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Grey matter abnormalities in ADHD and Bipolar disorder: two structural MRI meta-analyses on the shared mechanisms and differences in brain functioning

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RIASSUNTO

Nell'ultimo decennio la comorbidità tra il disturbo da deficit di attenzione e iperattività (ADHD) e il disturbo bipolare (BD) ha suscitato notevole interesse nell'ambito della ricerca scientifica. Difatti, nonostante i due disturbi differiscono fenomenologicamente, numerosi studi hanno rilevato alcune similitudini dal punto di vista sintomatologico fra ADHD e BD (per esempio, l'impulsività e la disregolazione emotiva). Lo scopo della nostra ricerca è stato quello di evidenziare somiglianze e differenze nelle anomalie della materia grigia dei pazienti ADHD e BD durante l'età adulta, per indagare un potenziale legame tra questi due diversi disturbi mentali (ad esempio, un modello comune di atrofie del volume della materia grigia in regioni cerebrali simili). Attraverso una selezione precisa e accurata di studi condotti con la tecnica di neuroimmagine strutturale *voxel-based morphometry*, sono state condotte due meta-analisi separate: una prima meta-analisi sul campione di pazienti adulti con ADHD, e una seconda meta-analisi sul campione di pazienti adulti con BD (*drug-naïve* o al primo esordio maniacale/ipomaniacale). Dalla ricerca è risultato che i due campioni di pazienti presentano atrofie della materia grigia differenti, ma queste atrofie sono per lo più localizzate in una regione comune, la corteccia cingolata. Poiché, questa regione è direttamente connessa al lobo limbico e alla corteccia prefrontale, anomalie strutturali e funzionali della corteccia cingolata possono essere tradotte in deficit delle funzioni esecutive ed emotive. Conseguentemente, ipotizziamo che l'impulsività, la disregolazione emotiva e l'incapacità di gestire le emozioni spiacevoli che sono direttamente collegate all'ADHD e al BD, potrebbero essere la conseguenza dell'atrofia presente nella corteccia cingolata in entrambi i disturbi.

ABSTRACT

In the last decade several studies recognized that bipolar disorder (BD) and attention deficit-hyperactivity disorder (ADHD) frequently co-occur. Despite the fact that the two disorders are phenomenologically different, numerous studies have found some symptomatologic similarities between ADHD and BD (e.g., impulsivity and emotional dysregulation). The purpose of our research was to study similarities and differences in gray matter abnormalities of ADHD and BD patients during adulthood, and to investigate a potential link between these two different mental disorders. Through a precise and careful selection of voxel-based morphometry studies, two separate meta-analyses were conducted: the first meta-analysis was focused on a sample of adult ADHD patients, whereas the second meta-analysis included a sample of adult BD patients (drug-naïve or at first manic/hypomanic onset). The research showed that the two patients' samples have different gray matter atrophies: nonetheless, these atrophies are mostly located in a common region, the cingulate cortex. As this region is directly connected to the limbic lobe and the prefrontal cortex, structural and functional abnormalities of the cingulate cortex can be translated into deficits in executive and emotional functions. Consequently, we hypothesize that impulsivity, emotional dysregulation, and inability to manage unpleasant emotions, that are directly related to both ADHD and BD, could be the consequence of atrophy found in the cingulate cortex in these disorders.

INTRODUCTION

The overlap between Attention Deficit and Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD) is one of the most enthralling comorbidities in mental health research. Although the well-known differences between these two disorders, several studies observed the co-occurrence between them.

In this dissertation our purpose is to highlight similarities and differences in the grey matter abnormities of ADHD and BD patients during adulthood, to investigate a potential link between these two different mental disorders (e.g., a common pattern of grey matter volume atrophies in similar brain region). As a matter of fact, ADHD and BD share various clinical features (particularly during the elated phases of bipolarism), such as distractibility, impulsivity, and incapacity to appease. According to our hypothesis of similar grey matter abnormalities in ADHD and BD, this symptomatology overlap may be mediated by shared or disorder-specific neurostructural abnormalities.

In the first chapter of the dissertation the clinical manifestations of ADHD and BD will be discussed, with particular emphasis on the clinical characteristics, the epidemiology, the comorbidity, the pathophysiology, the neuropsychological characteristics (structural and functional abnormalities) and the most important therapeutic approaches.

The second chapter will focus on the comorbidity. Specifically, we will review the clinical differences and similarities in ADHD and BD, continuing with a brief overview of the most relevant studies on the comorbidity, explaining the most notable data overlap in the scientific literature.

The third chapter will be outlined the meta-analysis. In this section will be described the method (search criteria, database and tools used), the data analysis and the results achieved.

In the final chapter, the results of our research will be discussed, outlining weakness and strengths, and providing potential insights for future studies.

CHAPTER 1

CLINICAL FEATURES OF ADHD IN ADULTHOOD AND BIPOLAR DISORDER

1.1. EPIDEMIOLOGY, CLINICAL MANIFESTATION AND TREATMENT

1.1.1 Attention Deficit and Hyperactivity Disorder (ADHD)

The term ADHD stands for Attention Deficit and Hyperactivity Disorder and it is a neurodevelopmental disorder, most commonly recognized during schooling age, characterized by distractions, forgetfulness, impulsivity and motor restlessness. However, even though ADHD is considered a typical developmental-age disorder, it is also present during adulthood (Ross & Ross, 1976; Barkley, Fischer, Smallish & Fletcher, 2002) and it may persist as a disorder or may remain only certain symptoms (Faraone, Biederman & Mick, 2006). Past evidence has shown that in 30% to 70% of patients with ADHD during childhood, the disorder persists into adulthood (Lara et al., 2009; Mannuzza, Klein, & Moulton, 2003; Pary et al., 2002; Silver, 2000), but with different manifestations: the inattention level increases, there is the occurrence of interpersonal problems and coexisting psychiatric and substance abuse disorder are extremely frequent (Volkow & Swanson, 2013). Recently, it has been estimated by the Centers for Disease Control and Prevention (CDC, 2019) that the prevalence of ADHD in American children is 9.4% between the ages of 2-17 years (half of them belonging to ages 12-17). Instead, according to the most recent epidemiology study of ADHD in adults (Peige Song et al., 2021) the prevalence of persistent ADHD in adult age is 2.58%, and for symptomatic adult ADHD is 6.76% (translating to 139.84 million and 366.33 million affected adults in 2020 globally).

In the last edition of Diagnostic and Statistical Manual of Mental Disorders (DSM 5, 2013) the diagnostic criteria are more suitable for better identifying adults with ADHD: fewer symptoms (from six to five) are required in term of inattention and hyperactivity/impulsivity; age at onset was raised from age 7 years up to 12; new clinical examples relevant to an adult population have been added (APA, 2013).

Regarding the gender ratio, in ADHD adults there is a certain balance in the occurrence between male and female compared with ADHD children's populations (male predominance of about 3-4:1). This suggests that adult women are more often diagnosed than men, perhaps due to greater awareness of their own attentional and organizational difficulties (Cortese et al., 2016; Barkley et al., 2010).

An adult with ADHD shows up with the following mean features: low attention span, difficulty in planning, poor organizational skills, fluctuations in mood and changes in state of mind, impulsive behaviors, and chaotic communication. An adult with ADHD is a sensation seeking person, an individual that constantly searching on exciting situation and putting him/herself in danger, because he/she can focus better only acting that way. Substances and/or alcohol abuse is common, as a matter of fact 10% of individuals with ADHD meet the diagnostic criteria for a substance use disorder (SUD; Fayyad et al., 2007). Moreover, sometimes these patients could be inactive, slow to respond, and sluggish. Due to this symptomatologic and behavioral picture, ADHD affects many aspects of the adult's life, regardless of the grade of symptoms remission. Researchers have observed the impact of ADHD in patients' life noting that there is a long-term persistence of poor interpersonal skills, which led not only to fewer close friendships in adulthood, but also to more remarriages than control subjects (Bagwell, Molina, Pelham, & Hoza, 2001; Ingram, Hechtman, & Morgenstern, 1999; Murphy & Barkley, 1996;

Wilson & Marcotte, 1996). Likewise, patients with ADHD exhibit low academic performance, which results into lower educational attainment (Ingram et al., 1999; Murphy & Barkley, 1996), limiting their access to skilled employment positions. In the occupational area, patients with ADHD present particularly chaotic situations: indeed, it common to change jobs, either because they leave or they are dismissed (Barkley, 1998; Murphy & Barkley, 1996; Weiss, Hechtman, Milroy, & Perlman, 1985).

It has been found that the best treatment for adults with ADHD should follow a multimodal, multidisciplinary approach that includes psychoeducation, pharmacotherapy, cognitive behavior therapy (CBT), and coaching for ADHD. The participation within the treatment plan of adult's partner, family or close relationships is strongly recommended and, in some cases, systemic (family) therapy might be necessary when severe disruption to family relationships and family functioning is present (Kooij et al., 2019). In relation to pharmacotherapy, the recent systematic review and network meta-analysis on the comparative efficacy and tolerability of medications for ADHD in children, adolescents, and adults by Sam Cortese et al. (2019) showed that the first pharmacological choice for ADHD in adults are amphetamines. The amphetamines are as well tolerated as methylphenidate, and they are the only compounds with better acceptability than placebo. However, stimulants are the treatment of choice for adults with ADHD. Long-lasting, extended-release formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing. In European countries and beyond there is the necessity of stimulants license for ADHD adults. The non-stimulant atomoxetine is recommended as a second line

treatment, while there is limited evidence in adults for guanfacine, bupropion, tricyclic antidepressants and reboxetine in controlled studies (Kooij et al., 2019).

1.1.2 Bipolar Disorder (BD)

The bipolar disorder (BD) is one of the most disabling psychiatric disorders and it ranks as the 17th leading source of disability among all diseases worldwide (Vigo, 2016). The onset of bipolar disorder is around the age of 20 years, and earlier onset is often associated with a poorer prognosis, longer treatment delays, more severe depressive episodes, and higher prevalence of concurrent anxiety and substance use disorders (Carvalho, 2020). The hallmark of bipolar disorder is the presence of manic or hypomanic episode that may alternate with depressive episode. There are three types of BD: bipolar I disorder (presence of overt maniac episode); bipolar II disorder (more frequent depressive episodes with hypomania); cyclothymic disorder (recurring depressive and hypomanic states that do not meet the diagnostic threshold for a major affective episode). According to DSM-5 (2013), to be diagnosed with bipolar I disorder, a manic state should be present for at least 1 week and for the diagnosis of bipolar II a hypomanic episode should last at least 4 days with a 2-week depressive episode. The World Mental Health Survey Initiative reported lifetime and 12-month prevalence estimates for bipolar disorders of 2.4% and 1.5%, respectively, even if prevalence rates vary by country. The gender ratio is nearly equal for male and female, except for bipolar II that is more frequent in women. The educational and occupational spheres in people with BD are particularly affected, as the disorder occurs during the formative years and cognitive and psychosocial dysfunctions during acute episodes or in periods of remission compounds the situation (Carvalho et al., 2020).

A critical problem for BD patients is suicide, due to the fact that approximately 6 to 7% of persons with bipolar disorder commit suicide (suicide rates among persons with bipolar disorder are 20 to 30 times as high as the rates in the general population) (Plans et al., 2019).

The treatment management of BD patients is complex, and it depends on the phases that the subject is experiencing. When the patient is facing a manic episode, antipsychotics or mood stabilizers are commonly used, but when the patient is not responding to treatment, it is useful to combine these two types of medications. Non-pharmacological treatments can also be used for individuals who are resistant to medication or have severe mania. In addition, ECT (bifrontal electroconvulsive therapy) is indicated for cases of refractory mania and for patients with aggressive behavior or psychotic symptoms, as a single therapy or in addition to pharmacological treatment. With the respect to the depressive episode (DE) (the most frequent, but the least studied), there are few drugs approved by the FDA (Food and Drug Administration) to cope with such affective events. Antipsychotic and mood stabilizing medications are both necessary for DE, as clinically significant improvement has been shown in the scientific literature. In addition, the use of 2nd generation antidepressants (effective for short-term treatment of bipolar depression) has been suggested for the treatment of DE. Finally, the use of non-pharmacological treatments such as ECT and different types of psychotherapy (CBT and mindfulness CBT, psycho-education, etc.) resulted to be effective for BD treatment (Carvalho et al., 2020).

1.2 AETIOLOGY, PATHOPHYSIOLOGY AND GENETICS

ADHD is a heritable, chronic, neurobehavioral disorder that is characterized by hyperactivity, inattention, and impulsivity. The range of hereditability is estimated

between 70% and 80% (Faraone, 2004). Twelve significant risk loci were successfully identified from the Genome-wide Association studies although these associations accounted for approximately 22% of the heritability of the disorder.

Substantial risk factors for the onset of the disorder are prenatal, perinatal, and postnatal issues. It is shown that prematurity and low birthweight are consistently associated with ADHD. Moreover, intrauterine exposure to tobacco and alcohol, maternal stress and obesity during pregnancy are also associated with ADHD (Posner et al., 2020). With regard to postnatal factors, it has been observed by experimental evidence that exposure to artificial food dyes and flavors increases the severity of ADHD symptoms (but the effects are small). Whereas studies conducted to link ADHD and exposure to pollutants and pesticides are largely correlational (Posner et al., 2020).

Associations between ADHD and parenting style have been investigated, nonetheless they are the effect of an evocative gene-environment correlation whereby a child's behavior elicits severe and unsupportive parenting, that in turn fosters the rising climax of problems and the coercive cycles within families. Another evidence that supports the social causes of ADHD is the naturally created experiment of neglected children during the Communist regime in Romania in the late 1980s. Following on from earlier studies showing an association between institutional neglect and ADHD, Kennedy and colleagues (2016) reported a 7-times increase in ADHD in individuals who had experienced more than 6 months of deprivation as children compared with those who experienced less than 6 months. The magnitude of this effect, combined with the strength of the design (contrasting those with more and less than 6 months deprivation), means that this outcome is unlikely to be attributable to pre-existing genetic or intrauterine risk.

On the other hand, largescale prospective studies such as the UK Biobank and the US-based ECHO and ABCD tried to better explain the gene-environment interactions and ADHD causality. These studies include biospecimens for genome-wide sequencing, detailed measures of phenotypic variance, and longitudinal assessments of environmental exposures, with adequate power to detect interactions and small effects (Posner, 2020). Another hypothesis that attempts to explain the causes of ADHD are the hypoactive and hyperactive catecholamine hypotheses of ADHD (Figure 1). As a matter of fact, the primary symptoms of attention deficit/hyperactivity disorder (ADHD) include poor impulse control and impaired regulation of attention. Researches have shown that the prefrontal cortex (PFC) is essential for the "top-down" regulation of attention, behavior, and emotion, and that this brain region is underactive in many patients with ADHD (Arnsten et al., 2011). At the same time, the PFC is known to be especially sensitive to its neurochemical environment and alterations in the pathways mediating catecholamine transmission can impair PFC function (Sharma and Couture, 2014).

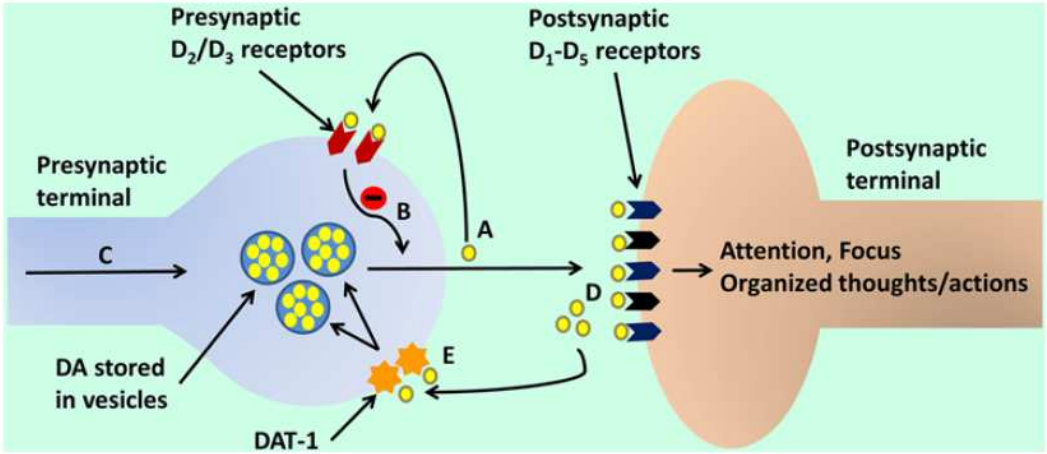

Figure 1. Integration of the hypoactive and hyperactive catecholamine postulates of ADHD. Adapted from Sharma and Couture (2014).

Even for BD there is a strong genetic component as well as ADHD, since it is highly hereditable. Estimates of heritability range from 70% to 90% (Gordovez, 2020). Genome-wide association studies have provided preliminary findings regarding the underlying genetics and potential neurobiological precursors of bipolar disorder, despite that the genetic variants found to be a risk for DB actually explain only 25% of all heritability of the disorder. In addition, it is necessary to recognized that common genetic variants interact with environmental risk factors.

The "kidling" hypothesis (Post, 2016) (i.e., sensitization to stress leading to manic and depressive episodes) has been proposed to explain the nature of BD. According to this theory, the first episode of BD occurs after exposure to a stressor, and subsequently other episodes may occur without being exposed to a stressful event. If the disease is never treated, or if the person is exposed to psychoactive substances or lifestyle risks (smoking or sedentary behavior) the mechanisms underlying the kindling hypothesis may be strengthened. Poorly characterized epigenetic mechanisms are also considered to contribute to the putative kindling phenomenon (Carvalho, 2020).

Notably, progressive changes in brain structure and function (neuroprogressione) have been observed in several studies to be associated with recurrent affective disorder events. It has been observed that the factors promoting neuroprogression in BD are epigenetic mechanisms, dysregulation of mitochondrial function, pathways subserving neuroplasticity, inflammation, and an increased oxidative and nitrosative stress (Berk, 2011). A dysfunction in the hypothalamic-pituitary-adrenal axis is also considered to be implicated in the psychopathology and progression of BD. Hypercortisolism could be also critic in the pathogenesis of depressive symptoms and cognitive deficits, which may in turn result from the neurocytotoxic effects of elevated cortisol levels. It seems that

manic episodes are preceded by an increased ACTH and cortisol levels, leading to cognitive problems and functional impairments. This hypothesis was also supported by the results obtained from manipulation of the HPA axis: indeed it has been shown to have therapeutic effects in preclinical and clinical studies, and recent data suggests that direct GR (glucocorticoid receptor) antagonism could be a future therapeutic strategy in the treatment of mood disorders (Daban et al., 2005). The process of neuroprogression contributes in part to the onset of co-occurring medical conditions, as well as premature death among people with bipolar disorder (e.g., type 2 of diabetes mellitus is higher among people with multi-episodic bipolar disorder compared with among those with single-episode bipolar disorder; Vancampfort et al., 2016).

1.3 NEUROIMAGING FINDINGS

In this section we will discuss the major findings from structural and functional neuroimaging studies in ADHD and BD. As a matter of fact, neuroimaging techniques are one of the most powerful tools we have for identifying endophenotypes among several diseases. Structural abnormalities and functional impairments in ADHD and BD will be presented in the following sections.

1.3.1 Structural abnormalities

Magnetic resonance imaging (MRI) and Diffusion Tensor Imaging (DTI) have been used to gain insight about structural brain alterations (differences in volume, cortical thickness, surface area, and gyrification) in ADHD and BD.

In ADHD patients, MRI have showed reduced total/whole brain and grey matter volume compared to controls, and abnormal grey matter volumes have been observed for the total cortical volume, in prefrontal and other frontal areas, as well as in the occipital and

parietal lobes. Abnormalities in the basal ganglia, prefrontal structures, and the corpus callosum have been the most consistently findings reported across studies in children and adults with ADHD compared to healthy subjects (e.g., Valera, 2007; Ellison-Wright, 2008; Nakao, 2011; Silk, 2016; Ambrosino, 2017; Wierenga, 2014).

Regarding the cortical volume, several studies have investigated different cortical markers (surface area, cortical thickness, gyri, volume) and that methodology allowed to disentangle of the relative morphological contributions to reduced volumes. In particular, it has been found that the surface area of the precuneus was a major driver of volume differences observed in ADHD patients (Silk et al., 2016).

Studies carried out with DTI found increased and decreased fractional anisotropy in multiple white matter traces in several ADHD studies, where the finding is the atypical interhemispheric connection by the corpus callosum (Albajara Saenz, 2018).

With the respect of BD, a large number of evidence has found associations between MRI-derived brain markers and bipolar disorder, showing that BD is associated with alterations in the neuroanatomical structured of emotion and reward processing (Phillips et al., 2014). In particular, these data showed lower volumes in subcortical structures (thalamus, amygdala and hippocampus) and abnormalities in temporal, frontal and insular cortices (Hajek, 2009, 2012; Rimol, 2010, 2012). In addition, widespread alterations in white matter (including fronto-limbic connections) were also found (Phillips, 2014).

1.3.2 Functional abnormalities

Functional studies in ADHD populations observed abnormalities in frontal striato-thalamic and fronto-parieto-cerebellar regions. This alteration could be responsible for attentional and executive function impairments (especially working memory and inhibition) and could reflect the structural abnormalities in brain regions hypothesized to

underlie these functions. In particular, a recent meta-analysis showed domain-specific brain dysfunctions. During motor response (Stop Signal Task, go/no-go), interference inhibition (Stroop, Simon, and Eriksen flanker tasks), and switching tasks, a reduced activity in bilateral fronto-basal ganglia network, as well as in occipital, parietal, and temporal areas was observed in the ADHD group compared to healthy controls (Lei, 2015; Cortese, 2012; McCarthy, 2014).

Furthermore, part of the default mode network (DMN) shows an increased activity in ADHD, while it is typically reduced during tasks and increased during resting-state (Lei D, 2015; Cortese, 2012; Sonuga-Barke, 2007)

Regarding working memory, there is evidence of reduced activity in the ADHD group in bilateral frontal and frontoparietal areas, and the insula. During attentional tasks, studies have shown reduced activation in the right prefrontal cortex, posterior basal ganglia, and thalamic and parietal regions, as well as increased activation in the cerebellum and the precuneus in individuals with ADHD relative to healthy subjects.

Moreover, studies on reward processing reported a ventralstriatal hypo-responsiveness during reward anticipation in individuals with ADHD compared to controls (Cortese, 2012; McCarthy, 2014; Hart, 2013; Plichta, 2014).

In conclusion, a meta-analysis of functional MRI on time perception reported reduced activation in typical areas supporting time processing, such as the left inferior prefrontal cortex/insula, the cerebellum, and the left inferior parietal lobe, as well as increased activation in the precuneus and the posterior cingulate, probably reflecting poor deactivation of the DMN (Hart, 2012).

The adult ADHD literature is still far less consistent than the childhood ADHD literature. Nonetheless, considering neuroimaging studies in adult ADHD, results appear in line

with those obtained in childhood ADHD, consisting in structural and functional abnormalities in the inferior and dorsolateral prefrontal lobe, in anterior cingulate, parietotemporal and cerebellar areas, as well as limbic areas of reward processing of ventral striatum and amygdala. studies that have found increased activation in the same brain regions in adult ADHD (Cubillo & Rubia, 2010).

With regards to bipolar disorder, functional MRI has shown alterations in frontal, temporal and striatal networks that regulate emotion and reward regulation in bipolar disorder. According to Phillips and Swartz (2014) bipolar patients show dysfunctions in prefrontal cortical (especially ventrolateral prefrontal cortex and orbitofrontal cortex) – hippocampal-amygdala emotion processing and emotion regulation circuits bilaterally, together with an "overactive" left-sided ventral striatal-ventrolateral prefrontal cortex reward processing circuitry, that may result in the characteristic behavioral abnormalities associated with bipolar disorder: emotional lability, emotional dysregulation and reward sensitivity (Figure 2)

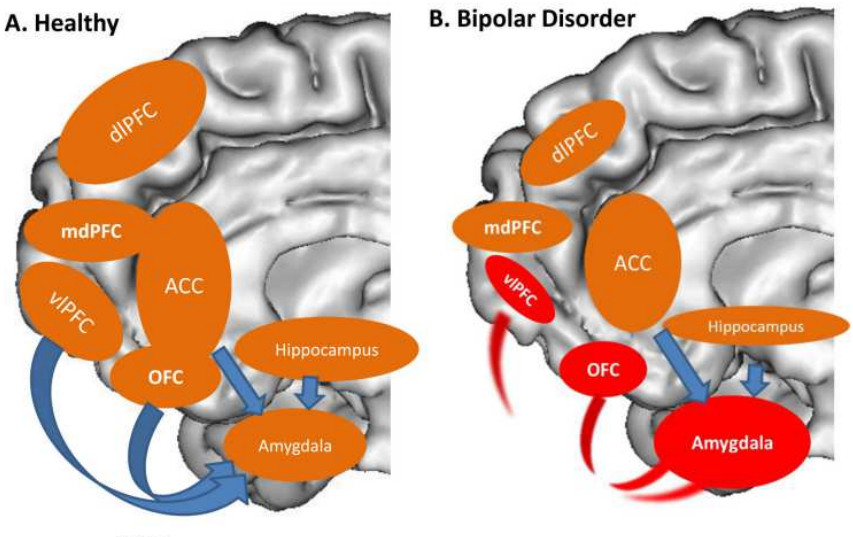

Figure 2. Emotion processing and emotion regulation: Healthy Controls vs Bipolar Disorder. Adapted from Phillips and Swartz (2014).

However, there are several issues in neuroimaging investigation among bipolar patients such as variable and sometimes conflicting results, in which is added patients' heterogeneity (e.g., age at onset, duration/severity of illness and treatment regimen). All these reasons represent a jamming factor for the improvement of replication and reproducibility of neuroimaging findings in bipolar disorder.

CHAPTER 2

THE COMORBIDITY BETWEEN ADHD AND BIPOLAR DISORDER

2.1 OVERLAPS AND INCONGRUITIES IN DIAGNOSTIC CRITERIA

Within the *Diagnostic and Statistical Manual of Mental Disorder* (DSM-5) ADHD and BD are placed in two different sections of psychiatric condition: the first takes place in the neurodevelopmental disorders, whereas the second belongs to the bipolar and related disorders.

ADHD is a chronic disorder, occurs during childhood and it may persist through adulthood. In DSM-5, ADHD symptoms are divided in two clusters: inattentions and hyperactivity/impulsivity.

In contrast, BD is an episodic disorder characterized by a lifetime history of at least one manic or hypomanic episode. Regarding the age of onset, the disorder has its peak in late adolescence or early adulthood, whereas juvenile presentation is rare although it is possible (Post et al., 2008).

Despite ADHD and BD are two different types of mental illness, their phenotypic expression shares several symptomatic manifestations. As a matter of fact, analyzing the diagnostic criteria of ADHD and BD in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) we can easily find similarities between them. For example, in the inattentive subtype of ADHD it is reported a criterion, i.e., "often easily distracted by extraneous stimuli", that can directly overlaps with the bipolar criterion of "distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed." Furthermore, from the hyperactive/impulsive

cluster there are at least two symptoms that may overlap with bipolar disorder criteria. The ADHD criterion "is often 'on the go,' acting as if 'driven by a motor'" appear to overlap with the bipolar disorder criterion "increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal directed activity)". Similarly, there is the ADHD criterion that states: "often talks excessively" that is genuinely close to the bipolar symptom "more talkative than usual or pressure to keep talking". Additionally, there are two other criteria in ADHD symptoms, i.e., "often blurts out an answer before a question has been completed" and "often interrupts or intrudes on others" that could overlap with the symptom "talkativeness" of BD (Brus et al., 2014).

Then, frequently patients with ADHD are extremely chaotic and full of energy, and these behavioral characteristics are comparable to those of a manic phase, where bipolar patients are shaken and never seem to tire (Edinoff et al., 2022). Moreover, both disorders share sleep disturbances, but in different ways: ADHD patients have difficulty settling to sleep, whereas BD patients have decreased need to sleep (Scheffer, 2007). Additionally, untreated ADHD patients frequently have dysphoric mood (bad feelings) that is highly comparable to depressive symptoms of bipolar depression. The most commonly symptomatology experienced in both disorders during dysphoric mood is psychomotor retardation, fatigue or loss of energy, hypersomnia, loss of interest or pleasure.

Nevertheless, the manic episode is a far cry from the usual behavior of a patient with ADHD, as we will analyze more thoroughly later. The problem arises when we compare certain presentations of bipolar II disorder with adult ADHD patients. As a matter of fact, hypomania lacks many of the classic features of maniac states, such as euphoria, grandiosity, a decreased need to sleep, and an increase in productive behavior. Instead,

hypomanic patient experiences irritable mood, distractibility, talkativeness, racing thoughts, and non-goal directed psychomotor agitation, that may appear close to the clinical signs shown by an adult patient with ADHD. For example, "psychomotor agitation (i.e., purposeless non-goal directed activity)" closely resembles the ADHD symptoms of "fidget[ing] with or tapp[ing] hands or feet or squirm[ing] in seat," "feeling restless," "leav[ing] seat in situations when remaining seated is expected," and being " 'on the go,' acting as if 'driven by a motor'" (Brus et al., 2014).

Emotional lability is another common feature among bipolar and ADHD patients, as cyclothymic temperaments have been described in both disorders. Despite this, mood liability takes on different shades depending on the illness: in bipolar disorder mood liability vary from euthymia to depression or elation, or from depression to elation; otherwise, ADHD patients show an impaired emotional self-regulation, which can cause outbursts and low frustration tolerance in response to stress.

To sum up, ADHD and BD have several diagnostic criteria in common, including inattention; executive disfunction; impulsivity; sensation seeking; restlessness; substance use comorbidity; talkativeness; forgetfulness; functional impairment; sleep disturbance.

A Venn diagram of the overlap and different symptoms between ADHD and BD patients is shown in Figure 3 (Edinoff et al., 2022).

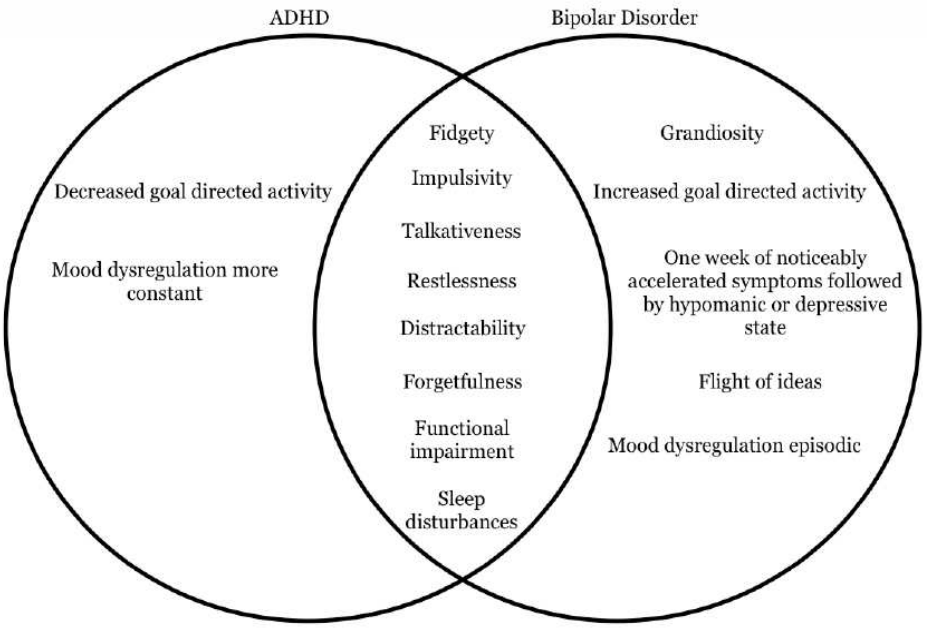

Figure 3. Diagnostic criteria of ADHD versus BD. Adapted from Edinoff et al. (2022).

Notwithstanding the resemblances, as previously stated, ADHD and BD are phenomenologically different. ADHD is a neurodevelopmental disorder, which means that the age of the onset is typically during development, but the disorder can persist throughout life (life-long disorder from Barkley, 2002) although with a different symptomatic manifestation. DSM-5 requires that "several" ADHD symptoms appear before age 12 years, higher than the age 7 cutoff used in the previous edition (DSM-IV-TR).

In contrast, BD is categorized in DSM-5 as a disorder separated from both depressive disorders and schizophrenia spectrum disorders, characterized by mood instability, with fluctuation between manic or hypomanic episodes and depressive episodes. In particular, the age of onset of BD is on average 20 years, differently from ADHD and, as noted in DSM-5, "bipolar disorder is rare in preadolescents". In a work by Post and colleagues (2008), the authors reported that the onset of bipolar disorder before age 13 years occurs in just 2%-16% of cohorts in Europe.

Furthermore, ADHD is a persistent disorder which means that adult patients with ADHD can display symptoms throughout life at any time as a baseline characteristic, while bipolar patients have mood fluctuations that don't represent the usual state of the subject (Brus, 2014). Anyway, ADHD symptomatology and functioning decrease over time, and only half of cases of ADHD persists into adulthood (Lara, 2009).

Previously, it has been reported that "many ADHD symptoms overlap with the symptoms of mania" (APA, 2013), but there are some elements that distinguish a maniac episode from a typical ADHD behavior. Indeed, it is frequent in the manic episode to have grandiose or erotomaniac delusions; make foolhardy choices, such as take sexual, financial, or physical risks; stay up for days to pursue inconclusive projects. This is very far from even the extreme forms of ADHD, which don't have delusions or formal thought disorder.

Two other crucial features that distinguish the two disorders are the occurrence in bipolar disorder of psychosis and high suicide rates, that are rare in ADHD patients, especially during a psychosis episode.

2.2 INCIDENCE AND REASONS OF CO-OCCURANCE

Recently, several clinical and epidemiological studies have sought to clarify the complex co-occurance between ADHD and BD.

In a survey of The National Comorbidity Survey-Replication (NCS-R), one of the wider and most representative mental health poll conducted in USA, has been estimated the prevalence of BD in the 21.2% of ADHD patients (Kessler, 2006).

In Europe, two large nationwide population studies conducted in Norway and Sweden investigated the prevalence of BD in respectively 40000 and 61000 subjects with a

diagnosis of ADHD, finding quite homogeneous rates of BD in 8.9–9.4% of men and 13.5–18% of women (Solberg, 2018; Chen, 2018).

On the contrary, the NCS-R estimated that ADHD occurred in 31.4% of BD patients and it has been observed that BD subjects had a 6.7-times higher risk for co-occurring ADHD than the US general population (Merikangas, 2007). Furthermore, in the WHO Mental Health Survey initiative carried out over 11 countries, it has been found that ADHD could be diagnosed in the 19.8% of 1573 patients with BD (Merikangas, 2011).

Clinical studies also show high rates of ADHD in patients with BD-I. An extensive study of ADHD comorbidity in populations with bipolar disorder found a lifetime prevalence of ADHD of 9.5% (14.7% among males, 5.8% among females) in the first 1000 patients with bipolar disorder who enrolled in the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).

In a report from the International Mood Disorders Collaborative Project by McIntyre and colleagues (2010), it has been found that 17.6% of patients with BD, interviewed with a structured diagnostic interview, had comorbid ADHD. The bipolar sample was characterized by an earlier age at onset, more comorbid anxiety disorders and lower quality of life. It is important to note that the age of onset as ADHD comorbidity could depend on this factor. As a matter of fact, in the Nierenberg et al.'s evaluation (2005) the 13% of BD patients with an onset before 18 years met ADHD criteria and, among these with disease onset at age 18 or older, only 5% met criteria for ADHD.

Significant evidence is also provided by longitudinal studies that have tried to assess whether children with ADHD would develop (hypo)manic episodes over time. In a 10-year follow-up study, boys with ADHD had a 7.9-times higher risk than healthy controls for developing BD by the age of 21 (Biederman et al., 2006).

In a similar 11-year longitudinal study, the same research group compared girls with ADHD and healthy controls and found that ADHD had an even higher rate than males, a 10-fold risk for developing BD by the age of 22 compared with controls (Biederman et al., 2010).

In another longitudinal study, Biederman and colleagues (2009) followed up on 168 adolescents with a history of major depression for 7 years: in those with comorbid ADHD, a manic episode occurred in 28% of cases, versus only 6% in those without ADHD. Finally, a Taiwanese nationwide study followed up on 58000 young adults with major depression at baseline, of which around 1200 had a diagnosis of ADHD. After 10 years, the 19% of patients with baseline ADHD comorbidity would be diagnosed with BD versus the 11% of controls, with a 50% higher risk of developing BD after controlling for several confounding factors, among all psychiatric comorbidity (Chen et al., 2015).

Therefore, the reviewed clinical studies found that around 10–20% of adult patients with BD has comorbid ADHD, with even higher rates in those with earlier age at onset (Brus et al., 2014). The abovementioned meta-analysis, pooling together population and clinical studies, found a combined prevalence of ADHD in the 17% of adult patients with BD (Schiweck et al., 2021).

On the other hand, youths with ADHD are more at risk to develop BD in young adulthood, with incidence rates of 7–21% (Wingo, 2007; Skirrow, 2012). The comorbidity between ADHD and BD appears to be a negative prognostic feature as it may confer a greater severity and liability for other psychiatric disorders, together with an overall worse functioning and burden of disease.

Regarding the possible reasons of the comorbidity, a shared, genetic-effect hypothesis has been considered, due to the high occurrence of BD and ADHD in family-based studies.

In a meta-analysis by Faraone et al. (2012), it was observed that relatives of probands with BD had a significantly higher chance of manifesting ADHD, and among relatives of ADHD probands, BD-I occurred more frequently (the relative risk was doubled each way). In an recent work by Schiweck et al. (2021) previous meta-analysis data were confirmed, indeed the authors reported that higher comorbidity rates of ADHD or BD were found in first degree relatives of probands with BD or ADHD respectively, compared with relatives of controls.

Moreover, a recent study with the largest data sample provides only a small significant genetic correlation ($rg = 0.14$, $p < 0.001$) (Consortium et al., 2019). This small genetic correlation suggests that rare variants, main effects of environmental risk factors or gene by environment interactions must explain the extent of cross-transmission of ADHD and BD seen in family studies. The Genome-Wide Association Studies (GWAS) performed a cross-disorder meta-analysis of eight psychiatric disorders including BD and ADHD and identified eight pleiotropic loci with shared risk (Consortium et al., 2019). Interestingly, among the most significant pleiotropic loci showing association with both ADHD and BD were some genes involved in neuronal development and corticogenesis (Manitt et al., 2013) or synaptic functioning (Hamada et al., 2015). This is a significant outcome since delayed cortical and subcortical maturation may have a role in the pathophysiology of both disorders (Najt et al., 2016; Shaw et al., 2012).

Overall, many researchers are still examining the genetic overlap between ADHD and BD that may impact processes involved in brain maturation and neuronal signaling

(Delghandi et al., 2005; Hamada et al., 2015; Manitt et al., 2013). Nevertheless, no lead SNP (single-nucleotide polymorphism) was shared between studies, and for this reason the achievements are inconsistent. Accordingly, it is necessary that future studies include larger samples to detect shared genetic risk factors.

2.3 NEUROBIOLOGICAL MARKERS

Over the last few years several researchers investigated differences and similarities in brain functioning of ADHD and BD aiming to discover neurobiological features. In this section, a brief review is provided, outlining cognitive performance, task-related brain activation patterns, and brain volumes. However, scientific literature on adults is extremely sparse, as most studies have been conducted primarily on children.

Regarding cognitive performance, in a study of Walshaw et al. (2010) ADHD and BD childhood were compared reporting that response inhibition and visual and spatial working memory (total digit span and spatial span) was not dissimilar between the two disorders. Nevertheless, researchers found discrepancies in some cognitive measures: such as interference control, planning and set shifting impairments were enhanced in BD, whereas impairments in phonemic fluency, spatial working memory, and verbal working memory (backwards digit span) were pronounced in ADHD.

Moreover, cognitive deficits were examined in adult with ADHD, BD-I and controls in a study by Torralva and colleagues (2011), using a large battery of cognitive tests. ADHD and BD-I patients obtained similar scores in immediate verbal recall and letter-number sequencing task, outlining an equivalent impairment, although verbal and visual recognition deficits were mainly found in individuals with BD. Though, the results obtained from the two mentioned studies are discordant, indeed Walshaw et al. (2010)

identified grater working memory deficits in ADHD, whereas Torralva et al. (2011) did not find specific differences in this measure.

Moreover, response time differences in ADHD and BD, were investigated in two studies by Dickstein et al. (2005) and by Mattis et al. (2011). In the first study, researchers compered groups of children (ADHD, BD-I, comorbid ADHD+BD and controls) on timed repetitive and sequential tasks. The results showed that clinical groups have performed worse compared with controls (slower reaction times). In particular, ADHD children had a specific impairment on the repetitive task, whereas BD children and comorbid sample on sequential tasks. In the second study, Mattis et al. (2011) compared children with ADHD, BD and comorbid BD+ADHD on sequential tasks, reporting faster and less variable reaction times in AHD children compared to the other groups. Moreover, BD children and comorbid sample were slower and more variable as the inter-stimulus time was increased.

Focusing on functioning brain differences, Passarotti et al. (2010) used fMRI during an inhibitory function task in ADHD children and BD-I, reporting similar performance deficits in both clinical groups compared to healthy control. However, the researchers also found two distinctive abnormal activations, as it has been observed an extensive and more severe decreased prefrontal activation in ADHD compared to BD, with a subcortical overactivity.

fMRI studies on the emotional-face processing have been also conducted. Brotman et al. (2010) investigated three different clinical groups: BD, ADHD, and children with severe mood dysregulation (SMD) (compared to healthy control). All the subjects had to rate of facial expression (from fear to neutral faces) and the authors identified specific amygdala activation pattern of each of the three clinical groups. In another study of Passarotti et al.

(2010), emotional-face processing was studied in children with BD, ADHD and healthy controls, revealing that both clinical groups showed reduced and increased activity in cortico-subcortical circuitry in response, to angry faces and happy faces, respectively. Nevertheless, discrepancies in brain activation were observed in clinical subgroups: emotion regulation regions (left medial prefrontal cortex, and subgenual anterior cingulate cortex) were highly activated in BD group, whereas working memory and premotor regions in the left hemisphere were strongly activated in the ADHD group.

Finally, regarding brain structural data, few studies investigated brain volumetric differences between ADHD and BD. The first study was conducted by Biederman et al. (2008), who compared adult BD-I, ADHD, and comorbid BD-I+ADHD. The researchers found that ADHD was associated with reduced grey matter volume in the superior prefrontal cortex, anterior cingulate cortex, and cerebellum, whereas BD showed increased thalamic and smaller orbital prefrontal volumes. Another study (Lopez-Larson et al., 2009) investigated children with ADHD, BD-I and comorbid BD+ADHD group. Distinct differences in subcortical regions were found in individuals with ADHD (smaller caudate, putamen amygdala volumes) compared to groups of controls and those with BD (including the comorbid group). Moreover, they observed larger nucleus accumbens volumes in both the BD and comorbid groups.

Finally, Makris et al. (2013) investigated the cortical thickness in adult with ADHD, BD and comorbid ADHD+BD group. The results observed by the author supported the hypothesis that the comorbid sample presents a morphometric profile that reflects an additive effect of ADHD and BD cortical abnormalities. Individuals with comorbid ADHD+BD showed cortical thinning within both the dorsal-cortical system (dorsolateral and medial frontal pole, anterior cingulate and paracingulate gyrus) as well as in the

ventral-limbic system (medial frontal cortex and ventral frontopolar cortices) bilaterally. Figure 4 shows the effect of ADHD controlling for BD. Colored regions show clusters with significant cortical thinning due to an independent ADHD effect. Color bar represents beta values from regression model. Overall, these alterations in prefrontal limbic circuitry reflect a disruption in regions governing cognitive control of affective and hedonic functions, as well as self-monitoring, attention, and executive functions (Makris et al., 2013).

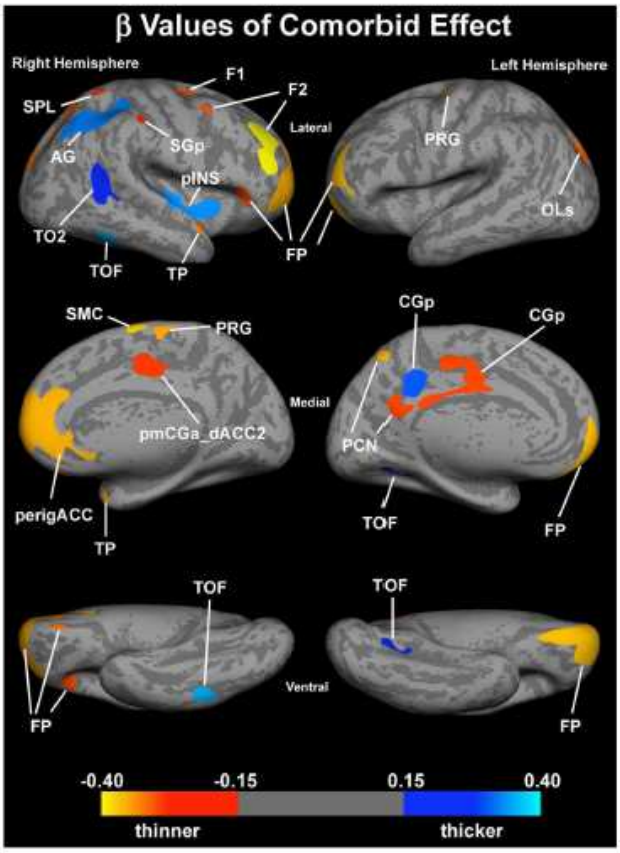

Figure 4. Effect of ADHD controlling for BPD. Adapted from Makris et al. (2013).

CHAPTER 3

THE RESEARCH

3.1 INTRODUCTION

Recently, numerous studies demonstrated that attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) may occur in the same patient at the same time, and the concurrence of these conditions frequently results in complications for clinicians and patients. ADHD is a neurodevelopmental disorder with a typical childhood-onset and it is characterized by a deficit of attention and motor hyperactivity leading to significant impairment in academic/occupational, familiar and social functioning. Although, ADHD is commonly known as a childhood disorder, it can occur during adulthood, but with a different expression of symptom. Adult ADHD is often characterized by symptoms such as impulsivity, distractibility, restlessness, and they may be unable to hold a job or maintain personal relationships (Salvi et al., 2021).

In contrast, BD is a mental disorder with a typical age onset in young adulthood characterized with abnormal shifts in mood, energy, activity, sleep and cognitive functions during episode of mania or hypomania and depression.

The phenotypic expression of ADHD and BD shares many common symptomatic manifestations, such as fidgety, impulsivity, talkativeness, restlessness, distractibility, forgetfulness, functional impairment, and sleep disturbance.

Besides the diagnostic criteria overlap, as previously stated, ADHD and BD frequently occur together. As a matter of fact, approximately 20% of adult patients with ADHD show bipolar disorder, while 10%–20% of patients with bipolar disorder have adult ADHD (Brus, 2014). Moreover, in a recent meta-analysis by Schiweck and colleagues

(2021) 1 out of 13 patients with ADHD had BD, and nearly 1 out of 6 patients with BD were diagnosed with ADHD.

The main aim of this study was to carry out quantitative voxel-based morphometry (VBM) meta-analyses of all published whole brain structural MRI studies of gray matter abnormalities in adult ADHD and BD, to establish shared and disorder specific structural abnormalities. Our hypothesis was to find atrophies in grey matter volume of ADHD and BD patients in correspondence of the frontal areas, as the two disorders share executive function impairments, and in the subcortical areas, as both disorders are also characterized by emotional dysregulation (Brus, 2014).

3.2 METHODS AND PROCEDURES

3.2.1 Studies selection

A comprehensive literature search was performed using the PubMed and PsycInfo databases. The keywords used in the ADHD research were: (attention-deficit) AND (structural MRI); (attention-deficit) AND (structural magnetic resonance imaging); (ADHD) AND (structural MRI); (ADHD) AND (structural magnetic resonance imaging); (attention-deficits) AND (voxel-based morphometry); (ADHD) AND (voxel-based morphometry); (ADHD) AND (VBM); (attention-deficits) AND (VBM) (for both Pubmed and PsycInfo). The keywords used in the BD research were: (((magnetic resonance imaging) OR (MRI)) AND (bipolar disorder)) AND (first episode); (((magnetic resonance imaging) OR (MRI)) AND (bipolar disorder)) AND (first episode-mania); (((magnetic resonance imaging) OR (MRI)) AND (bipolar disorder)) AND (drug naive) (for both Pubmed and PsycInfo). In addition, manual searches were conducted among the reference sections of retrieved studies and review articles. Included studies

provided whole-brain voxel-based comparisons of adult ADHD and BD patients at their first maniac episode or drug naive relative to controls, using VBM or structural MRI. Regarding ADHD search, 3752 papers were found in database search, while for BD search 423 studies were detected. Studies that met the following inclusion criteria have been included in the current research:

(i) studies using structural magnetic resonance imaging (sMRI) or voxel-based morphometry (VBM);

(ii) studies performed a whole brain analysis (i.e., articles that performed only region of interest (ROI) or small volume correction (SVM) analysis were excluded);

(iii) studies including more than 5 participants;

(iv) studies that report results in a standardized coordinate space (e.g., Talairach and Tournoux, 1988, or Montreal Neurologic Institute –MNI).

Studies were excluded if they had no case-control comparisons, no cluster correction, used only ROI analyses, submitted samples of children or adolescents, used drugs, had comorbidities, and had no MNI or Talairach coordinates.

3.2.1 *Systemic review*

The literature screening and final selection has been performed according to the PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009). This procedure is summarized in the PRISMA flow diagrams (Figure 5 and Figure 6). Applying the PRISMA procedure, a total of 29 original articles were found eligible to be included in the ADHD systematic review, and 17 original articles were found eligible to be included in the BD systematic review. Afterwards, the studies effectively included within the systematic review were 10 and 8 for ADHD and BD, respectively.

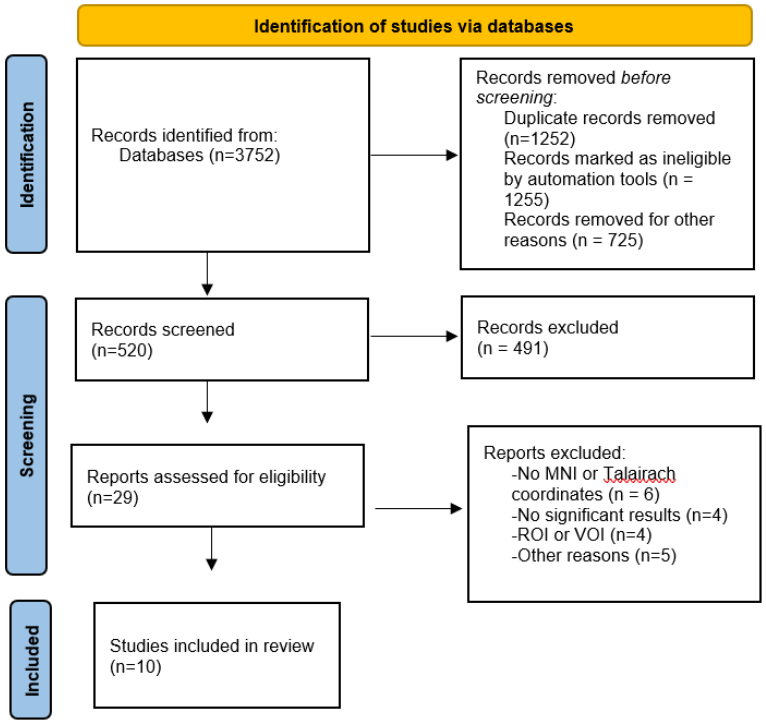

Figure 5. PRISMA flow-chart on study selection of ADHD.

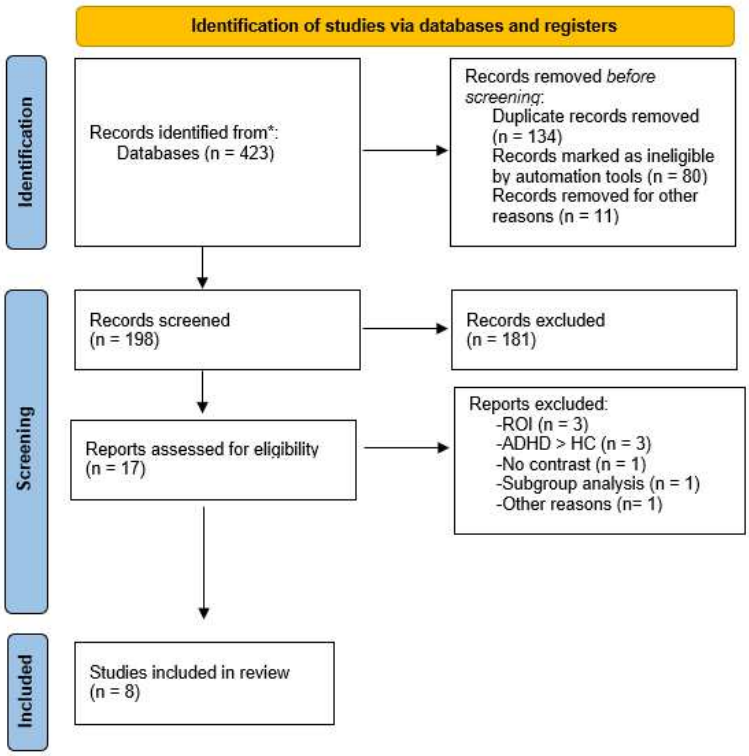

Figure 6. PRISMA flow-chart on study selection of BD.

3.3 META-ANALYSES

The current study followed the most recent guidelines for the meta-analysis (Muller et al., 2018). Talairach coordinates were reported into MNI space before performing the meta-analysis using a linear transformation (Laird et al., 2010; Lancaster et al., 2007). We adopted in our statistical analysis the GingerALE software (version 3.0.2), a novel quantitative voxel-based method that can be used to estimate consistent change of gray matter (or functional image) from an array of imaging studies which reported peaks of gray matter alteration or functional activation of statistical significance (Laird et al., 2005). ALE requires that peak foci of clusters be reported in stereotactic coordinates (in "x, y, z" format). All reported foci were retrieved from articles and imported into the software. ALE approach, the technique of which has been described (Laird et al., 2005; Turkeltaub et al., 2002), models each alteration focus as the center of a spherical Gaussian probability distribution. In the updated version of ALE algorithm (GingerALE 3.0.2 http://brainmap.org) (Eickhof et al., 2009), all reported foci (coordinates of maximum activation) for a given study are modelled as the peaks of stereotactic Gaussian probability distribution. A "modelled activation" (MA) map is computed, representing a summary of the coordinates from the specific study. ALE values are then calculated on a voxel by-voxel basis by taking the union of these individual MA maps, with higher ALE value indicating more significance in a voxel. This revised analysis tests for convergence between studies (which is random-effects) rather than foci (which is fixed-effects). Statistical significance of our analysis was assessed with a P-threshold corrected for comparisons using the familywise error (FWE) (Eickhof et al., 2012; Genovese et al., 2002) which is, and an uncorrected P which is more liberal. The results are presented at $P<0.05$ with 5000 thresholding permutations FWE corrected for multiple comparisons,

and an uncorrected P<0.05. In the two meta-analyses, for as much as each coordinate referred to the contrast between two groups (ADHD patients *vs.* healthy controls and BD patients *vs.* healthy controls), the analysis relied on the *N* of the smaller of the two samples to yield a more conservative activation likelihood estimation.

3.4 RESULTS

3.4.1 Search results and sample characteristics

As previously reported, the studies included in the research were 10 for ADHD meta-analysis and 8 for BD meta-analysis.

The ADHD dataset comprised 494 patients with a mean age of 33.17 years and 476 healthy controls (HC) with a mean age of 34.31 years (demographics information's are shown in Table 1).

Table 1. Sample Characteristics of ADHD research.

Sample Characteristics							
Author	**HC**	**Age**	**IQ**	**ADHD**	**Age**	**IQ**	**Total Sample**
Chaim et al., 2014	22	28.7	/	22	28.8	/	44
Moreno-Alcázar et al., 2016	44	32.57	105.97	44	31.61	105	88
Kappel et al., 2014	20	23.7	108.45	16	23.5	97.8	36
Klein et al., 2021	34	68.9	113.23	25	66.9	113.88	59
Roman-Urrestarazu et al., 2016	34	22.95	112.2	49	22.23	96.6	83
Ahrendts et al., 2011	31	31.5	/	31	31.2	/	62
Duan et al., 2018	176	28.93	108.19	214	25.4	103.54	486
Proal et al., 2011	80	41.3	110	59	41.1	101	139
Montes et al., 2010	20	27.57	100.15	20	28.95	102.85	40
VanWingen et al. , 2013	15	37	99	14	32	104	29

The BD dataset included 195 patients with a mean age of 28.24 years and 220 HC with a mean age of 27.91 years (demographics information's are shown in Table 2).

Table 2. Sample Characteristics of BD research.

Sample Characteristics							
Author	**HC**	**Age**	**IQ**	**BD**	**Age**	**IQ**	**Total Sample**
Farrow et al., 2005	22	20.5	/	8	18	/	30
Yatham et al., 2007	15	36	/	15	36	/	30
Keramatian et al., 2016	56	22.28	/	55	22.92	/	111
Berk et al., 2017	20	21.46	/	26	21.40	/	46
Chen et al., 2020	22	27.4	/	22	28.1	/	44
Jianga et al., 2021	30	26.47	/	15	27.20	/	45
Sun et al., 2020	31	33.61	/	30	36.30	/	61
Watson et al., 2012	24	35.6	106	24	36.0	106	48

Since the ADHD patient sample consisted of adult subjects, we considered the possibility that they might be on medication or might have a drug history. In Chaim (2014), Montes (2010) and VanWingen (2013) articles, patients were not under pharmacological treatment; in Ahrendts (2011) experiment, all subjects had been free of medication at the time of MRI scanning for at least 6 months (except one never been treated with methylphenidate and no medication history before the 6-month period was recorded); Duan (2018) reported that medicated participants were required free of medication at least 48h and in Proal (2011) study nearly all probands (57 [97%] of those scanned) were treated with methylphenidate hydrochloride in childhood from ages 6 to 12 years for an average of 2.2 years; in Roman-Urrestarazu (2016) experiment, only one subject was taking ADHD medication at the time of the scans, and no other participants had been treated with stimulants previously; in Klein (2021) investigation four individuals (14%) in ADHD group reported noncontinuous use of methylphenidate (none of these individuals were on medication during the evaluations); finally, Moreno-Alcázar (2016) and Kappel (2014) reported that medicated patient suspended their treatment two weeks before the experiment. Overall, most subjects in the ADHD samples during the scans period were not on any drug therapy.

Regarding BD patients, there is no medical history issue as one of the basic criteria for the meta-analysis inclusion was to be drug-naïve.

3.4.1 ADHD VBM

The meta-analysis of all the studies exploring grey matter atrophies in ADHD adult patients compared with healthy controls included 72 foci from 10 experiments. The minimum cluster size for the cluster to be considered statistically significant was 6448 mm^3. Only one cluster emerged from the analysis in the right hemisphere with a cluster size of 9712 mm^3 from the MNI coordinate X=4, Y=-16, Z=0 to X=32, Y=14, Z=50 centered at X=17.5, Y=1.8, Z=26.1, with 5 peaks with a max value of ALE=0.0105 (p=0.00012239473, z=3.67) at X=10, Y=8, Z=34 (cingulate gyrus). The cluster analysis revealed that atrophies in gray matter are located in the cingulate gyrus (limbic lobe) at Brodmann's area 24 (X=1, Y=10, Z=8) and (X=1, Y=18, Z=2), in the caudate (X=16, Y=-8, Z=22 and X=18, Y=6, Z=22) and in the lentiform nucleus (X=26, Y=2, Z=8) (Table 3; Figure 7).

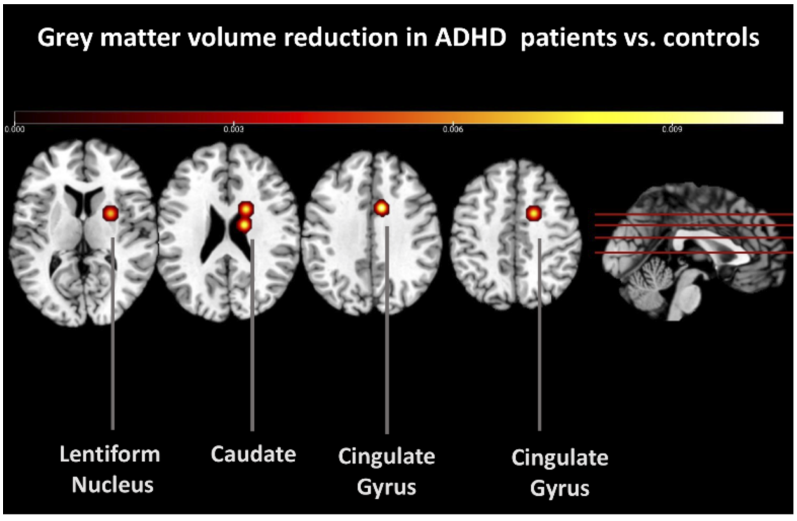

Figure 7. Grey matter volume reduction in ADHD patients vs healthy controls.

3.4.2 BD VBM

The meta-analysis of all the studies exploring grey matter atrophies in BD patients compared with healthy controls included 23 foci from 8 experiments. The minimum

cluster size for the cluster to be considered statistically significant was 13392 mm³. Only one cluster emerged from the analysis with a cluster size of 22280 mm³ from the MNI coordinate X=-18, Y=28, Z=-32) to X=24, Y=58, Z=20) centered at X=1.9, Y=42, Z=-4.6) with 5 peaks with a max value of ALE = 0.0096 (p= 0.000044341483, z= 3.92) in the left anterior cingulate (X=8, Y=40, Z=-6). The cluster analysis revealed that atrophies in gray matter are located in the anterior cingulate (limbic lobe) at Brodmann's area 24 (X=-8, Y=40, Z=-6) and (X=10, Y=42, Z=-12) for the left and right hemisphere respectively; in the left anterior cingulate at Brodmann's area 32 (X=1, Y=-4,Z= 42); in the right frontal gyrus at Brodmann's area 10 in the left medial frontal gyrus (X=14, Y=48, Z=6); in the medial frontal gyrus at Brodmann's area 11 (X=-2, Y=38, Z=-26). (Table 3; Figure 8).

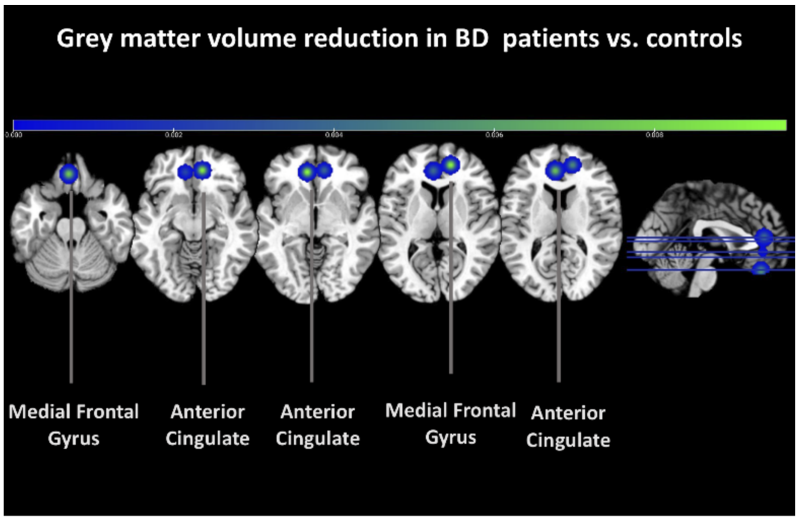

Figure 8. Grey matter volume reduction in BD patients vs. healthy controls.

Table 3. Summary of significant findings of structural atrophy in ADHD and BD patients from our meta-analyses. Top: GMV loss correlated in ADHD sample vs HC. Bottom: GMV loss found in BD samples vs HC.

ADHD meta-analysis: GMV atrophies in ADHD patients compared with healthy controls								
Cluster	**x**	**y**	**z**	**ALE**	**P**	**Z**	**Label**	**BA**
1	10	8	34	0.0105092	0.000122395	3.6676512	Cingulate Gyrus	24
	16	-8	22	0.0088949	0.00095289	3.1045353	Caudate	
	18	6	22	0.0084138	0.001504457	2.9668257	Caudate	
	18	2	44	0.0084106	0.001504457	2.9668257	Cingulate Gyrus	24
	26	2	8	0.0073319	0.003325098	2.7138715	Lentiform Nucleus (Putamen)	
BD meta-analysis: GMV atrophies in BD patients compared with healthy controls								
Cluster	**x**	**y**	**z**	**ALE**	**P**	**Z**	**Label**	**BA**
1	-8	40	-6	0.0096391	0.000043414	3.9196374	Anterior Cingulate (Left)	24
	14	48	6	0.0096379	0.000043414	3.9196374	Frontal Gyrus (Right)	10
	10	42	-12	0.0096379	0.000043414	3.9196374	Anterior Cingulate (Right)	24
	-2	38	-26	0.007876	0.000434668	3.329719	Medial Frontal Gyrus (Left)	11
	-4	42	10	0.00761	0.000527756	3.2752964	Anterior Cingulate (Left)	32

CHAPTER 4

DISCUSSION AND CONCLUSIONS

4.1 DISCUSSION

In the two meta-analyses carried out, we found a different pattern of gray matter atrophies in adult ADHD and BD patients. ADHD sample showed less gray matter in the right hemisphere in region located in the cingulate gyrus, caudate, and lentiniform nucleus; whereas in BD sample we observed abnormalities in gray matter in the right and left anterior cingulate gyrus, in the right frontal gyrus and in the left medial frontal gyrus. Notably, our observations for both ADHD and BD samples replicated already published observations.

With the respect to the ADHD results, the entire cingulate cortex is engaged in the structure/function abnormalities in ADHD, particularly impaired impulse control and cognition often trace to anterior midcingulate cortex (aMCC) in Go/No-go tests, decoding and reading, the Stroop Color and Word Test, and the Wisconsin Card Sorting Test (WCST), with volume deficits in anterior cingulate cortex (ACC) and posterior midcingulate cortex (pMCC) (Vogt, 2019). However, Onnink and colleagues (2014) discovered reduced caudate volumes in ADHD adult patients which was correlated with severity of the illness and more ADHD symptoms (primarily hyperactive/impulsive symptoms). Moreover, in a voxel-based meta-analysis by Nakao and colleagues (2011) the main findings show that individuals with ADHD, compared with healthy control subjects, display significantly and robustly smaller gray matter volumes in the right lentiform nucleus, extending to the caudate, and larger gray matter volumes in the left posterior cingulate cortex.

Regarding BD results, Ellison-Wright et al. (2010) reported in their meta-analysis gray matter reductions in the anterior cingulate cortex and Bouras et al. (2001), in a quantitative post-mortem study, found that patients with bipolar disorder had a substantial decrease in laminar thickness and neuron densities in layers III, V, and VI of the subgenual part of area 24 (ACC). In addition, atrophies in the medial frontal gyrus were detected in an integrated MRI/PET study of Altamura and colleagues (2017). Furthermore, Nery and colleagues (2015) reported that smaller GM volumes were found in the right anterior cingulate cortex and right medial frontal gyrus as the genetic risk for BD increased among first-degree relatives.

As it turned out, no real overlap in gray matter atrophies was at last found between ADHD and BD. Despite this, cingulate gyrus structural impairment is seen in both disorders, although different areas of this region are involved. The cingulate gyrus has a fundamental role as it lies in a unique position in the brain, with connections to both the "emotional" limbic system and the "cognitive" prefrontal cortex. As a matter of fact, the anterior cingulate cortex (ACC) is involved in the integration of neuronal circuitry for affect regulation and can be identified as a distinctive region in understanding psychopathology (Stevens et al., 2011). Therefore, structural and functional abnormalities of this region may be translated in cognitive and affective impairments, such as impulsivity, dysregulation of affect and failure to manage unpleasant emotions that are directly linked to ADHD and BD. As it is stated in the previous chapters, both disorders display in their symptomatic manifestation deficits of impulse control and emotion management and our findings suggests that this impairment can be traced to the common disruption of the cingulate cortex.

4.2 STUDY LIMITATIONS AND FUTURE DIRECTIONS

Our findings should be interpreted in light of some methodological limitations, such as the number of studies found within the research databases and an unreliable P-value used in the data analysis ($P<0.05$) for both meta-analyses. Notably, these two aspects of the research do not properly follow the meta-analysis guidelines (Müller et al., 2018). Nevertheless, the sample size and the little consistence of the P-value were due to the choice of adopting rigorous and precise criteria in the selection of articles with the aim of obtaining a homogeneous sample and as much control over the data as possible.

Future research should focus on common brain disruptions that occur in ADHD and BD patients to better understand this complex comorbidity, and particularly analyze this co-occurrence during childhood as the chance of experiencing this comorbidity is more widespread in children (Marangoni et al., 2015). Indeed, our research included adults participants for two reasons: the first reason is that the analysis of a developing brain is more confounding than the study of an adult brain, and the second reason is the lack of scientific articles regarding gray matter alterations in bipolar children.

To the best of our knowledge, this is the first comparative VBM meta-analysis study carried out between adults ADHD and BD patients documenting a different structural alteration in grey matter atrophies in both disorders, nevertheless with a common alteration in the cingulate cortex. The cingulate cortex plays a significant role in mediating cognitive influences on emotions, and our interpretation is that this common alteration may underlie the shared symptoms among ADHD and BD.

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