Specifiers of severity, ranging from mild to severe. These indicate the level of severity of the disease, understood as the number of symptoms of the patient and the degree of interference with the patient's daily life;
2. Type of disorder: indicate whether it is a bipolar disorder with multiple manic, hypomanic or major depressive episodes;
3. Specifiers of the course of pathology: The disorder can be relapsing, therefore presenting itself in the form of recurrent episodes, or cyclical, with patients presenting with manic, hypomanic or depressive episodes that follow one another frequently;
4. Content: indicates whether the patient has features of mixed bipolar disorder or with psychiatric features, such as delusions;
5. In addition, it can be indicated whether the patient should be in partial remission, with improved symptoms, but not disappeared, or in complete remission, with symptoms no longer present (American Psychiatric Association, 2013).

Specifiers are very useful for understanding how the patient works, so as to improve treatment, in order to make it as personalized as possible (McIntyre, R. S., & Calabrese, J.R., 2019).

Other disorders related to bipolar disorder are cyclothymic disorder, bipolar disorder and related disorders with another specification, bipolar disorder and related disorders without other specification, bipolar disorders caused by another medical condition or caused by a drug condition. In particular, cyclothymic disorder is a condition characterized by a chronic and fluctuating mood alteration, which presents numerous phases with depressive or hypomanic symptoms, which, however, do not fully meet the criteria for depressive or hypomanic episodes.

According to the DSM-5-TR, the main features of cyclothymic disorder are:

1. High mood and excessive optimism in hypomanic phases, with characteristics similar to bipolar disorder, but with less intense manifestations;
2. During depressive phases, the presence of sadness, despair and apathy, but with milder intensity, so much so that it is not possible to diagnose the presence of a major depressive episode.

For the diagnosis of cyclothymic disorder, symptoms must last for at least two years in adults; If there are symptom-free periods, they should not last more than two consecutive months. (American Psychiatric Association, 2013).

As already mentioned, although mood can be so altered that it significantly affects patients' lives, generally the level of functioning remains high, but the risk of developing complete bipolar disorder later remains high. Sometimes, in fact, cyclothymia can be considered the precursor for the development of forms of bipolar disorder or other mood disorders (Alloy, L. B., & Abramson, L. Y., 2010).

Bipolar disorders with another specification indicate all those symptoms that do not fully meet the previously mentioned criteria for bipolar disorder. To fall into this category, the specialist must communicate the reason why the patient does not fully meet the criteria for bipolar disorder (otherwise, if the reason is not specified, it is called bipolar disorder without any other specification).

Bipolar disorder induced by drugs/substances is characterized by an alteration in mood due to intoxication or, on the contrary, by withdrawal from psychotropic substances, or as a consequence of taking drugs.

Finally, if bipolar disorder occurs due to another medical condition, mood appears elevated or, conversely, highly irritable, and this change in mood is caused directly by an underlying organic condition.

Bipolar disorder, in all its manifestations, is characterized by the euphoric nature of mood and is characterized by a strong enthusiasm for interpersonal interactions, especially sexual, or work. Subjects show high sociability, sometimes even very intrusive (Dempsey, R. C., Dodd, A. L., Gooding, P. A., & Jones, S. H., 2024).

Bipolar disorder has comorbidities with many other psychiatric disorders, such as substance abuse (particularly alcohol, drug abuse and smoking) and anxiety disorders. It is quite difficult to determine whether these conditions are separate from bipolar disorder, as they could be risk factors for the development of the disorder, prodromal expressions of the disease, or bipolar subtypes (Salagre, Dodd, Aedo, et al., 2018).

Hypothesis pathogenesis bipolar disorder

From an etiological point of view, there would be specific genetic markers that would activate the disorder, many of which would be in common with those of other disorders, such as major depression and schizophrenia (Gordovez, F. J. A., & McMahon, F. J., 2020). Despite the various advances made, even today the genetic risk of bipolar disorder is difficult to analyze with certainty; With current knowledge, it is estimated that the probability that the close relatives of a subject with bipolar disorder also suffer from the disorder is around 10-15%, while studies on twins would affirm a heritability of the disorder of 70-90%. To genetically study bipolar disorder, genetic markers closer to those genes responsible to produce specific proteins, such as the serotonin transporter, were sought, but this was not effective, probably due to the difficulty in finding those proteins most involved with bipolar disorder. The most effective strategy to study borderline genetics has been Genome-wide association studies (GWAS), a technique whereby genetic markers are studied and then analyzed to assess their association with a given trait (Gordovez, F. J. A., & McMahon, F. J., 2020). With this technique, at least three genes would have been associated with bipolar disorder with the study by Gordovez and McMahon (2020): firstly, ANK3, which would be attributed to the coding of a protein used for axon myelination, especially in brain structures.

Another gene would be CACNA1C, which would encode for a voltage-gated ion channel, important for neuronal development and synaptic signaling.

Finally, TRANK1 would encode for a protein that is also widely present in brain tissues and would also play an important role in maintaining the blood-brain barrier.

Recent research states that bipolar disorder is a neuroprogressive disorder; This means that the disease could cause neuropsychological problems, especially in the

advanced stages of the disorder, but it would be preceded by a prodromal phase, in which the symptoms would be present, but in an extremely reduced form. Salagre, Dodd, Aedo et al. (2018), taking up the studies of Kapczinski et al. (2009), cited the genetic-environmental model (i.e., the genetic component of the individual influences how he interacts with the environment in which he lives) to explain the etiology of the disorder: a genetically more vulnerable subject, therefore, would have a greater risk of developing the disease. The same authors, thanks to neuroimaging studies, discovered a reduction in gray matter in patients with bipolar disorder. Also, thanks to neuroimaging techniques, it is noted that subjects with bipolar disorder manifest an enlargement of the white matter, with cortical lesions (Salagre, Dodd, Aedo, et al., 2018). In addition, it is shown that people with bipolar disorder have less gray matter in the hippocampus and cerebellum, reduced volume in the prefrontal cortex, and an increase in size in the amygdala. The anterior cingulate and ventrolateral prefrontal cortex are also affected by the disorder.

Thanks to functional magnetic resonance imaging (fMRI) studies, several areas fundamental for the development of mood disorders such as bipolar disorder have been discovered: in particular, abnormalities would be present in the areas corresponding to the ventromedial and ventrolateral prefrontal cortex, the orbitofrontal cortex, the anterior cingulate and the amygdala; the instrument would also reveal an abnormal activation of the reward circuit in the bipolar, controlled by the dopamine circuit (Wu, Y., Su, Y. A., Zhu, L., Li, J., & Si, T., 2024). The prefrontal cortex and amygdala would be modulated by serotonin.

The circuits of norepinephrine, serotonin and dopamine are involved in mood disorders; The first neurotransmitter is a catecholamine released by the sympathetic

nervous system that mediates the "fight or flight" response and is associated with the regulation of various functions, such as sleep, memory and emotions.

Serotonin, on the other hand, is present in every neuron of the nervous system and influences the transmission of all other neurotransmitters. It is also present in the cells of the gastrointestinal tract and in the raphe nucleus, in addition to the hippocampus, the corpus callosum, the thalamus, the hypothalamus, the nucleus accumbens and in the frontal cortex.

Dopamine is involved in the reward mechanism and is present in the cortex, midbrain, and diencephalon. The dopaminergic pathway includes the mesolimbic and mesocortical pathways, which appear to control emotion-influenced behavior.

Mood disorders would also be determined by monoamines, as changes in the presence of monoamines in the central nervous system could lead to a worsening of symptoms. Therefore, mood disorders could also be caused by neurotransmitter receptors: a reduction in the neurotransmitter, in fact, leads to a compensatory regulation of the post-synaptic, but this may not happen, following problems at the molecular level, in particular in the transduction of the signal and the gene expression most suitable for that signal (Pasquini, M., Berardelli, I., & Biondi, M., 2014).

In addition, as stated by Muneer (2017), several studies have also been carried out investigating the importance of the main neurotransmitters involved in mood disorders: serotonin, norepinephrine and dopamine. It has been noted that bipolar patients treated with tricyclic antidepressants tend to have an increase in the frequency of manic and hypomanic episodes in about 70% of cases; This would be a cause of the very functioning of antidepressants. These drugs, in fact, would be more focused on the reabsorption of serotonin and norepinephrine in the post-synaptic terminal and the

two neurotransmitters at the same time would seem to cause a higher frequency of manic and hypomanic episodes than specific drugs for serotonin reabsorption (Muneer A., 2017). The same happens when drugs are used that act on both blocking the reabsorption of dopamine and norepinephrine together. Increasing synaptic levels of norepinephrine and dopamine, therefore, would significantly increase both manic and hypomanic episodes and also the conditions of mixed states.

Increased dopamine and norepinephrine would also cause an increase in manic episodes (Muneer A., 2017).

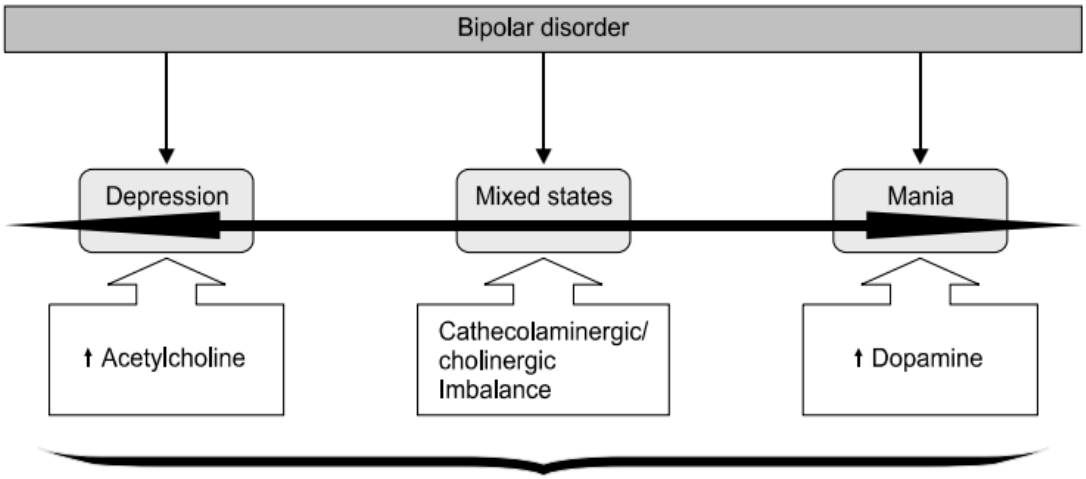

Figura 1: The figure shows the problems in the bipolar patient associated with neurotransmitters: an increase in acetylcholine would increase depressive states, while mania would be determined by an excess of dopamine. Mixed states of the disorder would be associated with an imbalance of catecholamines. Muneer, A. (2017). Mixed states in bipolar disorder: etiology, pathogenesis and treatment. Chonnam medical journal, 53(1), p. 5.

In addition to this component, the effects of neuroinflammation on the development of bipolar disorder, particularly the importance of autoantibodies, are increasingly being studied. These, if the blood-brain barrier were damaged, would be able to penetrate it very effectively, causing damage to the brain (Gur, S., Taler, M., Bormant, G., Blattberg, D., Nitzan, U., Vaknin-Dembinsky, A., et al., 2020). This was discovered thanks to the post-mortem analysis of the prefrontal cortices of patients with

depression and bipolar disorder: in their cortices, in fact, alterations in the expression of the AQP4 gene, responsible for body immunity, would have been found (Gur, S., Taler, M., Bormant, G., Blattberg, D., Nitzan, U., Vaknin-Dembinsky, A., et al., 2020).

As previously stated, the genetic component is also essential to develop the disorder, with a 60-80% probability that a person with bipolar disorder has other cases of the disease in the family.

Therapy.

From a pharmacological point of view, bipolar disorder is mainly treated with mood stabilizers, in particular lithium, often with a combination of several drugs, also due to the high resistance to treatment. This is because medications for bipolar disorder must reduce acute episodes of mania and depression, but also be effective in preventing them from occurring (Jiang, X., Mio, M., Dimick, M. K., Zou, Y., Sultan, A. A., & Goldstein, B. I.. 2022). The first improvements with the treatment are already noticeable after two weeks, although lithium shows its full effect from 3-4 weeks.

Lithium is the primary treatment for bipolar disorder. In particular, it is used for the management of acute and mixed manic episodes and in maintenance treatment in patients 7 years of age and older (Chokhawala, K., Lee, S., & Saadabadi, A., 2022).

Lithium influences the level of serotonin, dopamine and norepinephrine in the brain, thus stabilizing mood and preventing manic and depressive peaks (Hart, D. A., 2024). In addition, it would stimulate the proliferation of adult neural progenitor cells, likely causing increased neuronal resilience during episodes of the disorder and an increase

in neural proliferation (Wolter, J. M., Le, B. D., Matoba, N., Lafferty, M. J., Aygün, N., Liang, D., et al., 2023).

Lithium is usually administered orally. Because many patients experience only a partial reduction in symptoms, it is important to monitor plasma levels of the drug and adjust the dosage accordingly. The recommended dosage for adults is 600 mg, administered 2 to 3 times a day, so as to reach a serum lithium concentration of 0.8 to 1.0 mEq/L. Maintenance therapy should also be between 300 and 600 mg in order to maintain serum lithium concentrations between 0.8 and 1.0 mEq/L. Treatment should be closely monitored and tailored to the patient's specific needs, such as disease progression, kidney function, and the age group the subject is in (Chokhawala, K., Lee, S., & Saadabadi, A., 2022).

Defining with certainty how the patient will react to lithium surgery could be quite complicated, but there are some factors that can indicate a better response to the drug. A strong predictor is family history, since if first-degree relatives with bipolar disorder have responded well to therapy, the patient is also more likely to respond positively to the drug. This factor indicates genetic influence: in particular, genes related to sodium transport and serotonin metabolism would seem to play a fundamental role in the positive response to lithium (Rybakowski, J. K., 2014). Another important predictor is the well-defined episodic course (i.e., distinct manic and depressive episodes); on the contrary, if the patient has mixed episodes, the response to the drug is less favorable. Rapid cyclicity is also associated with lower efficacy of lithium. Another factor is the absence of significant comorbidities with the disorder, as substance dependence or anxiety disorders could cause a worse response to treatment. Finally, patients who develop bipolar disorder later would show a better response to lithium than subjects with early onset of the disease (Rybakowski, J. K., 2014).

Despite the fact that it is frequently used for treatment, there may be potential dangers arising from its toxicity to the body. Lithium intoxication involves several symptoms, including severe tremors, gastrointestinal upset, and widespread weakness. You may also experience significant weight gain. Several factors can affect lithium levels in the blood (lithiemia), especially the patient's kidney function, taking other medications and the body's balance of mineral salts. Lithium levels should be measured once every six months and whenever the dosage is changed. In the long term, the patient who is given lithium for more than 15 years may develop hypothyroidism, hypercalcemia, and significant kidney damage.

For the treatment of bipolar disorder, anticonvulsant drugs, especially valproate, lamotrigine and carbamazepine, may also be given. These drugs also act on neurotransmitters, stabilizing activity at the neuronal level, thus decreasing episodes of humoral instability in bipolar patients. (Huang, H., Nissen, N., Lim, C. T., Gören, J., L., Spottswood, M., & Huang, H., 2022).

Valproate is one of the main drugs used for the treatment of bipolar disorder, especially regarding the control of manic episodes and the prevention of relapse (Huang, H., Nissen, N., Lim, C. T., Gören, J., L., Spottswood, M., & Huang, H., 2022). As with lithium, there are predictive factors that can indicate a better response to valproic acid. Unlike lithium, valproate is considered extremely effective in mixed episodes (Calabrese, J.R., Shelton, M. D., & Rapport, D.J., 2002). Valproate would seem to be more effective than lithium even in cases where the patient has bipolar disorder characterized by rapid cyclicity. In addition, it would be particularly indicated in patients who present aggression during manic symptoms. Even in the case of substance addictions, valproate would be more effective than lithium, as well as in the case of comorbidities with anxiety disorders, due to its stabilizing effects on mood. Another

factor that may indicate a good response of valproate is the age of onset of bipolar symptoms: in fact, patients who experienced bipolar symptoms for the first time during adolescence or early adulthood are more likely to develop mixed states of bipolar disorder, making valproate the treatment of choice in these cases (Calabrese, J.R., Shelton, M. D., & Rapport, D.J., 2002).

Carbamazepine is also used as a mood stabilizer, even in patients who do not respond effectively to other medications. Finally, lamotrigine is a fundamental drug especially for the prevention of depressive episodes.

These are as effective as lithium, but without causing severe kidney failure and with a greater therapeutic margin (Huang, H., Nissen, N., Lim, C. T., Gören, J., L., Spottswood, M., & Huang, H., 2022). The main adverse effects found are nausea, dizziness, drowsiness and weight gain. The most serious adverse reactions are rare and include pancreatitis, hepatotoxicity and bone marrow aplasia. The prescription of these drugs, however, should be avoided during pregnancy, as there is a high teratogenicity (Holmes, L. B., Harvey, E. A., Coull, B. A., Huntington, K. B., Khoshbin, S., Hayes, A. M., & Ryan, L. M., 2001). Valproate causes an increased risk of congenital malformations, particularly neural tube defects. Carbamazepine and lamotrigine have a slightly lower risk of causing congenital malformations, but it is still essential for pregnant women to carefully plan therapy and control following the intake of these drugs.

The disorder can be treated with antidepressants, which, however, do not have to be the drug treatment of first choice, as it would significantly increase the risk of manic episodes; they are therefore to be used with antimanic drugs. In fact, while antidepressants alone are effective for treating major depression, they are not as

effective for BD. Ineffective treatment in bipolar patients can cause long periods of depression and an increased risk of suicide (Morishita, Kameyama, Toda, et al., 2020). For this reason, it is best for doctors to discover the mania first, as this would lead to better prognosis. This is not always the case, since about two-thirds of patients go to the hospital after a depressive episode, in the absence of previous counterpolar episodes, making it more difficult for doctors to make a correct diagnosis of the disorder (Morishita, Kameyama, Toda, et al., 2020).

As far as psychological support of patients with bipolar disorder is concerned, psychoeducation could be a very important approach to complement pharmacological treatment (Dean, O. M., Gliddon, E., Van Rheenen, T. E., Giorlando, F., Davidson, S. K., Kaur, M., et al., 2018). Psychoeducation is about providing patients with a greater understanding of what bipolar disorder means, increasing their awareness of the condition and urging them to maintain a healthy lifestyle and follow the psychiatrist's prescriptions. It has been seen how this approach increases medical compliance and reduces manic, depressive and mixed episodes.

Another very important approach for the treatment of bipolar disorder turns out to be mindfulness, as it also increases the patient's awareness, while focusing on stress reduction and relaxation techniques. Mindfulness is often accompanied by a cognitive therapeutic approach (mindfulness-based cognitive therapy, or MBCT). This approach would seem to significantly improve the performance of bipolar subjects, especially with regard to executive functions, memory and attention, while simultaneously reducing episodes of depression and anxiety (Dean, O. M., Gliddon, E., Van Rheenen, T. E., Giorlando, F., Davidson, S. K., Kaur, M., ... & Williams, L. J., 2018).

Finally, due to the cognitive involvement of the bipolar patient, cognitive remediation techniques are increasingly developing (Dean, O. M., Gliddon, E., Van Rheenen, T. E., Giorlando, F., Davidson, S. K., Kaur, M., ... & Williams, L. J., 2018). This type of therapy is rehabilitative, especially with regard to the cognitive flexibility of the pathology, enhancing underused brain areas and activating new neural connections. Cognitive remediation is also based on an improvement in executive functions, memory and attention. This technique was mainly designed for psychotic pathologies but was later tested on bipolar patients as well. Post-intervention (about 10 weeks), neuroimaging techniques showed an improvement in executive functions and a significant change in brain activations during different tasks (Dean, O. M., Gliddon, E., Van Rheenen, T. E., Giorlando, F., Davidson, S. K., Kaur, M., ... & Williams, L. J., 2018). The treatment would also significantly reduce depressive episodes in bipolar patients.

2. Hashimoto’s thyroiditis

Thyroiditis is the presence of an inflammatory process on the thyroid. These are heterogeneous disorders for clinical and etiology, which account for about 20% of all disorders affecting the thyroid (Heizmann, O., Oertli, D., 2012). Depending on the evolution of the disease, acute, subacute, chronic or subclinical thyroiditis can be distinguished. Thyroiditis, in addition, can have an autoimmune origin (the most frequent), or non-autoimmune. The most common form of autoimmune thyroiditis is Hashimoto’s, which is part of the subgroup of chronic lymphocytic thyroiditis (Heizmann, O., Oertli, D., 2012).

The etiology of Hashimoto’s autoimmune thyroiditis is said to be linked to the production of antibodies against thyroid peroxidase, following a reduced tolerance of the thyroid gland (Heizmann, O., Oertli, D., 2012). Like all autoimmune disorders, it is caused by antibodies that attack the affected organ. It is one of the most common autoimmune diseases in the general population and causes progressive primary hypothyroidism in both children and adults (Waliszewska-Prosół, M., & Ejma, M., 2022). It is most common in the population aged 40-65 years and affects more frequently female sex (with a ratio of about 10:1) (Waliszewska-Prosół, M., & Ejma, M., 2022). The reasons why the body produces antibodies against the thyroid are not yet entirely clear, but there are factors that have been implicated in the development of the pathology, particularly hereditary factors (Mutations have been detected in particular on the IL2RA, human leukocyte antigen (HLA), PTPN22 and CTLA4) genes, dietary (mainly due to the intake of large amounts of iodine) and related to hormonal factors (this would explain why this disorder is much more common in women than men). Other factors that may influence the development of the disorder are past infections,

hepatitis C virus, stress, pregnancy, smoking, alcohol, lithium and alterations in intestinal bacterial flora (Ragusa F., Fallahi P. et al, 2019) (Zhang, J., Chen, Y., Li, H., & Li, H., 2021).

Autoantibodies involved in autoimmune dysfunction can cause severe thyroid hormone levels to be impaired (Heizmann, O., Oertli, D., 2012). The etiopathogenesis of the disorder is very complex, but it is known that the disease develops following different stages.

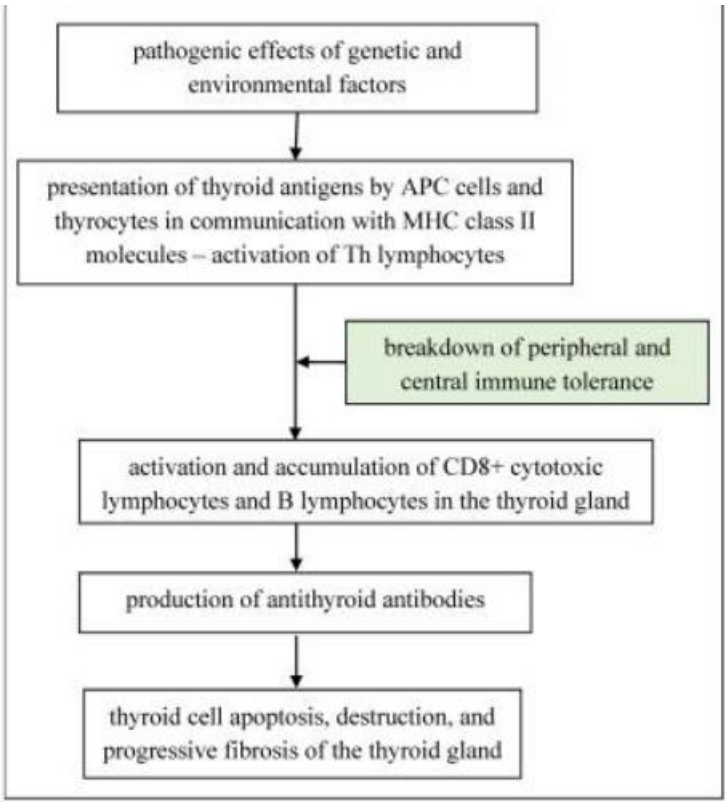

Figure2 The figure shows the different steps that could lead to the development of Hashimoto's thyroiditis. Waliszewska-Prosół, M., & Ejma, M. (2022). Hashimoto encephalopathy—still more questions than answers. Cells, 11(18), 2873, pag. 4.

As shown in this image, the first step in HT pathogenesis is the activation of unsensitized CD4+ T lymphocytes, which recognize autoantigens. Peptides derived

from the proteolytic fragmentation of thyroid antigen (such as TPO or Tg) are presented by antigen-presenting cells (APCs), which include not only "professional" APC cells (such as dendritic cells) but also the thyroid cells themselves, acting as "non-professional" APCs. Activation of T lymphocytes requires antigen recognition via the T cell receptor (TCR) (signal 1) and interaction between CD80/86 molecules in APCs and CD28 molecules in T cells (signal 2). The absence of signal 2 leads to anergy of T-lymphocyte, which does not activate. If the tolerance control system does not work properly, some self-reactive T cells escape control and become active. At a later stage, the peripheral (in the secondary lymphoid organs) and central (in the thymus) tolerance is compromised, which under normal conditions would allow the elimination or anergy of self-reactive lymphocytes. Tolerance breakdown can be triggered by a deficiency or malfunction of the regulatory T cells (Treg), which are crucial for suppressing excessive immune responses.

Th1 lymphocytes are activated (resulting in pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-2 and IL-6), th2 lymphocytes (which in turn stimulate the B lymphocytes in the production of antibodies against Tireoperoxydasi (TPO) and Thyreoglobuline (Tg)) and Th17 lymphocytes (involved in the production of cytokines, especially IL-17, which cause apoptosis of thyroid cells).

All these processes lead to programmed cell death (apoptosis) of the thyroid cells and subsequent fibrosis of the thyroid tissue, which in turn causes progressive loss of thyroid function. (Waliszewska-Prosół, M., & Ejma, M., 2022).

The first symptom to appear is often hyperthyroidism; Once the inflammatory phase has passed, thyroid activity may return to normal or develop into chronic hypothyroidism. Another common symptom may be a non-painful goiter on the neck,

indicating an enlarged thyroid. The symptoms of thyroiditis, therefore, are often mild or nonspecific. They can be either local, mainly due to goiter in the thyroid area (dysphonia and dysphagia), or systemic, mainly due to hypothyroidism. The most important symptoms include: significant weight gain, fatigue and weariness, cold chills, constipation, brachycardia, enlarged heart muscle, hypotension, menstrual imbalances in women, hair loss and dry skin (Ralli M, Angeletti D. et al., 2019). Other systemic involvement may be present in the form of problems related to the regulation of prolactin, total cholesterol and triglycerides. The nervous system may also be damaged, causing neuropathy and in severe cases develop into encephalopathy. Hypothyroidism can also cause very important psychiatric symptoms: as also stated by the recent studies of Zhou & Zhu, (2024), there is a significant correlation between hypothyroidism and some psychiatric disorders, in particular generalized anxiety disorder, Schizophrenia and major depressive disorder. The latter would be the most frequent in patients with hypothyroidism problems (Osnaya-Brizuela, N., Valenzuela-Peraza, A., Santamaría-del Ángel, D., García-Martínez, Y., Pacheco-Rosado, J., Pérez-Sánchez, G., & Sánchez-Huerta, K., 2024). Patients who do not treat hypothyroidism would be significantly more likely to develop depression, especially female patients. In the study of Osnaya-Brizuela, Valenzuela-Peraza et al. (2024), the PHQ-9 questionnaire was used to assess the degree of depression in patients with hypothyroidism and most patients presented the disorder in a mild or moderate way (about 44.4% and 33.3%), but with a moderate-severe and severe case rate (16.7% and 5.6%).

Regarding generalized anxiety (measured by the Beck anxiety inventory), patients with hypothyroidism would have a higher probability of suffering from this disorder than those who do not present hypothyroidism (Osnaya-Brizuela, N., Valenzuela-Peraza,

A., Santamaría-del Ángel, D., García-Martínez, Y., Pacheco-Rosado, J., Pérez-Sánchez, G., & Sánchez-Huerta, K., 2024). As in most patients with autoimmune diseases, up to ¼ of the subjects with Hashimoto's thyroiditis have spontaneous healing.

The diagnosis of the disease is determined by clinical evaluation, evaluation by ultrasound of the gland and by the evaluation of hormones present in the serum of the subject. The T4 and thyroid stimulating hormone (TSH) should be evaluated. Initially, these tests show normal T4 and TSH levels but abnormal levels of thyroid antiperoxidase. The ultrasound may show nodules, with a heterogeneous structure or reduced vascularity of the gland. For the diagnosis is, therefore, particularly important the sonography of the thyroid, which results in a localized hypoperfusion. The diagnosis of Hashimoto's thyroiditis is also based on the study of autoantibodies: in patients with the disorder, there is infiltration into the thyroid gland by lymphocytes, caused by the autoimmune antibody-response mediated by autoantibodies against thyroid peroxidase (TPOAbs) (Klubo-Gwiezdzinska, J., & Wartofsky, L., 2022), which lead to the destruction of thyroid cells. TPOAbs are generally present in the blood of patients with Hashimoto's thyroiditis, although they may not be detected in about 5-10% of cases. They could be a risk factor for developing hypothyroidism. Autoantibodies against thyroglobulin (TgAb) are also important for diagnosis, as they would be significantly present in the patient (Hutfless, S., Matos, P., Talor, M. V., Caturegli, P., & Rose, N. R., 2011). Recent studies, such as that of Waliszewska-Prosół and Ejma (2022), have shown that these autoantibodies are not the only ones involved in the disorder: Other autoantibodies detected in the serum of patients with Hashimoto's thyroiditis are TSH receptor blocker or stimulator antibodies (TSHRAb) and thyroxine antibodies. These autoantibodies are found in the blood of about 97%

of patients with Hashimoto’s thyroiditis, but it is worth remembering that they are not specific for the diagnosis of this disorder, as they would also be present in other types of autoimmune thyroiditis (such as Graves' thyroiditis) and in other disorders involving the thyroid (for example, thyroid neoplasms). Histological tests can often be useful to assess the presence of lymphocytes, which are common in lymphocytic autoimmune thyroids.

If good gland function is maintained (euthyroidism), treatment may be based on observation of symptoms or non-steroidal anti-inflammatory agents and beta blockers in severe cases of hyperthyroidism. Thyroid hormone substitutes may be needed for life in cases where the autoimmune disorder develops into hypothyroidism (Heizmann, O., Oertli, D., 2012). The latter therapy is the most effective approach: in this case, the treatment is based on levothyroxine, which replaces the function of the hormone T4 (Wrońska, K., Hałasa, M., & Szczuko, M., 2024). Treatment with corticosteroids and immunosuppressants is not effective (indeed, it is potentially harmful).

In addition to medication, it is important to follow a high-fiber diet and adequate nutrient intake. Vitamin D-based treatment, an important supplement for immune and endocrine processes (Zhang, J., Chen, Y., Li, H., & Li, H., 2021), may also be useful. Surgery may be indicated in those patients who have pain or malignant thyroid nodules.

In some cases, especially when the damage to the central nervous system is significant, Hashimoto’s thyroiditis can progress rapidly and lead to a very serious disorder: Hashimoto’s encephalopathy (HE).

2.1. Hashimoto's encephalopathy (HE)

It is a disease characterized by autoimmune activation, in particular encephalitis linked to antithyroid antibodies, which involves impaired brain functions. This disease was first described in 1966 and, as the name suggests, can be associated with Hashimoto's thyroiditis (Ramalho[1], J., & Castillo, M., 2011). In fact, Hashimoto's encephalopathy may be a serious consequence of hypothyroidism caused by thyroiditis (Wrońska, K., Hałasa, M., & Szczuko, M., 2024). The term encephalopathy, however, was introduced in 1991 by Shaw et al., as the pathology was described as a disease which exhibited several signs indicative of neurological damage, along with a significant increase in thyroid antibodies and an excellent response to corticosteroid treatment (in fact, it is also called "Corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis" (Menon, V., Subramanian, K., & Thamizh, J. S., 2017). Encephalopathy can have a chronic, acute or subacute onset and may manifest itself with only one episode or recur with relapses. The prevalence of this disorder is 2 cases per 100,000 inhabitants, with a ratio of females: males of about 5:1 (Menon, V., Subramanian, K., & Thamizh, J. S., 2017). The onset is usually between 45 and 55 years (Menon, V., Subramanian, K., & Thamizh, J. S., 2017).

Despite the link with autoimmune thyroiditis, the etiopathogenesis of Hashimoto's encephalopathy is still unknown, due to the variety of manifestations with which it can present (Ilias, I., Karagiorga, V., Paraskevas, G., Bougea, A., Bourbouli, M., Pappa, A., ... &[2] Kapaki, E., 2015). The most suspected etiology is autoimmune, due to the response to corticosteroids. The etiopathogenesis of pathology is represented by

[1] Less frequently, however, the disease could also be a consequence of other autoimmune thyroid disorders, such as Graves' disease

[2] Gene that presents the immune system with all the antigens that do not belong to the self, eliciting the production of antibodies against the antigen itself.

autoimmunity against brain antigens cross-reactive with thyroid antigens (Ramalho, J., & Castillo, M., 2011). The causes that can cause the immune system to make this mistake are not completely known, but there are some hypotheses, such as bacteria or viruses that trigger an excessive reaction of the body. Another plausible cause could be a genetic mutation, even if the genes responsible have not yet been identified. There are risk factors that could lead to the development of the disease, including genetic factors. In particular, the positive HLA-DR5 gene significantly[3] increases the individual's risk of contracting the disease. Another gene that may be responsible for the disease is CTL-4 (Ramalho, J., & Castillo, M., 2011).

Other risk factors could be the lack or excess of certain metals in the body, especially the absence of selenium and excess iodine.

Another hypothesis sees Hashimoto's encephalopathy as belonging to the group of non-vasculitic meningoinflammatory autoimmune encephalopathies (Ramalho, J., & Castillo, M., 2011).

Hashimoto's encephalopathy typically presents two possible manifestations of the disease: it can present with recurrent episodes at acute onset (which could suggest vascular damage) with possible focal neurological signs and often more cognitive involvement. Or, more frequently, it may present gradual and progressive onset, which includes symptoms such as hallucinations, dementia, confusion and drowsiness (Gutch, M., Bhattacharjee, A., Kumar, S., & Pushkar, D., 2017). Other symptoms include epilepsy (occurring in about 51% of cases), memory loss, myoclonus,

[3] Protein that modulates the activity of the immune system.

psychotic symptoms, tremors and uncontrolled movements, speech and movement disorders (Tzakas, P.; Sit, SW, 2011).

Also covers a wide variety of psychiatric symptoms, especially psychotic ones, such as agitation, persecution delirium and theft, depression/high mood and hallucinations (Singh, & Verma, 2022; DeBiase, & Avasthi, 2020). There are several cases where patients come to the emergency room with anxiety, paranoia and intermittent psychotic delirium associated with a thyroid disorder.

Cognitive impairment, alternate hemiparesis and cerebellar ataxia are also common (Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich, C., DeBacker, D. L., & Marks, L., 2016).

Its diagnosis may be quite complicated, due to the high comorbidity with other diseases, such as sepsis, hepatic encephalopathy, renal failure, structural abnormalities (DeBiase, & Avasthi, 2020). For this, all these causes must be excluded first, by means of an electroencephalogram (EEG) and analysis of the cerebrospinal fluid and neuroimaging tests.

Routine blood tests are normal, with a slight increase in CRP or liver proteins (such as AST and GOT), indicating an unspecific inflammation. Markers indicating autoimmune disorder are also often identified (Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich, C., DeBacker, D. L., & Marks, L., 2016). Thyroid tests are normal in more than 30% of cases, or they may indicate subclinical hypothyroidism (35% of cases), manifest hypothyroidism (25% of cases) or hyperthyroidism (7% of cases).

MRI is normal in about 50% of patients with Hashimoto's encephalopathy, but brain atrophy abnormalities, cerebellar lesions and, although extremely rare, bilateral medial abnormalities may be found (Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich,

C., DeBacker, D. L., & Marks, L., 2016). The actual diagnosis, however, is made by the presence in the patient’s serum and spinal cerebrospinal fluid of antithyroid-oxidase antibodies and anti-treoglobuline antibodies (Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich, C., DeBacker, D. L., & Marks, L., 2016). Often alterations related to an inflammatory state are detected in CSF, with high concentrations of thyroid antibodies (Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich, C., DeBacker, D. L., & Marks, L., 2016).

The diagnostic criteria that must be met, therefore, to diagnose Hashimoto's thyroiditis are the following:

1. Exclusion of any other metabolic, toxic or infectious causes;
2. Euthyroidism or thyroid functional alteration that does not justify the symptoms;
3. Association with autoimmune thyroid diseases;
4. Positive response to corticosteroid therapy (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024).

It is treated with corticosteroids, due to their immunosuppressive and immunomodulatory effects, especially methylprednisolone first intravenously (3 to 5 days of therapy, starting at 30 mg/kg), with subsequent conversion to oral therapy via prednisone (1 mg/kg/day for about 4 months) (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024). It is also necessary to gradually reduce therapy, to avoid incurring iatrogenic Cushing's syndrome or osteoporosis.

If treatment is ineffective, methotrexate, cyclophosphamide, and intravenous injection of immunoglobulins (400 mg/kg/day for 5 days usually) should be used (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024).

Another useful approach would be that of levothyroxine, or some other antithyroid drug, to try to bring thyroid function back to normal as much as possible (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024).

Due to frequent seizures, it may be useful to administer an antiepileptic drug (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024).

With these therapies, the prognosis is good, with significant improvement just a few days after starting treatment with the steroid. However, even with this therapy, patients can often have relapses or need other immunosuppressive treatments to cope with encephalopathy. Steroids would be very effective if the disease is diagnosed early, but they may not be as effective in more advanced stages (or at least, it is not effective if used as the only treatment method) (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024). In any case, the patient should be monitored, as corticosteroid therapy could lead to severe side effects, mainly gastrointestinal, cardiovascular, endocrine, neuropsychiatric, dermatological and musculoskeletal (Pempera, N., Miedziaszczyk, M., & Lacka, K., 2024).

3. Objectives of the review

The main objective of this thesis is to examine the available scientific evidence regarding the relationship between Hashimoto's thyroiditis, with reference also to one of its possible clinical complications, namely Hashimoto's encephalopathy, and bipolar disorder, evaluating whether there is a significant association between these disorders. This work was carried out in order to elucidate the biological and pathophysiological mechanisms that could link the two conditions and the clinical implications that this relationship could bring.

More specifically, this *systematic review* has several objectives:

1. First, it aims to investigate the prevalence of Hashimoto's thyroiditis, and possible encephalopathy resulting from it, within the population of bipolar patients (and vice versa). Differences within samples (with reference to the gender of the participants) and specific subgroups (such as pairs of twins) are also considered to investigate the possible relationship between the subject's genetics, activation of the immune system and the likelihood of developing bipolar disorder. This work therefore tries to answer the question of whether there is a greater probability of developing bipolar among patients with Hashimoto's thyroiditis disorder and vice versa.
2. In addition, the review investigates the mechanisms underlying the relationship between the two disorders. In particular, the following are analyzed:

- The influence of thyroid autoantibodies (particularly TPO and TG-Abs) in the modulation of bipolar disorder;

- ❖ The role of genetics and the presence of other biological markers (in particular, blood levels of thyroid hormones, such as TSH) that could promote the development of a disorder of the two conditions.

3. A fundamental objective is to investigate all the clinical implications, paying particular attention to:

- ❖ The influence of Hashimoto's thyroiditis on the clinical course and treatment of bipolar disorder, and vice versa.
- ❖ The importance of monitoring thyroid function in patients with bipolar disorder in order to be able to use an approach that is as suitable as possible for the patient's clinical needs.

Investigating the relationship between Hashimoto's thyroiditis and bipolar disorder could provide new, more specific treatment strategies for each patient's different needs, improving their quality of life. This work could also encourage the evaluation of thyroid function in patients suffering from mood disorders, such as bipolar mood, to avoid a treatment that could prove to be ineffective for the patient, reducing complications or recurrences of the psychopathological condition.

3.1. Methods

Study design

This thesis was conducted as a systematic review of existing literature, with the aim of collecting and analyzing the available evidence regarding the relationship between bipolar disorder and Hashimoto's thyroiditis (or encephalopathy). This approach was chosen to offer as exhaustive and rigorous a synthesis as possible of the available literature. Indeed, systematic reviews are particularly effective in interdisciplinary contexts, such as the intersection between immunology and psychopathology, as they facilitate the integration of highly heterogeneous data and provide a comprehensive, synthesized understanding of the subject matter.

How the bibliographic search was carried out

The bibliographic search of the articles was carried out through the main database, in particular PubMed and Web of Science, on the basis of the string *“("Hashimoto's thyroiditis" OR "chronic autoimmune thyroiditis" OR "lymphocytic thyroiditis" OR "autoimmune thyroiditis") AND ("bipolar disorder" OR "bipolar spectrum disorders" OR "bipolar I disorder" OR "bipolar II disorder" OR "cyclothymia" OR "manic disorder" OR "hypomania" OR "mania" OR "bipolar depression" OR "atypical depression") NOT (review[Publication Type] OR meta-analysis[Publication Type])”.* At the time of writing, 44 articles on the subject were detected on PubMed, while on Web of Science there were 63 articles. For the research work, the Boolean operators “AND” and “NOT” were used: the first to search the databases for all those articles that mentioned both bipolar disorder and thyroiditis or Hashimoto's encephalopathy; the second operator, on the

other hand, was used to exclude all reviews and meta-analyses already present in the literature. All the articles used for this review were in English and covered a time interval from 1985 to 2024. Case-control, observational, cross-sectional, longitudinal, prospective, Mendelian randomization, cohort, retrospective, and case report studies were considered. In the end, 18 articles were included in the research.

Criteria for inclusion and exclusion from research

The articles included in the research met certain inclusion criteria, allowing the exclusion of the less relevant ones. Articles in which the sample was represented by patients diagnosed with bipolar disorder and/or Hashimoto's thyroiditis (or encephalopathy) were taken into consideration. These patients also had to have an evident immune dysfunction resulting from thyroid problems: this criterion was added to investigate not only the relationship between the two conditions, but also to verify the association between bipolar disorder and the presence of thyroid autoantibodies in the blood of patients, regardless of the diagnosis of hypothyroidism, autoimmune thyroiditis and other diseases involving the thyroid.

On the other hand, all reviews and meta-analyses of the literature have been excluded, to avoid the repetition of studies already included in the present thesis. Moreover, they were also excluded in order to avoid redundancy and ensure that only new evidence is used. Articles that cited both conditions, but described other aspects, such as the development of autoimmune thyroiditis following lithium treatment of bipolar disorder, or autoimmune activation not directly related to the thyroid gland in relation to bipolar disorder, were also excluded.

Selection of articles

The selection of the items was conducted in several steps:

1. In the first place, a preliminary screening of the articles was carried out, evaluating the title and abstract in each of them, to make an initial skimming and eliminate the less relevant ones;
2. Evaluation of the full text to verify that it met the criteria and objectives of the research;
3. Final inclusion of items that met the predefined criteria.

The choice of articles was also taken care of by another reviewer to increase the reliability of the selection, analyzing the titles, abstracts and finally the article in its entirety.

All the items were then placed on a table to collect them, in order to organize them in a more rigorous and precise way.

Data extraction

Study	Title	Ab/ markers thyroiditis	Thyroid function	Study design	Populations	Thyroid disease
Menon, 2014	Hypothyroidism and Bipolar Affective Disorder: Is There a Connection?	For hypothyroidism, T4 values <0.92 ng/ml are found with TSH levels >4.2 µU/ml	72/82 with normal thyroid functioning (85.72%); hypothyroidism in 14% of cases	Case-control and observational study	84 BD (58% women, 42% men), 18-71 years of age / of these 84, 12 with hypothyroidism (14.28%)	Hypothyroidism
Degner et al., 2014	Association between autoimmune thyroiditis and depressive disorder in psychiatric outpatients.	TPO; T3 and T4 levels are measured using chemiluminescence tests; as well as TSH levels; TSH antibodies by assay of autoreceptors; anti-thyroperoxidase autoantibodies are measured by DYNO-anti-TPO thyroid ultrasound test	In the bipolar group, 70.2% had normal thyroid functioning (9/13); the rest of the bipolar sample suffered from autoimmune thyroiditis	cross-sectional study	Out of 71 patients, 52 were uni-bipolar depressed and 19 suffered from schizophrenia (HC).	Hypothyroidism
Soheili-Nezhad, 2023	Exploring the Genetic Link Between Thyroid Dysfunction and Common Psychiatric Disorders: A Specific Hormonal or a General Autoimmune Comorbidity	TPO; TPO and increased production of cytokines derived from monocytes and T lymphocytes; Overt psychiatric disorders produce mild elevations, as well as decreases in TH levels, and attenuation of the thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) stimulation	454987 with normal thyroid function (91.4%); the rest of the sample suffered from hypothyroidism	cross-sectional study	n=497,726, age 56.6 ± 8.1; 269,940 women (54%); 741 with BD; 18,792 with overt hypothyroidism and 23,947 with self-reported hypothyroidism	Hypothyroidism
Hillegers, 2007	Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents	TPO; TPO-Ab was measured by an ELISA test, the test with a level of 25 U/ml or higher is considered positive. Thyroid insufficiency is considered	presence of thyroid insufficiency linked to anti-TPO antibodies	prospective study	T1: 86 BD parents and 140 children aged 12 to 21. T2: 132 subjects aged between 13 and 23 years. T3: 129	Hypothyroidism

		present if a patient has a TSH greater than 4.0 mU/l			subjects (mean age 20.8 years, SD = 2.7, range 16-26 years). Of the 80 families participating in the study, 32 (40%) had a bipolar father and 48 (60%) had a bipolar mother.	
Vonk et al,2007	Is Autoimmune Thyroiditis Part of The Genetic Vulnerability (or an Endophenotype) for bipolar disorder?	TPO; Serum samples to evaluate TPO antibodies are analyzed by ELISA (TPO positive ≥ 25 U/mL)	Autoimmune thyroiditis linked to the presence of anti-TPO antibodies	Cross-sectional study	51 pairs of twins between 18 and 60 years old, with at least one twin affected by BD. 35 pairs of healthy twins. There were 68 women (67%).	Hypothyroidism
Koc et al., 2022	Association between thyroid autoimmunity and antidepressant treatment-emergent mania in pediatric mood disorders	TPO; FT4, TSH and Anti-TPO levels	Autoimmune thyroiditis linked to the presence of anti-TPO antibodies	cross-sectional study	60 patients between 12 and 18 years old (mean age 14.5 ± 3.3). Of these, 29 are considered ATEM+ (antidepressant treatment emergent mania, manifestation of BD) and 31 ATEM- (HC).	Hypothyroidism
Boukouaci et al., 2018	Association between CRP genetic diversity and bipolar disorder comorbid complications	Single nucleotide polymorphisms	Of the bipolar group, 84.7% did not have thyroiditis	case-control study	568 patients with BD (including 58.5 women), with a mean age of 42.4 ± 13.1. Of these, 15.3% had thyroiditis. There are 163 HCs (38.7% women), with an average age of 41.2 ± 11.6.	Hypothyroidism/ hyperthyroidism
Su et al., 2024	Association of anxiety disorder, depression, and bipolar disorder with autoimmune thyroiditis: A bidirectional two-sample mendelian randomized study	Use of single nucleotide polymorphisms (SNPs)	385018 did not have thyroiditis	Mendelian randomization	612 with autoimmune thyroiditis and 385018 HC. 41917 with BD, 371549 HC	Hypothyroidism

Calabrese et al, 1985	Autoimmune thyroiditis in manic-depressive patients treated with lithium	T4 and TSH measurement (measured using radioimmunology techniques)	100% of patients maintained good thyroid function	prospective study	16 patients with manic-depressive syndrome (now BD), with mean age 44 years (range 17-61 years). 62.5% were women	Good thyroid functioning
Kupka et al., 2002	High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure	TPO	83% with good thyroid function	before-after study	226 BD outpatients (50.4% women) with bipolar I and II disorder (age range 23-83). 2 HC: 1st group: 252 participants (60% women; age range 55-60); 2nd group: 3190 participants (55% women; age range 20-90).	Hypothyroidism
Müssig et al., 2005	Hashimoto's encephalopathy presenting with bipolar affective disorder	Thyroxine and TPO; At the beginning, TSH decrease and free thyroxine increases. TPO-Abs were extremely elevated. 4 weeks later, hypothyroidism developed, with increased TSH and decreased free thyroxine levels	Presence of hypothyroidism after 4 weeks of abnormal tests	case report	32-year-old woman who developed BD after the birth of her first child. Subsequently, she was diagnosed with Hashimoto's encephalopathy.	Hypothyroidism
Lin et al., 2013	Acute mania in a patient with hypothyroidism resulting from Hashimoto's Thyroiditis	TPO; Free levothyroxine (T4) level low (0.24 ng/dl), while thyroid stimulating hormone (TSH) was elevated at 18.79 mIU/L, as were his thyroglobulin antibodies (445 IU/ml) and anti-thyroid peroxidase (411 IU/ml).	Presence of hypothyroidism after 4 weeks of abnormal tests	case report	41-year-old woman	Hypothyroidism
Gan et al., 2019	Rapid cycling bipolar disorder is associated with antithyroid antibodies, instead of	TPO and Tg-Abs; Evaluation of T4, TSH, TPO-Abs with these reference values: FT4 = 11.5-22.7 pmol/l, FT3 = 3.5-6.5 pmol/l, TSH =	Hypothyroidism following anti-TPO antibodies	cross-sectional study	352 subjects, age 27.5 ± 11.6. Females 58.5%	Hypothyroidism

	thyroid dysfunction	0.55-4.78 µIU/ml, TPO-Abs or Tg-Abs = 0-60 U/ml. Hypothyroidism is diagnosed if FT4 < 11.5 pmol/l or TSH > 4.78 µIU/ml and with TPO-Abs it is 60 U/ml				
Barbero et al., 2014	Thyroglobulin antibodies and risk of readmission at one year in subjects with bipolar disorder	TPO and Tg-Abs; TPO-Abs and TG-Abs were determined using an EliA™ system (cut-off: 10 units/mL for TPO-Abs and 15 units/mL for TG-Abs); TSH and T4 were then determined.	Autoimmune thyroiditis due to anti-TPO antibodies	cohort study	77 subjects (58.4% women) with an average age of 45.1 years suffering from type 1 BD	Hypothyroidism/ hyperthyroidism
Kraszewska et al., 2015	A cross-sectional study of thyroid function in 66 patients with bipolar disorder receiving lithium for 10–44 years	TPO, Tg-Abs and TSH-R; TSH, free thyroxine (fT3), and free triiodothyronine (fT4) with reference ranges were 0.35-4.90 µIU/mL, 1.71-3.71 pg/mL, and 0.70-1.48 ng/, respectively dL. Furthermore, serum thyroid peroxidase (TPO) antibodies, thyroglobulin (TG) antibodies and TSH receptor (TSH-R) antibodies were measured, with reference values of < 5.61 IU/mL respectively, < 4.11 IU/mL and < 1.0 U/L.	No thyroid abnormalities in men; on the contrary, women had hypothyroidism in 22% of cases	cross-sectional study	66 patients average age 62 ± 13 (68% women) with BD and treated with lithium for 10-44 years (21 ± 9 on average)	Hypothyroidism
Radhakrishnan et al., 2013	Thyroid dysfunction in major psychiatric disorders in a hospital-based sample	TPO; T3= range=0.1-8 ng/ml; T4=range=0.5-30 µg/dl; TSH=range=0.01-100 µIU/ml; FT3=range=0.88-30 pg/ml; FT4=range=0.25-6 ng/dl and anti-TPO=range=0.25-1000 IU/ml.	77% of bipolar patients did not have hypothyroidism	retrospective study	468 patients in total (122 diagnosed with BD). Data available for thyroid function was 343 subjects [Male = 173 (50.4%), Female = 169 (49.3%), Missing = 1 (0.3%). Mean age: 37.46 ± 13.56 years.	Hypothyroidism
Snijders et al., 2017	The seroprevalence of antithyroid	TPO; Serum samples to evaluate TPO		Longitudinal study	Bipolar family trios: 140 children	Hypothyroidism/ hyperthyroidis

	peroxidase antibodies in bipolar families and bipolar twins: results from two longitudinal studies	antibodies are analyzed by ELISA (TPO positive ≥ 25 U/mL).			(average age 16 years, range 12-21); 103 subjects are present at follow-up. As regards twins, 25 pairs of twins affected by BD (10 MZ discordant, 2 DZ concordant and 13 DZ discordant) and 18 pairs of control twins were followed.	m
Kupka et al., 2002	High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure	TPO and anti-thyroperoxidase; Single nucleotide polymorphisms (SNPs), correlated with the presence of anti-thyroid antibodies (such as anti-thyroperoxidase antibodies, TPO-Ab) and with parameters of thyroid dysfunction, such as elevated levels of TSH (thyroid stimulating hormone).	385,018 patients did not have hypothyroidism, while 612 cases did have the condition	Mendelian randomization	41,917 cases of BD and 371,549 controls there are then 612 cases of AIT and 385,018 controls	Hypothyroidism

From the selected articles, various data, both qualitative and quantitative, were extracted and entered the table. In particular, the following have been included in it:

- **Study**: in the first column the name of the author has been inserted followed by the year of publication on the database;
- **Title of the research;**
- **Antibodies/ markers of hypothyroidism:** in this section, biological components considered in the study to investigate the presence of Hashimoto's thyroiditis (both hormones, such as TSH, and thyroid autoantibodies, such as TPO), with normal ranges, are also included;

- **Thyroid function:** it is investigated (if available, also through quantitative data) whether the subjects of the study have normal thyroid functioning or not;
- **Study design:** type of study (e.g. longitudinal, cross-sectional, case report, etc....);
- **Population:** Reference sample of patients with bipolar disorder (with or without Hashimoto's thyroiditis, depending on the study) and any controls:
- **Thyroid disease:** this section explores if the population is affected by any thyroid disease (hypothyroidism or hyperthyroidism), linked to an autoimmune condition;

In the following section, results based on this table will be explained.

4. Results

Data were extracted from 18 selected studies and are organized to include information on the antibodies analyzed, the markers for diagnosing autoimmune pathology, the characteristics of the populations studied, and the results emerging from the articles, with both qualitative and quantitative data. The publication dates of the included articles spanned the period from 1985 to 2024. Most of the studies used a prospective, retrospective, or cross-sectional design, but longitudinal approaches, case reports, and Mendelian randomization were also analyzed. Sample sizes ranged from a minimum of one patient in the case of case reports to very large samples of nearly five hundred thousand units, although most studies examined relatively small samples (about 60-70 patients). In total, 1,716,256 subjects were analyzed: although not all studies provided the exact gender ratio, most articles show a predominance of female subjects, around 54% for the 10 studies reporting gender differentiation.

Analysis of Thyroid Antibodies

Thyroid antibodies, with a particular focus on anti-TPO antibodies, were accorded substantial importance. Their prevalence was assessed in 14 out of the 18 studies, revealing significant variability across the articles. In some studies, such as that of Kraszewska et al. (2015), abnormally high TPO levels were found in patients with bipolar disorder. This finding corroborates the increased susceptibility to thyroid dysfunction among the studied patients, particularly in the female population (68% of the sample) receiving lithium treatment. However, the same author suggests that thyroid and immune system responses, leading to elevated anti-TPO antibodies, may be directly influenced by bipolar disorder. The study further emphasizes an increase in

anti-TG antibodies, which are also linked to thyroid dysfunction. Similarly, Degner et al. (2014) describe the importance of anti-TPO presence for the development of bipolar disorder. Their results reveal a strong association between anti-TPO levels and the disorder. Moreover, they showed an increased risk of developing bipolar disorder in patients with chronic autoimmune thyroiditis, even in the absence of significant thyroid imbalance (Spearman's q = 0.175; p = 0.153).

The findings of this study align with those of Hillegers et al. (2007), who observed more TPO antibodies, especially in women with bipolar disorder, a result statistically significant compared to healthy controls. Hillegers also reported a 55% increase in anti-TPO presence in the offspring of bipolar patients, particularly in female subjects. This suggests the hereditary nature of the condition, with genetic transmission of brain dysfunction and immune cells involved in developing the disorder.

Supporting this hypothesis, Vonk et al. (2007) considered 51 pairs of twins aged 18 to 60, with at least one twin affected by bipolar disorder, and 35 pairs of healthy twins. In this study, anti-TPO antibodies were positive in 27% of twins with bipolar disorder, 29% of bipolar monozygotic twins, 17% of non-bipolar dizygotic twins, and 16% of control twins. There was also a significant increase in average anti-TPO levels in discordant twin pairs compared to healthy twins. These results confirm that autoimmune thyroiditis correlates not only with bipolar disorder itself but also with genetic vulnerability to develop the condition, identifying anti-TPO antibodies as markers of autoimmune thyroiditis, a potential endophenotype for bipolar disorder.

Snijders et al. (2017) conducted a longitudinal study involving bipolar families: 140 offspring (mean age 16 years, range 12-21); 103 subjects were present at follow-up. Regarding twins, 25 pairs of twins with BD were followed (10 discordant monozygotic,

2 concordant heterozygotic, and 13 discordant heterozygotic), along with 18 control twin pairs. The article highlights an increased prevalence of anti-TPO antibodies during follow-up in bipolar offspring and bipolar twins, again supporting an increased hereditary risk of severe mood disorders, recurrent chronic inflammation, and thyroid autoimmunity (albeit with limited odds ratios between 1 and 2).

Another study emphasizing the relationship between anti-TPO antibodies and bipolar disorder is that of Gan et al. (2019). This cross-sectional study evaluated thyroid hormone levels (such as T4 and TSH) and anti-TPO antibodies in blood samples. Anti-TPO levels were significantly elevated in bipolar patients, without necessarily leading to thyroid dysfunction. Therefore, bipolar disorder is not associated with hypothyroidism ($p = 0.481$, $OR = 0.452$), unlike anti-TPO antibodies ($p < 0.001$, $OR = 5.130$). According to the author, anti-TPO antibodies may act directly on the corresponding antigen in the mood regulation center or directly influence brain function.

Similarly, Kupka et al. (2002) found higher anti-TPO levels in blood samples of bipolar patients compared to HC patients. Thyroid dysfunction due to anti-TPO antibodies was present in 17% of bipolar patients and significantly more frequent in women ($OR = 2.3$; $p = 0.04$). Men also showed elevated anti-TPO levels but did not exhibit thyroid dysfunction.

Koc et al. (2022) also found a correlation between anti-TPO levels and ATEM+ (treatment-emergent mania, a manifestation of BD). Specifically, antibody levels were significantly higher than in ATEM- conditions (representing HC). Furthermore, TPO-abs positivity was significantly associated with ATEM+, holding all other conditions equal ($OR = 3.67$).

An association between anti-TPO antibodies and bipolar disorder was also found in the study by Soheili-Nezhad (2023). However, unlike the previous studies, anti-TPO levels were only slightly altered. Hypothyroidism was positively associated with an increased risk of developing bipolar disorder (OR = 1.67), but without a strong genetic correlation between hypothyroidism and bipolar disorder.

Another type of antibody, anti-thyroglobulin (Tg-Abs), was also considered. Subjects with Tg-Abs appeared to have a better prognosis, especially when thyroiditis was associated with bipolar disorder. This could be due to the greater attention given to these patients, as high Tg-Abs levels are often associated with more severe thyroiditis. Additionally, detecting these antibodies seemed to help patients better recognize the severity of their psychiatric condition, increasing medication compliance, as Barbero et al. (2014) and Kraszewska et al. (2015) pointed out. According to the authors, these antibodies may serve as biomarkers of bipolar disorder. In the same study, TSH-receptor was also associated with bipolar disorder, though with less influence than TPO and Tg-Abs.

Thyroid Pathology Type

14 studies out of 18 identify hypothyroidism as the primary thyroid pathology associated with autoimmune disease. In the study by Soheili-Nezhad (2023), the author states that hypothyroidism is positively associated with a significant increase in the risk of bipolar disorder (OR = 1.67), although a genetic component to justify the relationship between the two conditions is excluded.

These findings partially contrast with those of the study by Vonk et al. (2007), which identifies a correlation between autoimmune thyroiditis and bipolar disorder, along with an association to genetic predisposition for the development of the condition. This suggests that autoimmune thyroiditis may represent a potential phenotype for bipolar disorder.

Menon (2014) also identifies a possible genetic connection between mood disorders and hypothyroidism, stating that genetic investigations could uncover the link between thyroid dysfunction and bipolar disorder.

The study by Radhakrishnan et al. (2013) confirms the existence of a correlation between autoimmune thyroiditis, hypothyroidism, and bipolar disorder, identifying thyroid abnormalities in 25.4% of patients with bipolar disorder.

Degner et al. (2014) identified a significant association between hypothyroidism resulting from autoimmune pathology and the occurrence of bipolar disorder, asserting that individuals with autoimmune thyroiditis exhibit an increased predisposition to develop this psychopathology compared to control subjects.

In contrast, the study by Kupka et al. (2002) did not find any causal relationship between hypothyroidism and bipolar disorder (OR = 1.103; p = 0.689). The author

suggests that the relationship between the two conditions could be influenced by an independent variable, such as lithium treatment for bipolar disorder.

Su et al. (2024) also found no significant correlation between autoimmune thyroiditis, hypothyroidism, and bipolar disorder (OR = 1.101; p = 0.355). Furthermore, inverse MR analysis did not support a causal relationship between genetic susceptibility to autoimmune thyroiditis and hypothyroidism and bipolar disorder (OR = 0.969; p = 0.118).

The study by Snijders et al. (2017) analyzes both hypothyroidism and hyperthyroidism, concluding that for both conditions, there is an increased hereditary risk of co-occurrence of mood disorders, such as bipolar disorder, and thyroid autoimmunity (with an OR between 1 and 2).

Case Reports

Case 1 (Lin et al., 2013)

A 42-year-old female patient was admitted to the emergency room with symptoms of excessively elevated mood, hyperactivity, reduced need for sleep, grandiose delusions, and visual and auditory hallucinations lasting a week. Three months prior, she had experienced symptoms of hypothyroidism, including excessive fatigue, weight gain, and menstrual irregularities. Clinical examinations revealed severe hypothyroidism, evidenced by low free levothyroxine (fT4) levels of 0.24 ng/dl (0.70-1.48 ng/dl) and elevated TSH levels of 18.79 mIU/L (0.35-4.94 mIU/L). Anti-thyroglobulin antibodies were 445 IU/ml (0-60 IU/ml), and anti-thyroid peroxidase (anti-

TPO) antibodies were 411 IU/ml (0-60 IU/ml). A thyroid ultrasound showed a heterogeneous and hypoechoic pattern without nodular lesions. A biopsy confirmed the presence of lymphoid cells, excluding malignancy.

Subsequent to a diagnosis of Hashimoto's autoimmune thyroiditis, levothyroxine therapy was started at a dosage of 90 mcg/day (1.6 mcg/kg). However, the patient manifested notable adverse effects, including nausea, headache, palpitations, and diaphoresis. The posology was reduced to 25 mcg/day and gradually increased to 50 mcg/day after five days. Simultaneously, the patient was administered valproate (800 mg/day) and quetiapine (400 mg/day). After three weeks, both the hypothyroidism and mood disorder symptoms significantly improved.

Two years after discharge, the patient remained in good health, taking levothyroxine (75 mcg/day for the first six months, reduced to 50 mcg/day for the next six months, then 25 mcg/day for a year, until discontinuation after two years). She was no longer taking psychotropic medications and exhibited no manic, psychotic, or depressive symptoms.

Case 2 (Müssig et al., 2005)

After giving birth to her first child, a previously healthy 32-year-old woman began to exhibit bipolar symptoms, particularly agitation, flight of ideas, labile mood (primarily irritability), and a decreased need for sleep. Twenty-three days postpartum, she was admitted to a psychiatric hospital, diagnosed with dysphoric manic syndrome, and treated with haloperidol and lorazepam. Upon discharge nine days later, she was nearly asymptomatic.

Five months later, the patient returned to the emergency room with depressive symptoms, including low mood, lack of feelings (even toward her child), fatigue,

anhedonia, abulia, insomnia, and loss of appetite. She was treated with mirtazapine and citalopram, along with low doses of perazine or chlorprothixene, but did not improve. Despite her symptoms, she was discharged after three months.

Six weeks later, following a suicide attempt, she was started on a combination of mirtazapine, venlafaxine, and lithium. She was discharged three months later with a slightly depressed mood.

Three months later, she was presented at a psychiatric outpatient clinic with moderate depressive symptoms. Routine blood tests revealed decreased thyroid-stimulating hormone (TSH) levels (<0.03 mU/L, normal 0.2-2.5) and elevated free triiodothyronine (684 pg/dL, normal 150-400) and free thyroxine (2.51 ng/dL, normal 0.8-1.7), indicating hyperthyroidism. Anti-thyroid peroxidase (TPO) antibodies were markedly elevated (2010 kU/L, normal <2), and anti-thyroglobulin antibodies were slightly elevated (1.1 kU/L, normal <1). Suspecting Hashimoto's thyroiditis, she was started on 10 mg of carbimazole daily. Since depressive symptoms did not improve despite thyroid stabilization, further tests confirmed hypothyroidism: elevated TSH (44.71 mU/L, normal 0.2-2.5) and decreased free triiodothyronine (134 pg/dL, normal 150-400) and free thyroxine (0.5 ng/dL, normal 0.8-1.7). TPO antibodies remained high (2700 kU/L, normal <2). Levothyroxine therapy was initiated at 37.5 mcg, increasing to 75 mcg after two weeks. For two years, she maintained this dose, keeping thyroid levels normal.

Despite treatment, an EEG showed generalized slowing with brief paroxysmal arrhythmia. Considering high anti-TPO levels and EEG abnormalities, a diagnosis of Hashimoto's encephalopathy was made. Glucocorticoid therapy with 70 mg of prednisolone (1 mg/kg) daily was initiated, gradually tapered off after two months.

Depressive symptoms significantly improved after corticosteroid treatment, and the EEG normalized.

Six months later, after discontinuing lithium due to weight gain, the patient experienced a relapse of depressive symptoms, treated initially with haloperidol and lorazepam, later replaced with lithium and oxcarbazepine.

A few months later, she presented significant depressive symptoms, requiring a three-month hospitalization. Elevated TPO antibodies (825.1 kU/L, normal <2) persisted. Depressive symptoms significantly improved with prednisolone, lithium, and maprotiline, alongside individual and group cognitive-behavioral therapy.

5. Discussion of the Results

This systematic review analyzed a total of 18 studies, encompassing various types of research (such as observational studies, case reports, case-control studies, prospective, retrospective, and longitudinal studies), aiming to investigate the relationship between Hashimoto's thyroiditis and bipolar disorder.

This thesis was conceived as an exhaustive analysis of all articles available on major search engines, such as PubMed and Web of Science, that met the previously defined inclusion criteria. This analysis ensures a comprehensive view of the current state of research, avoiding issues related to selection bias, and provides a detailed overview of the existing literature.

From the studies analyzed, it can be said that the two disorders seem to correlate significantly, even more so when considering anti-TPO antibodies. This association could derive both from a genetic predisposition and from a general inflammation following the autoimmune disease: as a matter of fact, it not only affects the affected organ (in this case the thyroid) but could also affect the brain areas associated with mood regulation. As a matter of fact, fifteen out of the eighteen studies highlighted a significant correlation between the two conditions: this indicates that patients with autoimmune thyroiditis have a higher risk of developing mood disorders, such as bipolar disorder, compared to healthy controls. This result provides an accurate summary of existing literature and also emphasizes the need for further investigations to address discrepancies present in various studies.

Indeed, despite most of the studies included in this thesis finding a significant positive correlation between bipolar disorder and autoimmune thyroiditis, some articles did not

observe a significant relationship. Notably, this was observed in the studies by Su et al. (2024), Gan et al. (2019), and Kupka et al. (2002). This discrepancy with other studies could be explained by several factors, such as small sample sizes and less specific analyses, which may not have captured more complex or gene-environment interaction-dependent causal relationships. Additionally, demographic differences in the samples examined could have significantly influenced the results, as the gender of the subjects examined, as different hormonal conditions could significantly influence the biological reaction following the development of the autoimmune disease. In fact, in the studies of Kupka et al. (2002) and Su et al. (2024), the percentages of each gender are not specified, and this may have had an influence, as it is known that female patients are more likely to develop significant thyroid symptoms following the presence of bipolar disorder, while male patients may only experience an abnormal increase in anti-TPO levels.

Moreover, methodological variations among the studies included in the review represent a major source of heterogeneity in the interpretation of the results. For example, many studies used different diagnostic criteria for Hashimoto's thyroiditis, considering patients with moderate/high levels of antithyroid antibodies, without thyroid dysfunction. In contrast, other studies included only patients with clinically confirmed autoimmune thyroiditis. As a matter of fact, for example, the study by Gan et al. (2019), showed that hypothyroidism would not be associated with hypothyroidism, but only with anti-TPO antibodies, thus not considering in its analysis all those patients who could later develop significant symptoms of Hashimoto's thyroiditis. These differences among the analyzed studies may have influenced the strength of the observed relationship between the conditions.

Biological Mechanisms of Autoimmune Thyroiditis

Several studies in this review suggest that the correlation between Hashimoto's thyroiditis and bipolar disorder may stem from inflammatory and autoimmune mechanisms. Particularly, as noted in the study by Gan et al. (2019), the production of anti-TPO autoantibodies could influence the development of mood disorders, as thyroid autoantibodies might directly act on the corresponding mood regulation center antigen. This is especially true for female subjects (Kupka et al., 2002).

Moreover, as highlighted by the study by Su et al. (2024), the relationship between autoimmune disorders and psychiatric disorders has been linked to the HLA gene, which influences both the psychiatric and autoimmune components by regulating the synthesis of cytokines that promote inflammation, such as interleukin-6 and tumor necrosis factor-alpha. These molecules affect thyroid function but might cross the blood-brain barrier, causing alterations in neurotransmission, which underlies mood regulation. Furthermore, dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis plays a crucial role, as it influences cerebral metabolism (Su et al., 2024).

Additionally, lithium for the treatment of bipolar disorder may contribute to the development of antibody-independent hypothyroidism. As stated by Calabrese et al. (1985), lithium could cause imbalances in normal thyroid function only when an autoimmune process is already present in the bipolar patient, although the drug could indeed lead to the development of the disorder due to its ability to inhibit T-cell function. This study aligns with that of Radhakrishnan et al. (2013): these authors claim that lithium would activate preexisting thyroid autoimmunity by activating lymphocytes rather than inducing TPO production on its own. Moreover, Kupka et al. (2002) state that lithium-associated thyroid insufficiency was present in patients who did not have

anti-TPO antibodies but was more frequent in subjects with such antibodies: this demonstrates that thyroid autoimmunity and lithium exposure are independent but cumulative risk factors.

Clinical Implications

The clinical implications of the relationship between bipolar disorder and Hashimoto's autoimmune thyroiditis are highly relevant for clinical practice, especially in the field of psychology and the mental health of patients.

A fundamental implication is the need to integrate both psychological and medical evaluations into various diagnostic processes. Indeed, patients with Hashimoto's autoimmune thyroiditis should be monitored not only for physical health issues arising from thyroid dysfunction but also for mood disorders, such as bipolar disorder. This consideration is also valid for symptoms associated with bipolar disorder: an analysis of thyroid function could reveal an underlying Hashimoto's thyroiditis, which must be considered in the patient's diagnostic framework. Therefore, a patient exhibiting depressive or manic episodes could benefit from a thyroid function investigation to determine the presence or absence of an autoimmune condition. This bio-psycho-social approach can significantly improve the patient's quality of life and lead to more targeted treatments.

Indeed, understanding the relationship between Hashimoto's thyroiditis and bipolar disorder could lead to greater personalization of therapies. For instance, patients with

bipolar disorder could benefit from frequent monitoring of thyroid function and anti-TPO antibodies, whose presence has been positively associated with an increased risk of developing mood disorders. The pharmacological treatment for thyroid disorders (such as replacement therapy with levothyroxine) could significantly improve bipolar symptoms, especially if integrated with effective psychotherapy, thus enhancing the patient's overall health.

Another important clinical implication is the possibility of early intervention and prevention activities. Knowing the potential correlation between these two conditions could lead to the early identification of at-risk patients, ensuring timely interventions to prevent the worsening of the mood disorder. For example, thyroid screening programs could be organized for patients with a family history of bipolar disorder or with mild symptoms, to verify if the symptoms are associated with a thyroid dysfunction condition.

Additionally, understanding the association between physical disorders, such as autoimmune thyroiditis, and mood disorders, such as bipolar disorder, could help reduce the stigma associated with psychiatric disorders, which often causes isolation and a sense of inadequacy in psychiatric patients.

Finally, the ongoing training of mental health professionals is crucial to more accurately analyze the interaction between autoimmunity and mental disorders. This is also relevant for clinical psychologists and those involved in prevention, to offer the most comprehensive and evidence-based care possible. This goal could be achieved through frequent refresher courses, which would ensure a better understanding of the implications of autoimmune diseases, promoting a bio-psycho-social approach for patients.

Limitations of the Review

Despite the methodological robustness employed, the review presents several significant limitations. First, the quality of the studies varies considerably, with some research featuring small samples (9 out of 18 studies), limiting their validity.

Additionally, some studies (4 out of 18) were conducted in clinical and hospital settings, excluding broader and more representative portions of the population. This could have introduced biases in the results, limiting their applicability to the population from which the sample was drawn.

Another limitation is the heterogeneity of the diagnostic criteria used for diagnosing Hashimoto's thyroiditis and bipolar disorder, which could have significantly influenced the results, such as differences in defining thyroiditis diagnosis, as already mentioned, or using DSM-IV or DSM-5 diagnostic criteria for bipolar disorder. Furthermore, some studies (8 out of 18) did not present control subjects, making it impossible to rule out other possible causes that could interfere with observations.

Finally, the observational nature of all the studies does not allow for definitive establishment of a direct causality between the variables considered. This means that it cannot be definitively determined whether Hashimoto's thyroiditis is a cause or a concomitant element in bipolar disorder.

Future Perspectives

The correlation between bipolar disorder and Hashimoto's thyroiditis is a research field that could offer several opportunities for future analysis.

It would be important to conduct more longitudinal studies, which can help better understand the causality between Hashimoto's thyroiditis and bipolar disorder, implementing a quasi-experiment and monitoring the development of bipolar disorder, manipulating different endocrine treatments, and evaluating whether early treatment of thyroid dysfunctions can prevent or reduce bipolar symptoms.

It would also be interesting to introduce studies investigating the presence of Hashimoto's thyroiditis as a factor that could influence the course of bipolar disorder, in order to establish whether this condition can actually change the severity of the psychiatric condition.

An important aspect is also the more in-depth study of the interaction between endocrine/immunological and psychiatric components. For example, examining thyroid hormone variations and how these influence brain components related to mood disorders could lead to a greater understanding of the underlying biology of bipolar disorder in patients with thyroid problems. Similarly, it could be beneficial to leverage more advanced neuroimaging techniques to clarify the brain changes due to the coexistence of Hashimoto's autoimmune thyroiditis and bipolar disorder, ensuring a more precise understanding of the pathophysiological mechanisms causing the simultaneous presence of the two disorders.

Furthermore, since all these studies focused on a sample of hospital patients with Hashimoto's thyroiditis, it would be important to evaluate non-hospitalized subjects who present the condition, in order to better generalize the results obtained.

Ultimately, these perspectives highlight the importance of a multidisciplinary approach and teamwork among psychiatrists, psychologists, immunologists, and neuroscientists, with the ultimate goal of developing integrated therapeutic strategies.

Conclusion

In this thesis, we aimed to answer whether there is indeed a relationship between bipolar disorder and autoimmune thyroiditis, with particular reference to Hashimoto's thyroiditis.

The research was conducted through a critical analysis of articles present in the main databases, using keywords that included both Hashimoto's thyroiditis and bipolar disorder, excluding all reviews and meta-analyses.

In light of the results obtained, we can affirm that such an association is indeed present in patients and that, therefore, those with one condition are at a higher risk of developing the other. This highlights the close relationship between the nervous system and autoimmune diseases. Patients with thyroiditis exhibit very high levels of body inflammation, evidenced by antithyroid antibodies such as anti-TPO, and the presence of cytokines (particularly interleukins), which are specific proteins that promote the proliferation of inflammatory cells in the body. This inflammation affects not only the immune system, triggering an immune response in the body but also the brain, causing mood disorders of varying clinical significance.

One of the most frequent side effects of autoimmune thyroiditis is hypothyroidism, which causes various severe problems in the individual. However, as shown by more recent studies, bipolar disorder does not depend so much on thyroid pathology but rather on the presence of anti-TPO antibodies and the associated inflammation, supporting the aforementioned assertion. Additionally, it was found that bipolar males and females have very similar TPO levels, but women are more likely to develop thyroid problems along with the mood disorder.

A crucial role in the relationship between the two conditions appears to be genetics: as demonstrated by studies on twins with bipolar disorder and the children of bipolar individuals, the levels of anti-TPO antibodies were higher than those found in control subjects. This suggests that autoimmune thyroiditis may be related not only to bipolar disorder itself but also to a genetic predisposition to developing the condition.

Finally, the role of lithium, a well-known drug used to treat bipolar disorder, in the development of autoimmune thyroiditis was explored. Studies reveal that lithium can indeed cause thyroid imbalances not mediated by antibodies, but this would only occur when an immune activation is already underway due to bipolar disorder. Furthermore, this type of reaction to the drug seems to depend on a genetic predisposition to developing an autoimmune condition, particularly in women.

This thesis has been characterized by the critical approach used for researching and analyzing the existing literature, allowing for a thorough exploration of the two conditions. However, several limitations must be acknowledged: firstly, the presence of several studies with small sample sizes, which does not allow for accurate generalization of the findings. Additionally, all the studies considered have an observational nature, preventing the definitive establishment of causality between the two conditions.

Despite most studies indicating a relationship between the conditions, some did not find a significant correlation between autoimmune thyroiditis and bipolar disorder: this aspect should be further investigated, particularly regarding the strength of this association.

From a clinical perspective, these results highlight the importance of monitoring the thyroid function of patients presenting with bipolar symptoms, to ensure more

personalized treatments, improving the patient's well-being and management of their condition.

For future research, it would be important to conduct more longitudinal studies to assess how autoimmune-origin inflammation might lead to biological and physiological changes contributing to the development of bipolar disorder. Furthermore, adopting an experimental approach is essential to establish a definitive causality between one condition and the other.

In conclusion, this work aims to contribute to a comprehensive understanding of the association between autoimmune thyroiditis and bipolar disorder, emphasizing the importance of a holistic approach to the person, integrating both the physical and psychological aspects of the patient. Certainly, the biological and physiological relationship between these disorders is very complex and requires further in-depth research, but these findings can be relevant for better managing patients affected by both conditions.

Bibliografia

Alloy, L. B., & Abramson, L. Y. (2010). The role of the behavioral approach system (BAS) in bipolar spectrum disorders. *Current Directions in Psychological Science*, *19*(3), 189-194. DOI: 10.1177/0963721410370292

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., text rev.).

Barbero, Juan & Garcia-Pares, Gemma & Llorens, Marta & Tost, Meritxell & Cobo, Jesús & Palao, Diego & Labad, Javier. (2014). Thyroglobulin antibodies and risk of readmission at one year in subjects with bipolar disorder. Psychiatry research. 219. 10.1016/j.psychres.2014.05.028.

Boukouaci, W., Oliveira, J., Etain, B., Bennabi, M., Mariaselvam, C., Hamdani, N., Manier, C., Bengoufa, D., Bellivier, F., Henry, C., Kahn, J. P., Charron, D., Krishnamoorthy, R., Leboyer, M., & Tamouza, R. (2018). Association between CRP genetic diversity and bipolar disorder comorbid complications. *International journal of bipolar disorders*, *6*(1), 4. https://doi.org/10.1186/s40345-017-0109-1

Calabrese, J.R., Gulledge, A., Hahn, K., Skwerer, R.G., Kotz, M.M., Schumacher, O.P., Gupta, M.K., Krupp, N.E., & Gold, P. (1985). Autoimmune thyroiditis in manic-depressive patients treated with lithium. *The American journal of psychiatry, 142 11*, 1318-21. https://doi.org/10.1176/ajp.142.11.1318

Calabrese, J. R., Shelton, M. D., Rapport, D. J., Kimmel, S. E., & Elhaj, O. (2002). Long-term treatment of bipolar disorder with lamotrigine. *Journal of Clinical Psychiatry*, *63*, 18-22.

Chokhawala, K., Lee, S., & Saadabadi, A. (2022). Lithium. National Library of Medicine. *National Center for Biotechnology Information. PubMed Central*.

Datto, C., Pottorf, W. J., Feeley, L., LaPorte, S., & Liss, C. (2016). Bipolar II compared with bipolar I disorder: baseline characteristics and treatment response to quetiapine in a pooled analysis of five placebo-controlled clinical trials of acute bipolar depression. *Annals of General Psychiatry*, *15*, 1-12. DOI: 10.1186/s12991-016-0096-0

Dean, O. M., Gliddon, E., Van Rheenen, T. E., Giorlando, F., Davidson, S. K., Kaur, M., ... & Williams, L. J. (2018). An update on adjunctive treatment options for bipolar disorder. *Bipolar disorders*, *20*(2), 87-96. https://doi.org/10.1111/bdi.12601

DeBiase, J. M., & Avasthi, D. (2020). Hashimoto's encephalopathy: a case report and literature review of an encephalopathy with many names. *Cureus*, *12*(8). DOI: 10.7759/cureus.9601

Degner, D., Haust, M., Meller, J., Rüther, E., & Reulbach, U. (2015). Association between autoimmune thyroiditis and depressive disorder in psychiatric outpatients. *European archives of psychiatry and clinical neuroscience*, *265*(1), 67–72. https://doi.org/10.1007/s00406-014-0529-1

Dempsey, R. C., Dodd, A. L., Gooding, P. A., & Jones, S. H. (2024). The types of psychosocial factors associated with suicidality outcomes for people living with bipolar disorder: a scoping review. *International journal of environmental research and public health*, *21*(5), 525. https://doi.org/10.3390/ijerph21050525

Gan, Z., Wu, X., Chen, Z. *et al.* Rapid cycling bipolar disorder is associated with antithyroid antibodies, instead of thyroid dysfunction. *BMC Psychiatry* **19**, 378 (2019). https://doi.org/10.1186/s12888-019-2354-6

Gordovez, F. J. A., & McMahon, F. J. (2020). The genetics of bipolar disorder. *Molecular psychiatry*, *25*(3), 544-559. DOI: 10.1038/s41380-019-0634-7

Gur, S., Taler, M., Bormant, G., Blattberg, D., Nitzan, U., Vaknin-Dembinsky, A., ... & Hochman, E. (2020). Lack of association between unipolar or bipolar depression and serum aquaporin-4 autoantibodies. *Brain, Behavior, and Immunity*, *88*, 930-934. DOI: 10.1016/j.bbi.2020.05.001

Gutch, M., Bhattacharjee, A., Kumar, S., & Pushkar, D. (2017). Graves' disease and idiopathic intracranial hypertension. *Medical Journal of Dr. DY Patil University*, *10*(3), 290-292. DOI:10.4103/0975-2870.206574

Haider, A. S., Alam, M., Adetutu, E., Thakur, R., Gottlich, C., DeBacker, D. L., & Marks, L. (2016). Autoimmune schizophrenia? Psychiatric manifestations of Hashimoto's encephalitis. *Cureus*, *8*(7). doi: 10.7759/cureus.672

Hart, D. A. (2024). Lithium Ions as Modulators of Complex Biological Processes: The Conundrum of Multiple Targets, Responsiveness and Non-Responsiveness, and the Potential to Prevent or Correct Dysregulation of Systems during Aging and in Disease. *Biomolecules*, *14*(8), 905. **https://doi.org/10.3390/biom14080905**

Heizmann, O., & Oertli, D. (2012). Thyroiditis. In *Surgery of the thyroid and parathyroid glands* (pp. 153-164). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-23459-0_10

Hillegers, M. H., Reichart, C. G., Wals, M., Verhulst, F. C., Ormel, J., Nolen, W. A., & Drexhage, H. A. (2007). Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents. *European neuropsychopharmacology*, *17*(6-7), 394-399. https://doi.org/10.1016/j.euroneuro.2006.10.005

Holmes, L. B., Harvey, E. A., Coull, B. A., Huntington, K. B., Khoshbin, S., Hayes, A. M., & Ryan, L. M. (2001). The teratogenicity of anticonvulsant drugs. *New England Journal of Medicine*, *344*(15), 1132-1138. DOI: 10.1056/NEJM200104123441504

Huang, H., Nissen, N., Lim, C. T., Gören, J. L., Spottswood, M., & Huang, H. (2022). Treating bipolar disorder in primary care: diagnosis, pharmacology, and management. *International Journal of General Medicine*, *15*, 8299. DOI: 10.2147/IJGM.S386875

Hutfless, S., Matos, P., Talor, M. V., Caturegli, P., & Rose, N. R. (2011). doi: 10.3389/fendo.2022.1081157

Ilias, I., Karagiorga, V., Paraskevas, G., Bougea, A., Bourbouli, M., Pappa, A., ... & Kapaki, E. (2015). Thyroid autoantibodies in the cerebrospinal fluid of subjects with and without thyroid disease: implications for Hashimoto's encephalopathy. *Journal of Thyroid Research*, *2015*(1), 819072. DOI: 10.1155/2015/819072

Jiang, X., Mio, M., Dimick, M. K., Zou, Y., Sultan, A. A., & Goldstein, B. I. (2022). Association of lithium and second-generation antipsychotics with neurocognition in youth with bipolar disorder. *Journal of Child and Adolescent Psychopharmacology*, *32*(1), 61-69. DOI: 10.1089/cap.2021.0093

Johnson, S. L., Tharp, J. A., Peckham, A. D., & McMaster, K. J. (2016). Emotion in bipolar I disorder: Implications for functional and symptom outcomes. *Journal of abnormal psychology*, *125*(1), 40. doi: 10.1037/abn0000116

Kapczinski, F., Dias, V. V., Kauer-Sant'Anna, M., Frey, B. N., Grassi-Oliveira, R., Colom, F., & Berk, M. (2009). Clinical implications of a staging model for bipolar disorders. *Expert review of neurotherapeutics*, *9*(7), 957-966. DOI: 10.1586/ern.09.31

Klubo-Gwiezdzinska, J., & Wartofsky, L. (2022). Hashimoto thyroiditis: an evidence-based guide to etiology, diagnosis and treatment. *Polish archives of internal medicine*, *132*(3). DOI: 10.20452/pamw.16222

Koc, D., Ince, E., San, T., Akan, P., Paketci, A., Bober, E., Tecirli, N. D., Inal, N., & Akay, A. P. (2022). Association between thyroid autoimmunity and antidepressant treatment-emergent mania in pediatric mood disorders. *Psychiatry research*, *314*, 114676. https://doi.org/10.1016/j.psychres.2022.114676

Kraszewska, A., Chlopocka-Wozniak, M., Abramowicz, M., Sowinski, J., & Rybakowski, J. K. (2015). A cross-sectional study of thyroid function in 66 patients with bipolar disorder receiving lithium for 10-44 years. *Bipolar disorders*, *17*(4), 375–380. https://doi.org/10.1111/bdi.12275

Kupka, R. W., Nolen, W. A., Post, R. M., McElroy, S. L., Altshuler, L. L., Denicoff, K. D., Frye, M. A., Keck, P. E., Jr, Leverich, G. S., Rush, A. J., Suppes, T., Pollio, C., & Drexhage, H. A. (2002). High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biological psychiatry*, *51*(4), 305–311. https://doi.org/10.1016/s0006-3223(01)01217-3

Lin, C. L., Yang, S. N., & Shiah, I. S. (2013). Acute mania in a patient with hypothyroidism resulting from Hashimoto's Thyroiditis. *General hospital psychiatry*, *35*(6), 683.e1–683.e6832. https://doi.org/10.1016/j.genhosppsych.2013.06.013

Maina, G., Bertetto, N., Domene Boccolini, F., Di Salvo, G., Rosso, G., & Bogetto, F. (2013). The concept of mixed state in bipolar disorder: From Kraepelin to DSM-5. *Journal of Psychopathology, 19*, 288.

McIntyre, R. S., & Calabrese, J. R. (2019). Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. *Current medical research and opinion*, *35*(11), 1993-2005. DOI: 10.1080/03007995.2019.1636017

Menon B. Hypothyroidism and Bipolar Affective Disorder: Is There a Connection? *Indian Journal of Psychological Medicine*. 2014;36(2):125-128. doi:10.4103/0253-7176.130966

Menon, V., Subramanian, K., & Thamizh, J. S. (2017). Psychiatric presentations heralding Hashimoto's encephalopathy: a systematic review and analysis of cases reported in literature. *Journal of Neurosciences in Rural Practice*, *8*(2), 261. doi: 10.4103/jnrp.jnrp_440_16

Morishita, C., Kameyama, R., Toda, H., Masuya, J., Ichiki, M., Kusumi, I., & Inoue, T. (2020). Utility of TEMPS-A in differentiation between major depressive disorder, bipolar I disorder, and bipolar II disorder. PLoS One, 15(5), e0232459. https://doi.org/10.1371/journal.pone.0232459

Muneer, A. (2017). Mixed states in bipolar disorder: Etiology, pathogenesis and treatment. *Chonnam Medical Journal, 53*(1), 1–7.

Müssig, K., Bartels, M., Gallwitz, B., Leube, D., Häring, H. U., & Kircher, T. (2005). Hashimoto's encephalopathy presenting with bipolar affective disorder. *Bipolar disorders*, *7*(3), 292–297. https://doi.org/10.1111/j.1399-5618.2005.00196.x

Osnaya-Brizuela, N., Valenzuela-Peraza, A., Santamaría-del Ángel, D., García-Martínez, Y., Pacheco-Rosado, J., Pérez-Sánchez, G., & Sánchez-Huerta, K. (2024). Is the acquired hypothyroidism a risk factor for developing psychiatric disorders?. *Frontiers in Psychiatry*, *15*, 1429255. https://doi.org/10.3389/fpsyt.2024.1429255

Parker, G., Graham, R., Hadzi-Pavlovic, D., McCraw, S., Hong, M., & Friend, P. (2013). Differentiation of bipolar I and II disorders by examining for differences in severity of manic/hypomanic symptoms and the presence or absence of psychosis during that phase. *Journal of affective disorders*, *150*(3), 941-947. https://doi.org/10.1016/j.jad.2013.05.018

Pasquini, M., Berardelli, I., & Biondi, M. (2014). Ethiopathogenesis of depressive disorders. *Clinical practice and epidemiology in mental health: CP & EMH*, *10*, 166. doi: 10.2174/1745017901410010166

Pempera, N., Miedziaszczyk, M., & Lacka, K. (2024). Difficulties in the Diagnostics and Treatment of Hashimoto's Encephalopathy—A Systematic and Critical Review. *International Journal of Molecular Sciences*, *25*(13), 7101. **https://doi.org/10.3390/ijms25137101**

Pillai, M., Munoli, R. N., Praharaj, S. K., & Bhat, S. M. (2021). Gender differences in clinical characteristics and comorbidities in bipolar disorder: a study from South India. Psychiatric Quarterly, 92, 693-702. https://doi.org/10.1007/s11126-020-09838-y

Radhakrishnan R, Calvin S, Singh JK, Thomas B, Srinivasan K. Thyroid dysfunction in major psychiatric disorders in a hospital based sample. Indian J Med Res. 2013 Dec;138(6):888-93. PMID: 24521631; PMCID: PMC3978977.

Ramalho, J., & Castillo, M. (2011). Hashimoto's encephalopathy. *Radiology case reports*, *6*(1), 445. https://doi.org/10.2484/rcr.v6i1.445

Ralli, M., Angeletti, D., Fiore, M., D'Aguanno, V., Lambiase, A., Artico, M., ... & Greco, A. (2020). Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmunity reviews*, *19*(10), 102649. https://doi.org/10.1016/j.autrev.2020.102649

Rybakowski, J. K. (2014). Response to lithium in bipolar disorder: clinical and genetic findings. *ACS chemical neuroscience*, *5*(6), 413-421. https://doi.org/10.1021/cn5000277

Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., ... & Grande, I. (2018). Toward precision psychiatry in bipolar disorder: staging 2.0. *Frontiers in Psychiatry*, *9*, 641. doi: 10.3389/fpsyt.2018.00641

Singh, A., & Verma, L. (2022). Hashimoto's encephalopathy with psychiatric presentation. *Industrial Psychiatry Journal*, *31*(1), 162-164. *DOI:* 10.4103/ipj.ipj_61_20

Snijders, G., de Witte, L., Mesman, E. *et al.* The seroprevalence of antithyroid peroxidase antibodies in bipolar families and bipolar twins: results from two longitudinal studies. *Int J Bipolar Disord* **5**, 1 (2017). https://doi.org/10.1186/s40345-017-0070-z

Soheili-Nezhad, S., Sprooten, E., Tendolkar, I., & Medici, M. (2023). Exploring the Genetic Link Between Thyroid Dysfunction and Common Psychiatric Disorders: A Specific Hormonal or a General Autoimmune Comorbidity. *Thyroid : official journal of the American Thyroid Association*, *33*(2), 159–168. https://doi.org/10.1089/thy.2022.0304

Solé, E., Garriga, M., Valentí, M., & Vieta, E. (2017). Mixed features in bipolar disorder. *CNS spectrums*, *22*(2), 134-140. doi:10.1017/S1092852916000869

Su, J., Zhang, J., Zhu, H., & Lu, J. (2025). Association of anxiety disorder, depression, and bipolar disorder with autoimmune thyroiditis: A bidirectional two-sample mendelian randomized study. *Journal of Affective Disorders*, *368*, 720-726. https://doi.org/10.1016/j.jad.2024.09.132

Tzakas, P., & Sit, S. W. (2011). Progressive impairment of cognition and motor function: Hashimoto encephalopathy. *CMAJ*, *183*(8), E495-E497 DOI: https://doi.org/10.1503/cmaj.100007

Vonk, R., van der Schot, A. C., Kahn, R. S., Nolen, W. A., & Drexhage, H. A. (2007). Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder?. *Biological psychiatry*, *62*(2), 135–140. https://doi.org/10.1016/j.biopsych.2006.08.041

Waliszewska-Prosół, M., & Ejma, M. (2022). *Hashimoto encephalopathy—still more questions than answers*. *Cells, 11*(18), 2873

Wolter, J. M., Le, B. D., Matoba, N., Lafferty, M. J., Aygün, N., Liang, D., ... & Stein, J. L. (2023). Cellular genome-wide association study identifies common genetic

variation influencing lithium-induced neural progenitor proliferation. *Biological psychiatry*, *93*(1), 8-17. https://doi.org/10.1016/j.biopsych.2022.08.014

Wrońska, K., Hałasa, M., & Szczuko, M. (2024). The role of the immune system in the course of Hashimoto's Thyroiditis: the current state of knowledge. *International Journal of Molecular Sciences*, *25*(13), 6883. DOI: 10.3390/ijms25136883

Wu, Y. K., Su, Y. A., Li, L., Zhu, L. L., Li, K., Li, J. T., ... & Si, T. M. (2024). Brain functional changes across mood states in bipolar disorder: from a large-scale network perspective. *Psychological Medicine*, *54*(4), 763-774. doi:10.1017/S0033291723002453

Zhang J, Chen Y, Li H, Li H. Effects of vitamin D on thyroid autoimmunity markers in Hashimoto's thyroiditis: systematic review and meta-analysis. *Journal of International Medical Research*. 2021;49(12). doi:10.1177/03000605211060675

Zhou, H., Zhu, H., Wang, J., Gao, X., & Jiang, C. (2024). Association between hypothyroidism subtypes and major depression: A two-sample Mendelian randomization study. *Journal of Affective Disorders*, *351*, 843-852. https://doi.org/10.1016/j.jad.2024.02.006

Nell’ottobre 2019, ho cominciato l’università a Genova. Non è stato un percorso facile: sono entrata per la prima volta nei corridoi con la testa bassa, piena di paura e dubbi sulla mia scelta.

In questi anni, però, ho incontrato persone che hanno veramente fatto la differenza nella mia vita, e voglio ringraziarle tutte con il cuore.

Un sentito ringraziamento al professor Gianluca Serafini, che fin dalla mia prima lezione mi ha trasmesso una passione autentica per la sua materia. Le sue lezioni mi hanno insegnato a guardare oltre i libri e a farmi sempre domande, un insegnamento che porterò con me nella mia futura carriera da psicologa.

Ringrazio di cuore la dottoressa Manuela Dall’Oro, perché il suo aiuto per la stesura di questa tesi è stato fondamentale. Ti ringrazio per la pazienza che hai avuto nei miei confronti e per la tua grandissima disponibilità, perché mi hai seguito in ogni momento. Ringrazio anche il dottor Andrea Escelsior per avermi dato l’opportunità di svolgere la tesi su un argomento a cui non avrei mai pensato, ma che si è rivelato essere estremamente arricchente.

Ai miei genitori, perché in questi cinque anni sono stati i miei più grandi sostenitori, anche quando ero arrabbiata o triste ed era impossibile starmi vicino. Grazie, perché soprattutto ultimamente mi sono resa conto del valore della vostra presenza nella mia vita e di quanto mi faccia piacere condividere tutti i miei traguardi, le gioie e i dolori con voi. Il tempo scorre e noi dobbiamo adeguarci ai cambiamenti che ne derivano, ma voi sarete sempre le mie colonne portanti. Vi ringrazio per l’amore che mi fate sentire tutte le volte che siamo insieme, ma anche quando non lo siamo, perché so che con il pensiero siete sempre rivolti a me.

A papà, che in questi anni di Università mi ha sempre dimostrato quanto credeva in me e nelle mie capacità. Grazie per tutte le volte che mi hai incoraggiata e mi hai fatto sentire forte, anche se mi sembrava che fosse tutto troppo grande per me. Da piccola, avrei fatto di tutto per renderti fiero di me e spero di esserci piano piano riuscita.

A mamma, che si è confidata con me ed è stata anche mia confidente quando mi sembrava di essere sopraffatta dal mondo intorno. Grazie per tutti i consigli che mi hai dato, perché a volte hanno davvero fatto la differenza. Da te ho preso la sensibilità e la curiosità per gli altri e queste sono qualità che mi porterò sempre dentro.

A te, Piero, che hai sempre cercato di tirare fuori il meglio di me, che mi hai sempre detto solo la verità, che, testardo come sei, mi hai preso la vita e me l’hai fatta brillare, in ogni ambito. Grazie per avermi motivato a dare sempre un po’ di più, nell’università, come nella vita, anche quando non sapevi di farlo. Quando credevo di non farcela e volevo solo ritirarmi dagli appelli, pensavo a te, alle tue parole d’incoraggiamento e al fatto che, esame dopo esame, mi avvicinavo sempre di più ad un futuro insieme a te, e questo mi bastava per avere la carica giusta per affrontare ogni ostacolo. Da ormai più di quattro anni, sei lo sguardo che voglio sempre rendere orgoglioso.

Alla nonna Rita, che da piccola mi aveva insegnato a stupirmi di fronte alle piccole cose. Ancora oggi, con il ricordo di quei momenti, mi emoziono davanti ai tramonti, alla luna e alla tranquillità del mare d’inverno.

A Martina, che è dovuta crescere in fretta per crescere William. All’inizio, eri la mia migliore amica pazza con cui vivevo i momenti più spensierati, ora sei molto di più. Ti ammiro per quello che sei diventata, per la tua determinazione, il tuo coraggio e la tua forza. Nonostante tutto, sei sempre stata al mio fianco, sia quando volevo ridere, sia quando volevo piangere. So che ci sarai sempre, come io ci sarò per te. Forse ora non faremo mai più i nostri folli giri a

Giussago, perché la vita cambia, ma spero che quello che ci unisce non cambierà mai. Ogni giorno che passa sono un po' più fiera di te.

Alle mie compagne di corso, Micol, Federica ed Elisa, che mi hanno sostenuta in questa magistrale e hanno reso meno noiose queste lezioni, altrimenti devastanti (ancora adesso tremo a ripensare ai bandi).

A tutti i miei amici di questi anni: a quelli che ho perso, ritrovato, conosciuto da poco e a quelli che ci sono sempre stati. Ognuno di voi ha lasciato un'impronta nel mio cuore e da ciascuno ho imparato qualcosa.

Voglio ringraziare, infine, la me del passato: a quella bambina, che aveva il sogno di aiutare chi soffriva e alla ragazza che aveva paura di deludere le sue stesse aspettative e si disperava perché non aveva passato il test di medicina. Alla me di ora, che non ha più dubbi su quale sia la sua strada e inseguirà quel desiderio con tutte le sue forze.

Nella vita, in un "mondo di John e di Paul, mi sono sempre sentita Ringo Starr", e mentirei se dicessi che a oggi questo pensiero è cambiato totalmente. In questo giorno della mia laurea, però, voglio essere fiera di me; il più grande augurio che mi faccio è che questo sia solo il primo di tanti giorni in cui lo sarò.

Il meglio per me deve ancora arrivare.