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"STRUCTURAL NEUROIMAGING IN ADHD: THE IMPACT OF FAMILIAL RISK FOR PSYCHOSIS ON CORTICAL CHARACTERISTICS"

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Table of contents

1. Attention Deficit and Hyperactivity Disorder

1.1 Definition, Epidemiology, and Main Symptoms

Attention Deficit and Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition characterized by pervasive features of inattention (IA), hyperactivity (HA), and impulsiveness (Imp): the diagnosis, which can be made also in adult life if the symptoms were present before age 12 years, ensuring an onset during neurodevelopment, must include at least six (or five, if the assessments are performed in older adolescents aged 17 or older and adults) symptoms of IA and/or HA that persisted longer than 6 months and to a degree that is inconsistent with developmental level [1]. This disorder often leads to significant functional impairment, comorbidities, and reduced quality of life. IA includes difficulties in sustaining attention, distractibility, forgetfulness, and carelessness toward responsibilities. Imp refers to acting without prior reflection, leading to hasty decisions, accidents, impatience, and intrusiveness. HA is characterized by excessive movement or restlessness in contexts that require calm or stillness. The overall prevalence of ADHD in children and adolescents is estimated at approximately 5.9%, with a decline in prevalence from preschool (10.5%) and elementary school (11.4%) to adolescence (8.0%) and adulthood (2.8%) [2–5]. As the prevalence decreases, sex differences also tend to diminish, shifting from a male-to-female ratio of 2:1 in early childhood toward more equal ratios later in life.

1.2 Trajectories and Presentations

ADHD can be reliably diagnosed by the age of 3 to 4 years [6]. In preschool children, symptoms of HA and Imp dominate the presentation, often manifesting behaviorally through overactivity or noncompliance [6]. At this age, IA is less noticeable, partly due to contextual factors [7], although ADHD may co-occur with neuropsychological deficits, intellectual delay, social or language difficulties, or autism spectrum disorders [8,9]. School entry represents a major life transition, often marking a peak in incidence. Children diagnosed after the first years of school are rarely considered de novo cases. During adolescence, the presentation typically shifts toward increased IA and Imp, while HA tends to decline. Adolescence also brings additional challenges such as low self-esteem, anxiety, low mood, and substance use [10,11]. In adulthood, ADHD symptoms

may become more apparent or newly identified due to increased demands for self-organization, responsibility, and social or occupational performance. DSM-5 criteria allow for a reduced symptom threshold (five instead of six) for diagnosis in adult life, but symptoms must have been present before age 12, even if impairment was not evident earlier. Adult ADHD is associated with higher risks of psychiatric comorbidities, educational and occupational difficulties, substance use, and impaired social functioning [12,13]

DSM-IV previously categorized ADHD into three subtypes—predominantly hyperactive-impulsive, predominantly inattentive, and combined. However, DSM-5 now defines these as *presentations*, acknowledging that symptom patterns can shift over time. For instance, HA and Imp tend to decline with age, while IA often remains stable, including in adulthood [14,15]. Despite being continuously distributed across the population as a spectrum, separating HA-Imp and IA remains clinically relevant. HA-Imp presentations are often linked to peer rejection, accidents, and aggressive behaviors, while IA is more strongly associated with academic difficulties, passive behavior in childhood, and lower adult life satisfaction [13].

1.3 Neurobiology of ADHD and Risk Factors

The neurobiology of ADHD has been closely linked to the dysregulation of the catecholaminergic system, particularly of dopamine (DA) signaling. Positron Emission Tomography (PET) studies indicate that the DA dysfunction is characterized by low tonic DA levels and variations of phasic release depending on task demands[16]. Polymorphisms in genes regulating the DA system, such as D4 and DAT1, were confirmed by genetic studies and confirm a central role of this monoamine[17]. From a clinical perspective, DA agonists are effective in reducing ADHD symptoms, likely by increasing extracellular DA levels[18].

At the same time, the clinical usefulness of non-DA-targeting medications such as imipramine and atomoxetine helped in the conclusion that the role of serotonin and norepinephrine has also to be highlighted[19]. When analyzing brain functional neuroimaging, recent studies demonstrate functional

differences in brain regions associated with executive functions, working memory, and attentional flexibility[20,21]. Specifically, hypoactivation in the prefrontal cortex (PFC) and dorsal striatum underlies deficits in these domains: the so-called 'reward system', that includes the orbitofrontal cortex (OFC) and ventral striatum, also showed some alterations, potentially explaining aversion to delayed rewards[13]; the 'default mode network' (DMN), a resting-state network centered on the medial PFC and posterior cingulate cortex/precuneus, also shows abnormal connectivity in ADHD[13]. Normally, this network is active at rest and deactivates when performing tasks. In ADHD, this connectivity is reduced at rest and inadequately modulated during task transitions[22,23].

Despite these advances, no biomarkers with sufficient diagnostic or predictive power have been identified[12]. ADHD may not represent a single neurobiological entity but rather an umbrella term encompassing multiple pathophysiological processes[13].

Different risk factors have been associated with ADHD, including, as already discussed, genetic predisposing factors, prenatal complications (e.g., maternal stress, tobacco smoking, alcohol use…), perinatal factors (e.g., low birth weight, preterm delivery), and other environmental influences such as traumas, neurotoxins, or psychosocial stress[24]. Familial history of psychopathology, especially mood and substance use disorders in parents, may increase offspring susceptibility.

The multifactorial etiology and the multiform pathophysiology of ADHD underlie a disorder that is difficult to treat and on which further research is needed to drive clinical improvements.

1.4 ADHD and psychosis

There is an association between childhood and adolescent ADHD and the risk of developing a psychotic disorder[25]. Individuals diagnosed with ADHD during childhood or adolescence had a significantly higher likelihood of developing psychotic disorders later in life, with an odds ratio of 4.74 (95% CI, 3.01–7.47) as identified in a recent analysis that included 12 studies with a total of 1,850,599 participants, among whom 124,405 had an ADHD diagnosis. This association highlights the importance of monitoring and prompt

intervention for psychotic symptoms in individuals with a history of ADHD. Possible biological explanations of this association may be found in shared genetic susceptibility, common neurodevelopmental trajectories, more general common social or environmental factors, as well as other risk factors such as prenatal exposures (e.g., neonatal complications or gestational diabetes), the use of psychoactive substances (e.g., cannabis)[25]. The effect of psychostimulant is still under debate: observational studies highlighted only a possible association—rather than causation—between the environmental factors and the comorbidity of ADHD and psychosis. For example, psychostimulants may not cause psychosis; instead, children and adolescents with ADHD who eventually transition to psychosis, regardless of treatment, may be those whose clinical presentation required earlier pharmacological intervention[26]. The widely held view that psychostimulants—methylphenidate in particular—cause psychosis is now being challenged. Recent evidence highlights the potential beneficial effects of psychostimulant medication, even in individuals with a history of psychosis[27].

ADHD has been identified also as a significant risk factor for the development of psychotic-like experiences (PLEs)[28,29]. ADHD may possibly facilitate the genesis of PLEs in an indirect manner, influencing pathways which involve emotional dysregulation and maladaptive coping mechanisms that may relate to increased exposure or sensibility to traumatic experiences, and subsequent rumination and increase in negative affect.

2. Affective and non-affective psychosis

2.1 Affective and non-affective psychoses

Schizophrenia (SZ) is a psychotic disorder characterized by alterations in thought processes, perception, emotions, cognition, and social interaction[1]. The clinical syndrome includes positive symptoms (e.g., delusions, hallucinations, disorganized speech and behavior); negative symptoms, such as affective flattening or avolition; and cognitive impairments. Other disorders within the schizophrenia spectrum (SSDs) include, but are not limited to, schizoaffective disorder, delusional disorder, brief psychotic disorder, and substance-induced psychotic disorder.
SZ is associated with reduced quality of life and life expectancy, with an average potential life loss of approximately 28.5 years[30,31], being SZ related to increased morbidity and mortality related to physical (e.g. for diabetes and metabolic disorders, cardiovascular disorders, cigarette-smoking and other addictions…) and mental health (about 4-10% of persons with schizophrenia die by suicide)[32]. Despite its relatively low prevalence, estimated between 0.25% and 0.75%, SZ ranks among the top 15 leading causes of disability globally[33] and is a significant economic burden[34].

Psychotic symptoms are not limited to SSDs but also occur in affective disorders, such as Bipolar Disorder (BD), a severe mental illness marked by extreme shifts in mood, psychomotor activity, and energy levels, which lead to recurrent mood episodes. Bipolar Disorder I requires at least one manic episode, while Bipolar Disorder II requires at least one hypomanic and one depressive episode; in both forms, delusions, hallucinations, and disorganized speech or behavior may occur, defining a Bipolar depressive or manic episode with psychotic symptoms (hypomania, by definition, cannot be psychotic, while psychotic symptoms can occurr in Bipolar II depressive episodes). BD has a global prevalence of approximately 2%, increasing to 4.4% in the United States[35,36].
It causes moderate to severe impairment across multiple domains of functioning[37,38] and significantly reduces quality of life[39] and social and laboral functioning, ranking 16th as leading cause of years lost to disability for all ages and being the 6th among younger samples (aged 10-24 years)[40]. Additionally, BD is associated with elevated psychiatric comorbidities, that can be present in up to 76.5 % of individuals with BD, and

it has a standardized mortality ratio for suicide approximately 20 times higher than the general population[41].

Both SZ and BD—classified broadly as affective and non-affective psychoses—share genetic correlations, high heritability in offspring[42,43], and some biological and clinical characteristics. Notably, both disorders typically emerge in late adolescence to early adulthood[44], although early onset (early-onset schizophrenia and juvenile bipolar disorder) is also seen. Some findings 's clinical progression does not begin with full-blown psychosis; instead, the first psychotic episode may represent a late stage in a broader, altered neurodevelopmen[45], with early signs forming a premorbid vulnerability phenotype. Early identification of these vulnerability markers could allow for prompt diagnosis and intervention. Neurodevelopmental aberrations, though typically milder, are thought to be implicated in some subtypes of BD as well[46]. Studying the offspring of patients with affective and non-affective psychoses has therefore become a valuable method for identifying disease vulnerability markers before symptom onset[47,48].

Stage	State
0	Genetic risk, no symptoms
1a	Aspecific symptoms, cognitive basic symptoms
1b	Attenuated psychotic symptoms (APS), genetic risk and deterioration syndrome (GRDS)
1c	Brief-limited intermittent psychotic symptoms (BLIPS)
2	First episode of psychosis (FEP)
3a	Incomplete remission
3b	Relapse
3c	Recurrencies
4	Severe and chronic disorder

Adapted from [49]

2.2 Neurobiological basis of psychotic disorders

2.2.1 Dopamine and Glutamate Hypotheses

The dopamine hypothesis was developed over 40 years ago, and states that dopamine dysregulation plays a fundamental role in psychosis[50,51]. This theory is based on two observations: first, antipsychotic medications reduce psychotic symptoms by blocking dopamine D2 receptors, thus decreasing the effects of DA[52]; second, amphetamines and other substances that increase dopamine levels can induce psychosis-like symptoms[53]. Neuroimaging studies using PET and single-photon emission computerized tomography (SPECT) showed that schizophrenia is characterized by presynaptic DA overactivity, which appears even in early stages of the illness, thus supporting these hypotheses.

The dysregulation in the DA system is related to psychotic symptoms basically because it affects two major pathways: 1. the mesolimbic pathway, which involves dopamine transmission from the ventral tegmental area (VTA) to the nucleus accumbens and other limbic structures and that is associated with reward and emotional processing, which correlate to positive symptoms of psychosis such as delusions and hallucinations; 2. the mesocortical pathway, which undergoes a decrease in DA activity and it is associated with negative and cognitive symptoms, including affective flattening, avolition, and impairments in executive function. The mesocortical pathway connects the VTA to the prefrontal cortex, an essential region for cognitive tasks and decision-making, which is also affected in other disorders that lead to cognitive dysfunctions. Taken together, these imbalances in dopamine function across different pathways contribute to the diverse symptomatology of psychotic disorders. Dopamine blockers, however, do not always effectively improve psychotic symptoms and frequently block multiple dopaminergic pathways beyond the targeted mesolimbic pathway: the mesocortical pathway (worsening negative symptoms), the nigrostriatal pathway, causing extra-pyramidal symptoms (EPS), and the tuberoinfundibular pathway (leading to hyperprolactinemia).

A dysregulation of the dopaminergic system also plays a trans-diagnostic role in the pathophysiology of BD. Like individuals with SZ, patients with BD have an increased dopamine synthesis capacity compared to healthy controls[54], as demonstrated with PET studies. However, the natural alkaloid reserpine, which depletes presynaptic stores

of norepinephrine (NE) and serotonin (5-HT) besides DA, has been shown to induce depression-like syndromes in animals and humans, and a monoamine oxidase (MAO) enzyme inhibitor that indirectly increases brain NE and 5-HT levels –iproniazid- can produce euphoria and hyperactivity. This led to the development of other MAO inhibitors (MAOi), tricyclic antidepressants (such as amitriptyline or clomipramine) and selective monoamine reuptake inhibitors (such as sertraline or venlafaxine), which have strong effects on mood regulation. The pathophysiology of BD and affective disorders is thus linked to a broader monoaminergic and neurotransmitter hypothesis, that includes more than the dysregulation of the DA system[55].

The trigger of prolonged psychosis in both humans and animal models after administration of N-methyl-D-aspartate (NMDA) antagonists, like ketamine, made glutamate's role become evident in the pathogenesis of psychosis[51,56]. Glutamate is an essential neurotransmitter for brain plasticity and neural network formation, but it is also neurotoxic at excessive levels, leading to cell degeneration. The NMDA receptor (NMDAR) hypofunction hypothesis states that a reduced activity of the NMDAR results in excessive cortical glutamate release, potentially contributing to psychosis[56,57]. However, variability in glutamate levels across different brain regions may suggest that glutamate dysfunction in schizophrenia involves more complex mechanisms[58]. Notably, the NMDA receptor antagonist ketamine also exhibits antidepressant effects, and elevated brain glutamate levels have been observed in individuals with bipolar disorder, highlighting an important role for glutamate in the pathophysiology of this disorder as well.

2.2.2 Synaptic Pruning Hypothesis

Emerging research also suggests that overactive synaptic pruning during adolescence could play a role in psychosis onset[59]. Synaptic pruning, a natural process of synapse elimination, may lead to grey matter loss during adolescence. Feinberg initially proposed that excessive pruning could disrupt neural integration, causing schizophrenia symptoms, a theory later expanded by Keshavan and Howes[59–61]. This hypothesis posits that genetic factors increase synaptic vulnerability, and environmental stress may further induce aberrant glial-mediated pruning. Abnormal pruning can disrupt the

balance of cortical excitation and inhibition, leading to cognitive deficits, dopaminergic dysregulation, and sensory processing issues, which contribute to psychotic symptoms.

2.2.3 Environmental risk factors

Environmental exposures play a crucial role in the complex interplay between genetic and environmental factors that modulate the risk of SZ[62]. Prenatal and perinatal conditions are particularly significant. For instance, maternal infections (i.e. rubella, influenza, Toxoplasma gondii) during pregnancy heighten the risk of developing schizophrenia, possibly due to immune-mediated neurodevelopmental reasons [63]. Folic acid, iron, vitamin D insufficiencies and other nutritional deficiencies during pregnancy may also elevate susceptibility[64]. Perinatal complications, such as fetal hypoxia and obstetric complications, further interplay with other factors and increase vulnerability by impairing critical brain development processes. Advanced paternal age can increase risk, possibly because it is related to de novo mutations in sperm. Exposure to urban environments, adverse socioeconomic conditions, and childhood trauma, have also demonstrated robust associations with schizophrenia[65].

Frequent and early cannabis use is another well-documented environmental risk factor of developing psychosis, particularly in genetically predisposed individuals [66]. These environmental risk factors often interact with genetic predispositions, creating a synergistic effect that disrupts neurodevelopmental pathways. This gene-environment interplay emphasizes the importance of early interventions targeting modifiable environmental exposures to mitigate risk and improve long-term outcomes for individuals susceptible to schizophrenia.

2.2.4 Genetic risk factors

As demonstrated by twin studies, and well known for decades, SZ is not only related to environmental factors: it is indeed a highly heritable disorder influenced by genetics. A large European study reported a concordance rate of 33% for SZ among identical twins, compared to 7% for fraternal twins, with heritability estimates at 79% for SZ and 73% when including SSDs [67]. Schizophrenia's polygenic nature has been confirmed with a major genome-wide association study identifying over 250 distinct genetic loci linked to

the disorder[68]. These genetic associations are primarily found in genes active in excitatory and inhibitory neurons within the central nervous system, including the dopamine receptor D2 and the GRIN2A subunit of the glutamate receptor. Beyond common genetic variants, several rare copy number and coding variants have also been associated with schizophrenia[68–71]. Although these rare variants contribute only modestly to the disorder's overall genetic risk, they represent some of the strongest individual risk factors identified to date[72].

A significant rate of vertical transmission is present also in BD, and heritability is estimated at 60-85%[73–75]. Various genes have been studied due to their possible relation to the pathophysiology of BD, including those implicated in dopaminergic and serotonergic pathways, neurotrophism, and circadian rhythms[75]. More recent genome-wide studies have highlighted the role of genes related to other specific biological pathways, such as insulin regulation, endocannabinoid signaling, and ion channel activity[76,77]. However, SZ and BD exhibit considerable clinical heterogeneity, which also reflects the highly polygenic architecture identified in recent Genome-Wide Association Studies (GWAS). These studies can overlap notably[78,79], but still show some condition-specific characteristics[80].

2.3 Psychosis and cognition

2.3.1 Cognitive impairment in schizophrenia and bipolar disorder

Cognitive impairments in SZ often begin before the onset of the full-blown illness and persist throughout the natural course, even if with a significant variability both between individuals and within the same individual over time, sometimes worsening with the natural progression of the disorder[81]. Complex interactions between genetic, neurodevelopmental, and environmental factors contribute to the pathophysiology of cognitive impairment in SZ. Dopamine and glutamate systems dysregulation possibly play a central role in cognitive deficits: dopaminergic abnormalities can disrupt prefrontal cortex function, leading to deficits in executive functions such as planning and decision-making[82], while glutamatergic dysfunctions affect synaptic plasticity, worsening learning and memory processes.
While it is known that the cholinergic system is involved in attention and memory, its role

in SZ is not yet fully understood: however, a dysregulation in the nicotinic and muscarinic signaling is likely to be partially involved, and also related to the release of GABA, another neurtransmitter[83].
Neuroinflammatory processes and oxidative stress can contribute to neuronal damage and loss, exacerbating the worsening of cognitive functions.
Structural brain abnormalities, including reduced grey matter volume in the prefrontal cortex and hippocampus, can correlate with cognitive deficits[81].

While cognitive deficits are present in various psychiatric disorders, those in SZ are typically more severe and pervasive[84] than those seen in BD. Recently, however, the vision that SZ is related to cognitive impairment while BD is characterized by full recovery between episodes has been brought into question: nowadays, it is known that cognitive deficits can be observed also during euthymia[85]. These deficits encompass attention, memory, executive function, and psychomotor speed, adversely affecting daily functioning and quality of life[86]. Despite their impact, there is a lack of FDA-approved treatments specifically targeting cognitive deficits in BD, and pharmacological interventions, including mood stabilizers and antipsychotics, have shown limited efficacy in ameliorating these impairments[86]. Nonpharmacological approaches, such as cognitive remediation therapy, have proven their efficacy in the treatment of cognitive deficits in SZ[87] and might offer potential benefits but require further research to establish their effectiveness in BD[86].

2.3.2 Neurocognitive aspects of psychotic symptoms

Neurocognitive sciences suggest that also other complex functions of cognition may be central in the pathophysiology of at least some psychotic symptoms. Cognitive models have been used to describe and explain delusions[88], hallucinations[89] and, recently, first rank symptoms in a unified theory[90]. Hallucinations, especially auditory verbal hallucinations, may come from a general disruption in the mechanisms that usually distinguish self-generated thoughts or speech from external auditory inputs. This mechanism involves a complex non physiological interplay of temporal and frontal areas, that may alterate the processing of the information together with a disruption in

the top-down mechanisms of control, which ‘shapes’ the signal transforming it into a perceived external source of sound rather than an internal one[91]. Also, delusions may be explained with neurocognitive models from two perspectives: deficits in cognitive processes (e.g. in Theory of Mind, Inference Processes…) may lead to jumping to conclusions, paranoid delusions, confirmation bias of the delusional belief; at the same time, an alteration in corollary discharge, a neural mechanism – that is also referred as efference copy- that distinguish self-generated actions from externally generated sensory inputs, sending to the sensorial regions of the brain a copy of the commands that the motor areas generate, has been linked to various first rank symptoms, unifying from a conceptual point of view delusion (delusion of influence) and disperceptions (somatic hallucinations, auditory hallucinations…)[92].

3. Familial and clinical high-risk for psychosis

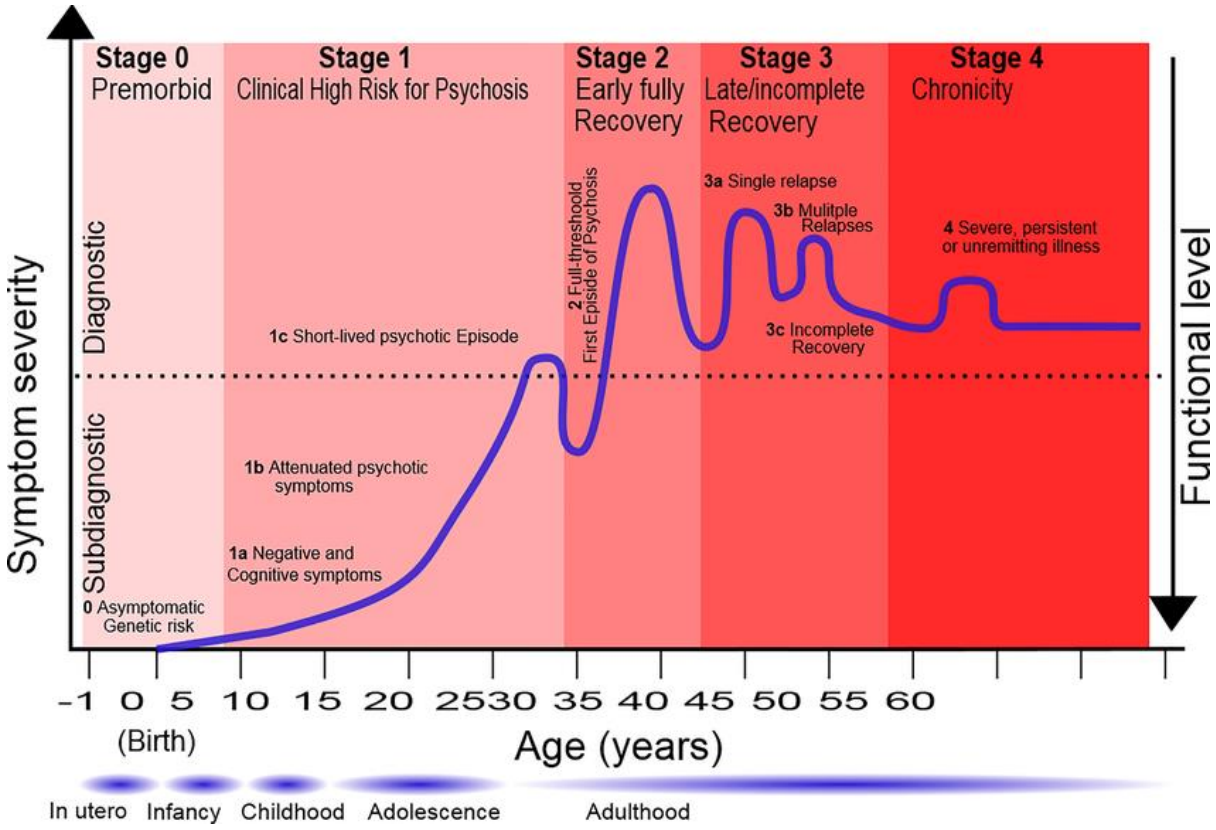
As previously discussed, a family history of psychosis is a very significant risk factor that must be considered when assessing an individual's risk of developing psychosis. The relative risk of developing a psychotic disorder increases 5.8-fold (95% CI: 4.2–7.9) for offspring with at least one parent diagnosed with a psychotic disorder, while offspring of a parent with bipolar disorder have a 5.1-fold (95% CI: 3.3–8.1) increased relative risk of developing the same disorder as the parents[93]. These findings highlight the critical role of genetic factors in the risk of both affective and non-affective psychosis.

3.1 Clinical high-risk for psychosis

Over the last decades, researchers have tried to identify and describe which physiopathological changes arise in the brain, behaviour or clinical characteristics of the individuals who will later develop a psychotic disorder. Retrospective studies have shown that most individuals who develop a psychotic disorder first experience prodromal symptom, lasting from a week to several years, with a median duration of around 12 months[94]. This prodromal phase is known as the CHR-P (Clinical High-Risk for Psychosis) state [95], though it has also been called the "at-risk mental state," "psychosis risk syndrome," or "ultra-high-risk" for psychosis [96]. It is marked by brief psychotic episodes, subthreshold positive or negative symptoms, and/or functional

impairments, which may precede the onset of full psychosis[97]. The growing research on CHR-P has supported early intervention strategies in clinical practice, leading to the introduction of the "attenuated psychosis syndrome" diagnosis in DSM-5 in 2013[1].

Traditionally, CHR-P inclusion criteria have encompassed three main clinical definitions: (1) attenuated positive psychotic symptoms (APS); (2) brief, limited, intermittent psychotic symptoms (BLIPS)—referring to short-lived psychotic episodes that resolve spontaneously within a week without the use of antipsychotic medication; and/or (3) genetic risk and deterioration syndrome (GRDS), characterized by having a diagnosis of schizotypal disorder and/or a first-degree relative with a psychotic disorder, along with a decline in overall functioning as observed during a clinical assessment.



Most CHR patients do not transition to psychosis within the first few years of presentation: after two years, 16% of CHR-P individuals transition to psychosis, with the risk continuing to increase, reaching 36% at 10–11 years of follow-up[98,99]. Meanwhile, only a small proportion of individuals who develop psychosis have previously been engaged by mental health services capable of detecting and monitoring ARMS[100], even

if it is estimated that most of the patients who develop SZ passed through some stages of prodromal syndromes.

3.2 Familial high-risk for psychosis

CHR-P differs from "familial" or "genetic" high risk alone (FHR), which includes individuals with a family history or genetic predisposition for psychosis, but who may not show prodromal symptoms nor a decline in general functioning. Considering that brain and behavioral changes associated with psychosis begin early in neurodevelopment—and that most studies on individuals at increased risk for psychosis have been conducted in adults—studying the FHR population may play a crucial role in designing early preventive strategies targeted at individuals who have not yet shown a clinical high-risk or symptomatic profile.

3.3 General and clinical trajectories of individuals at familial high-risk for psychosis

Several studies have demonstrated the increased risk of developing psychosis in first-degree relatives of patients with a psychotic disorder[93,101,102]. However, only a recent Finnish national register study aimed to identify the proportion of psychotic disorders that could be captured using the familial risk approach in child and adolescent service[103]. Healy and colleagues analyzed 368,937 children born in Finland between 1987 and 1992, studying the relationship between the subsequent development of psychosis and having at least one parent hospitalized for a psychotic disorder (FHR approach) or for any psychiatric reason, applying a transdiagnostic familial risk approach. They concluded that the transdiagnostic approach could capture 20.6% of individuals who subsequently developed a psychotic disorder, while 5.2% of cases could be predicted using the stricter FHR approach[103]. These data, although limited to children of patients who have been hospitalized, underline the limited but remarkable predictive value of familial history. While familial history is a key factor, additional factors are needed to significantly stratify the risk for psychosis.

3.4 Common mental health conditions in individuals at familial high-risk for psychosis

15.6% of individuals with a parental history of psychosis and 18.5% with a parental history of bipolar disorder were diagnosed with these conditions by age 28[104], and as

already discussed the homotypic relative risk of developing the same type of affective or non-affective psychosis as the parents can range between 5 and 9[93]. Additionally, percentages of affected FHR individuals may double when considering any psychiatric diagnosis by the same age[104]. This indicates that individuals with a positive first-degree familial history are more likely to develop a range of psychiatric disorders, not limited to the specific condition present in their family history: FHR individuals have about a two times higher heterotypic risk of having any psychiatric diagnosis than general population[93]. The most common heterotypic trajectories of offspring of patients with SZ are Disruptive Disorders (RR = 3.0 (95% CI: 1.0–9.1)), ADHD (RR = 2.8 (95% CI: 1.7–4.7)), Substance Use Disorder (RR = 2.0 (95% CI: 1.2–3.3)) and Depressive Disorders (RR = 1.9 (95% CI: 1.7–2.2)); for offspring of individuals with BD, RRs of Depressive Disorders, Substance Use Disorders and ADHD are similar, and also Anxiety Disorders are more frequent (RR = 2.1 (95% CI: 1.7–2.5)). Notably, offspring studies calculated that 52% to 77% of SzO and BpO develop a lifetime mental disorder[101,105].

3.5 ADHD and alteration in cognitive areas in individuals at FHR for psychosis

As previously mentioned, ADHD is more prevalent among individuals at FHR for psychosis compared to the general population[106]. A multicenter study conducted in 2015[107] examined the prevalence of various psychiatric disorders in a sample of 238 children and adolescents, categorized based on their parents' diagnoses as SzO, BpO, or offspring of community controls (CcO). The study found that ADHD prevalence was significantly higher in both FHR groups compared to CcO, where the prevalence was 7.5%. Furthermore, ADHD was present in 46.3% of SzO, a significantly higher percentage than the 17.6% observed in BpO[107].
ADHD has also been independently associated with an increased risk of developing psychosis. While various explanations for this correlation have been proposed, ADHD may also represent a direct neurodevelopmental vulnerability that contributes to the later emergence of a psychotic disorder[25,108].
At the same time, ADHD-like cognitive features are frequent in FHR children and adolescents: studies on samples of children and adolescent at FHR for SZ have identified difficulties in several cognitive areas (including verbal and visual memory, working memory, processing speed, attention, and executive functions)[109–113]. Attention is

perhaps the most extensively studied cognitive area, and attention deficits (specially, sustained attention) or attention deviation (as measured by the Attention Deviance Index, ADI) in FHR for schizophrenia can be a predictor of cases that will develop psychosis in adulthood[111,114–116].

3.6 Transdiagnostic Symptoms and Characteristics in ADHD and Familial High-Risk Populations

Children and adolescents at familial high risk (FHR) for schizophrenia (SZ) who have a diagnosis of ADHD show greater impairments compared to healthy controls than those at FHR without ADHD: the FHR group with ADHD showed more pronounced neurological dysfunction and elevated psychosis-like clinical features (such as magical ideation and perceptual aberration), suggesting that the presence of ADHD may represent a distinct subgroup within the FHR population[60] . A more specific analysis of the neurobiological and clinical characteristics of this subpopulation has not been fully studied yet.

However, recent research suggests that ADHD in children and adolescents may present distinct features depending on the familial risk for BD. ADHD youth with FHR for BD exhibit more severe symptoms compared to those without a family history of BD. These symptoms include heightened hyperactivity/impulsivity, mania, and emotional dysregulation[117]. Furthermore, ADHD youth at FHR for BD show pronounced brain structural abnormalities that differentiate them from non-FHR ADHD youth, such as reduced cortical surface area (in the orbitofrontal, superior frontal, parietal, and temporal regions) and decreased subcortical volumes[118]. Significant differences have also been identified in microstructural measures, such as fractional anisotropy[119], as well as in functional and connectome analyses[120]. For example, while alterations in the DMN and central executive networks are observed across all ADHD individuals, changes in the salience network are predominantly seen in ADHD youth with FHR for BD. Moreover, neurofunctional responses in ADHD youth with FHR for BD display distinct activation patterns in the cingulate cortex and amygdala[121]. These youth also show greater disruptions in frontoparietal and frontolimbic connectivity compared to their non-FHR counterparts[120].

This suggests, on one hand, that familial risk influences the severity and presentation of ADHD. On the other hand, it highlights that certain clinical and phenotypical characteristics may be transdiagnostic.

4. Structural magnetic resonance imaging

Magnetic resonance imaging (MRI) is a valuable, non-invasive tool for investigating brain structure and physiology without the need for ionizing radiation [122]. Techniques such as structural MRI (sMRI), functional MRI, diffusion tensor imaging, and magnetic resonance spectroscopy offer detailed insights. SMRI, using T1-weighted sequences, produces high-resolution images that distinguish between grey matter, white matter, cerebrospinal fluid, and specific brain regions like the thalamus and frontal cortex. Over the years, it has been instrumental in examining brain maturation during childhood and adolescence, as well as in identifying abnormalities linked to neurological and psychiatric disorders. Advances in neuroimaging software now allow automated processing and statistical modeling with high precision. These methods enable the extraction of brain structural metrics, including grey matter volume, cortical thickness, and cortical surface area. Two main approaches have emerged for analyzing T1-weighted images: voxel-based morphometry (VBM) and surface-based morphometry (SBM).

4.1 Voxel-based morphometry and grey matter volume

VBM evaluates small-scale differences in grey matter by normalizing brain images into a standard space, segmenting tissues, smoothing data, and applying statistical models to identify group differences. The resulting parametric maps highlight regions with significant grey matter variations[123]. Grey matter volume, derived through VBM and other methods, measures tissue between the grey-white interface and the pia mater. Although widely used in psychiatric research, it is a composite measure influenced by cortical thickness and surface area, which follow distinct developmental and genetic pathways[124,125].

4.2 Surface-based morphometry: cortical surface area and cortical thickness

SBM, on the other hand, focuses on constructing and analyzing brain surfaces to assess parameters like cortical thickness and surface area[126]. Cortical thickness, averaging 2.5–3 mm across the brain, reflects changes in synaptic density, glial cells, and myelination[127–129]. Surface area, largely heritable and determined by the number of

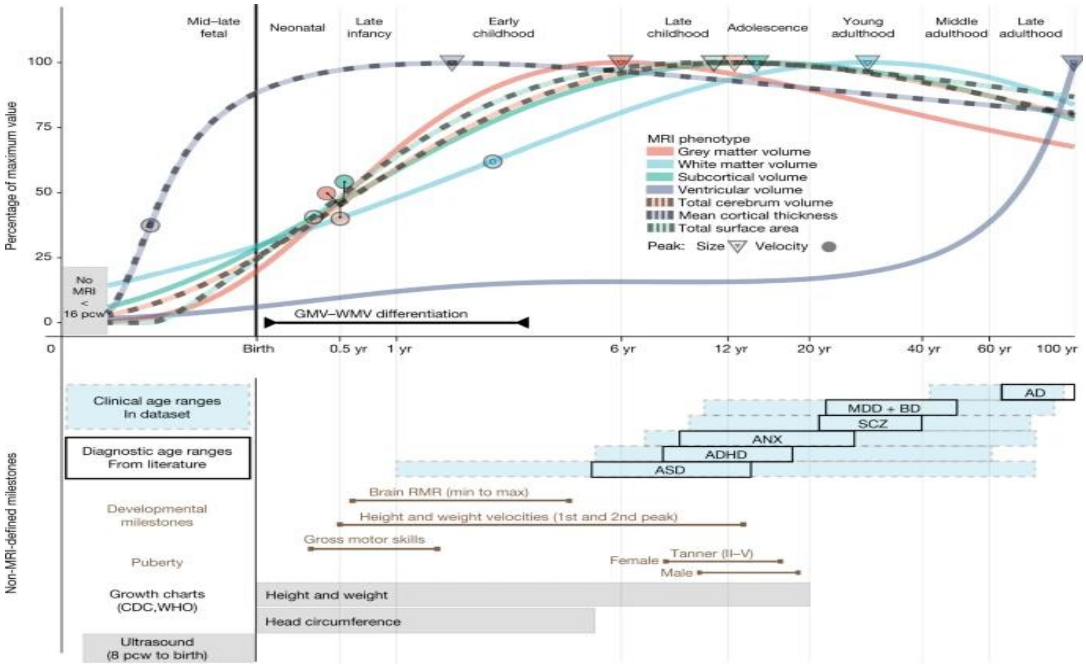
perpendicular ontogenetic columns, provides distinct insights into neural development and psychiatric conditions[130,131].

4.3 Metanalytical analysis of structural MRI data

Finally, meta-analytic tools like SDM-PSI integrate data from multiple studies, enhancing statistical power by combining VBM and SBM metrics, thus refining our understanding of brain structural variations[132].

5. Normative brain development and structural alterations in psychoses, ADHD and in individuals at FHR

Understanding typical brain development is crucial to interpreting structural abnormalities in adolescence. Early longitudinal studies revealed that white matter volume increases linearly from childhood through adolescence, while grey matter volume follows a non-linear inverted U-shaped curve[133,134]. A recent analysis of brain structure across 101,457 individuals over 100 years showed grey matter volume peaking at 5.9 years, followed by a near-linear decline. In contrast, white matter volume grows rapidly until peaking at 28.7 years, with an accelerated decline after age 50[135]. Regionally, grey matter peaks occur at varying ages (2–10 years), with sensory regions peaking earlier and declining faster than association cortices, reflecting a sensory-to-association gradient in development[136,137]. These patterns may result from synaptic pruning, myelination, glial, vascular changes, and cellular shrinkage during adolescence[138–141]. While grey matter volume is informative, studying cortical thickness and surface area independently provides deeper insight due to their distinct developmental paths and genetic influences.



Adapted from [135]

5.1 Cortical thickness normative development

Cortical thickness grows rapidly in the perinatal period and first year of life, reaching 97% of adult levels by age two[135,142,143]. Regions such as the insula, cingulate cortex, and speech areas grow faster than sensory and parietal cortices[131]. The occipital region, which is associated with primary visual processing, develops earlier than other regions, peaking during infancy and showing significant thinning thereafter. This early maturation is consistent with the critical role of visual processing during early life[144]. After peaking around 1.7 years[143,145], cortical thickness declines non-linearly, with significant thinning during late childhood and adolescence, followed by slower reductions in adulthood[144,146,147]. This thinning reflects synaptic pruning and white matter maturation, including myelination of adjacent regions[144,148,149]. Cortical thinning trajectories are similar between sexes, suggesting sex differences in grey matter volume arise from surface area variations[147].

5.2 Cortical surface area normative development

Cortical surface area increases significantly (114.56%) in the first two years, reaching 69% of adult values[142]. Regions like the lateral frontal and parietal cortices expand faster than others, such as the insula[150]. Surface area continues growing until around age 11, then declines subtly during adolescence and early adulthood[124,135,144]. Growth in surface area correlates with intracortical myelination and white matter tract maturation[151]. Unlike cortical thickness, sex-related differences in surface area are significant, with males showing more sustained growth and slower decline, resulting in greater total surface area[143,146,152].

5.3 Structural alterations in affective and non-affective psychosis

5.3.1 In schizophrenia

Neuroimaging research revealed significant structural brain differences between individuals with SZ and healthy controls. A widespread thinning of the cortex is a feature that has been observed across different studies, and affects prominently the frontal, temporal, and insula regions, which are thought to have crucial roles in cognitive, emotional, and sensory integration [153,154]. Cortical surface area is also globally and

locally reduced, for example in the frontal and temporal lobes[153,154]. The the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium emphasized specificity of specific parcels, identifying that significant thinning happens in areas such as the fusiform gyrus, inferior temporal gyri, and parahippocampal The effect of medication may be another significant factor: the ENIGMA study reported more pronounced cortical thinning in individuals treated with first-generation compared to second-generation antipsychotics or unmedicated individuals[153]. These structural abnormalities have critical functional implications: thinning of the frontal cortex may contribute to deficits in executive function, decision-making, and working memory; alterations in the temporal cortex are linked to auditory processing issues and language deficits, which may underlie hallucinations and thought disorders; changes in the insula are possibly linked with impaired self-awareness and emotional regulation, potentially explaining negative symptoms like social withdrawal and anhedonia; and structural abnormalities in the parahippocampal and fusiform regions could be responsible for other cognitive alterations, such as memory impairments and visual processing deficits, further exacerbating cognitive symptoms in SZ. Together, these findings illuminate the interplay between neurodevelopmental disruptions, cortical integrity, and the clinical manifestations of SZ.

5.3.2 In Bipolar Disorder

Structural MRI studies have identified also several brain abnormalities associated with BD. BD is associated with thinner frontal, prefrontal and temporal cortex[155]. The widespread cortical thinning was subsequently found to be especially relevant in the left pars opercularis (Cohen's d=−0.293), left fusiform gyrus (d=−0.288), and left rostral middle frontal cortex (d=−0.276)[156]. These cortical alterations have been also linked to some of the disorder's clinical manifestations, such as duration of illness[156], and could relate to impaired executive functions and reduced emotional regulation (PFC) and difficulties in recognition of emotional facial expressions, language processing and communication (temporal cortex).

Individuals with BD show significant changes also in subcortical structures: for example, reductions in the volumes of the hippocampus, amygdala, and thalamus, accompanied by enlargement of the lateral ventricles have been found[157]. Those subcortical

abnormalities may contribute to the emotional and cognitive dysregulation observed in BD. Taken together, these findings underline the importance of structural MRI in understanding BD's neurobiological underpinnings.

5.4 Structural alterations in ADHD

Anatomical MRI studies of ADHD have evolved through different stages, from findings of no clear anatomical abnormalities, to identifying with cross-sectional and longitudinal subsequent studies respectively group differences in frontal lobes, basal ganglia, and cerebellum and longitudinal developmental trajectories. Currently, multimodal imaging shows promise by analyzing brain morphology and connectivity, providing the strongest discriminatory power to date[158]. MRI meta-analyses, while benefitting from large sample sizes and robust methods and able to identify significant brain differences in ADHD, usually face significant limitations: weak hypotheses-driven theories, small effect sizes and limited insights into ADHD clinical subtypes or etiology. Complementary approaches are needed to fully understand ADHD-related brain differences[158].

What was found so far in individuals with ADHD from a structural point of view is that differences include smaller volumes in subcortical area**s** such as the amygdala, caudate nucleus, putamen, hippocampus, and nucleus accumbens, as well as reduced **cortical** surface area in regions like the frontal, temporal, and cingulate cortices[159,160]. Reductions in cortical thickness, mainly in the **fusiform** gyrus and **temporal** pole, were also observed in children but not in adults, when structural alterations become less evident[161,162]. Perspective studies highlight a developmental delay in brain maturation, particularly in the frontal and subcortical regions, with differences becoming less pronounced in adulthood[162,163]. The amygdala, which is essential for emotional regulation, has reduced volume in ADHD, and that has been linked to a common trait of individual with this disorder that is emotional dysregulation[159]. Similarly, parts of the basal ganglia involved in motor control and cognitive functions like attention (caudate nucleus and putamen), are consistently smaller in individuals with ADHD, which can be related with core ADHD symptoms of hyperactivity and inattention[161]. Also, the hippocampus, crucial for working memory and learning, exhibits reduced volume[163]. Reduced surface area in the **frontal** cortex[160], an area that is essential for executive

functions, decision-making and control of impulses, reflects deficits in these domains that may lead to symptoms of inattention and impulsivity[163]. Functional MRI studies reveal disrupted connectivity in key brain networks, such as the DMN and cognitive control network. These abnormalities include decreased synchrony within the DMN and impaired connectivity and modulation of activity between the DMN and prefrontal regions, potentially explaining attention and impulse control difficulties[161].

Although samples of individuals with ADHD sometimes include—or are limited to—young, drug-naïve subjects, and longitudinal studies are still needed to better understand the long-term effects of ADHD medication[163], several studies have investigated the impact of pharmacotherapy - primarily stimulants, including methylphenidate - on brain structure and function using neuroimaging techniques[164]. These studies provide evidence of a normalizing effect of ADHD medication on both brain structure[164,165] and functional brain activation patterns[164] in specific regions affected by ADHD. Additionally, pharmacotherapy appears to normalize the trajectory of cortical development[164], suggesting potential long-term benefits for brain maturation in individuals with ADHD.

5.4.2 Overlaps in brain structure of ADHD and pediatric BD

Some overlapping abnormalities in pediatric bipolar disorder (PBD) and ADHD was found[166]: both conditions are characterized by reduced grey matter volumes in the right insula and anterior cingulate cortex and can present cognitive and affective symptoms such altered emotion processing and attention. Specific deficits included decreased volumes in the orbitofrontal cortex and hippocampus for PBD, and the precentral and superior frontal gyri for ADHD. These findings show that further research is needed to understand the neuroanatomical basis for the shared and disorder-specific symptoms of ADHD and PBD.

5.5 Structural alterations in individuals at FHR for psychosis

5.5.1 Brain structure in first-degree relatives

The ENIGMA-Relatives Working Group in 2019 collected data pooled across multiple studies to conduct a meta-analysis to investigate brain morphological alterations in first-degree relatives (FDRs) of individuals with schizophrenia (FDRs-SZ) and bipolar disorder (FDRs-BD)[167], to help providing a comprehensive understanding of structural brain differences in FDRs as a whole and also in specific subgroups (offspring, siblings, parents, and twins), one of which might be considered the FHR construct earlier described.

When considering the broader groups of FDRs-BD and FDRs-SZ in comparison to control subjects, notable differences emerged. FDRs-BD exhibited larger intracranial volumes (ICVs), a finding that remained significant after statistical correction. In contrast, FDRs-SZ showed smaller thalamic volumes. For FDRs-BD, the apparent structural differences in brain measures largely disappeared after adjusting for total ICV, suggesting that the observed effects were mainly driven by overall larger ICV rather than by abnormalities in specific regions. FDRs-SZ, in contrast, showed significant reductions in total brain, cortical grey matter, cerebral white matter, cerebellar grey and white matter, and thalamic volumes, together with thinner cortices and an enlarged third ventricle. When comparing FDRs-BD and FDRs-SZ directly, FDRs-BD showed larger overall brain measures, including cortical and subcortical regions, as well as smaller third ventricle volumes than FDRs-SZ. These findings highlight distinct neuroanatomical profiles for FDRs-SZ, even after accounting for variations in ICV[167].

FHR for SZ and for BD may thus be characterized by divergent neurodevelopmental trajectories. FDRs-BD demonstrate overall larger brain size, while FDRs-SZ exhibit more localized reductions in brain volume and cortical thickness, consistent with a neurodevelopmental model of vulnerability for schizophrenia. These differences reflect some unique patterns of brain structure alteration associated with the genetic risk factors of each disorder. Interestingly, the findings for FDRs-BD contrasted with those in patients with BD, who do not typically show ICV enlargement. It is important to note in this case that FHR and, in general, FDR will manifest a clear disorder only in a small

percentage. Some illness-related factors may thus be responsible for biological markers of BD such as diminished ICV only in those who will develop a full-blown disorder, or even that larger ICV in FDRs-BD reflects resilience to developing the disorder. In SZ, however, the findings of brain volume reductions in FDRs-SZ align more clearly with patient findings, albeit with smaller effect sizes, reinforcing the hypothesis of a shared neurodevelopmental trajectory.

5.5.2 Brain structure in offspring

Considering previous discussions and evidence from animal models[168] and birth cohort studies[169], changes in the brain associated with the subsequent development of psychosis appear to begin during early neurodevelopmental stages. Despite this, most neuroimaging studies on psychosis have been conducted in adults. Additionally, analyses of subtypes of FDRs (e.g., offspring, siblings) initially showed no effect sizes that survived correction for multiple comparisons when contrasted with control subjects. However, significant differences emerged between these subtypes when directly compared, highlighting nuanced variations in brain structure across different FDR categories[167]. Given these premises, it is crucial to address sources of heterogeneity and confounding factors by clearly specifying which subtypes of FDRs are considered and employing narrower age ranges, with a particular focus on neurodevelopmental stages.

Recent studies built an interesting perspective on the structural alterations that can be found in the brain of offspring of individuals with schizophrenia (SzO) and bipolar disorder (BpO)[170–173]: differently from FDR, offspring may represent a less heterogenous group and thus deserve further study: the distinct neurodevelopmental trajectories that can be drawn from these high-risk groups may help understanding the implications of familial liability to affective and non-affective psychosis, and possibly to characterize the existing differences between these two nosographic cathegories from a neurodevelopmental point of view when considering children and adolescents SzO and BpO.

In SzO, reduced total grey matter volume (GMV) emerges as a consistent finding across studies. Sugranyes et al. (2017)[173] reported **global GMV reductions in SzO** during

childhood and adolescence, independent of surface area or cortical thickness. Van Haren et al. (2021)[172] confirmed this finding, highlighting that these deficits, which persist over time, were also linked to cognitive impairments and increased risk for psychopathology. Furthermore, Sugranyes et al. (2021) added new findings, demonstrating also a progressive **cortical thinning** in SzO: the region that was mainly involved is the occipital cortex, a region implicated in early cortical development[171]. Accelerated cortical thinning in SzO was found also in regions implicated in higher-order cognitive functions, such as the prefrontal cortex, compared to both controls and BpO[170]. Subcortical structures, such as the **hippocampus** and **thalamus**, also showed reduced volumes in SzO during development. These longitudinal changes, starting early in children and adolescents' lives, corroborate the neurodevelopmental implications of SZ: especially, adolescence appears to be a critical window during which SzO show different and non-linear trajectories of cortical development, that can lead to structural alterations in brain morphometry.

In contrast, **BpO** showed **subtler and more region-specific alterations**. A greater **cortical thinning** has been observed in BpO by Sugranyes et al. In 2021[171], especially in the temporal and frontal regions, over a four-year follow-up: interestingly, the thinning was more pronounced in individuals who developed psychotic spectrum symptoms. BpO demonstrated also delayed development of cortical **surface area** compared to controls, with regional effects most evident in the temporal and parietal lobes[170]. Notably, structural changes in BpO may signal clinical vulnerability rather than a stable trait: baseline surface area reductions in BpO were significantly present **in those BpO who later exhibited psychotic symptoms**[171]. Subcortical structures in BpO, such as the hippocampus and thalamus, were largely preserved or showed only subtle differences, suggesting a less global impact on neurodevelopment compared to SzO.

5.5.3 Relationship Between Brain Structure, Clinical Features and Neurodevelopmental pathways

These structural brain alterations have been associated with clinical outcomes, particularly with IQ and descriptive psychopathology. In SzO, lower IQ was strongly

linked to reduced grey matter volumes and areas: these brain measures may thus reflect neurodevelopmental deficits that play a key role in what is clinically detectable as cognitive impairment. At the same time, it was possible to point to possible protective factors for developing SZ: SzO with preserved surface area and less cortical thinning were less likely to develop psychotic spectrum symptoms[171]. In BpO, the relationship between structural alterations and clinical features was less direct: cortical thinning and reduced surface area were associated with psychotic symptoms but were not uniformly present across all BpO[171]. This suggests that BpO is a more heterogeneous group, that shows different patterns of neurodevelopmental risk, influenced by factors such as mood symptoms and environmental exposures. These findings underscore a neurodevelopmental continuum in SzO and BpO: SzO exhibit more severe and global structural deficits, which may be the result of early and pervasive neurodevelopmental disruptions; BpO, in contrast, demonstrates subtler, region-specific changes, that may reflect later or more context-dependent neurodevelopmental processes. Longitudinal data become thus useful to track developmental trajectories, because alterations in morphometric measures may help stratify risk and inform early intervention efforts[171]. As discussed earlier, ADHD—which has been clinically and epidemiologically associated with familial high risk (FHR) for psychosis—is also characterized by smaller cortical surface areas. However, in individuals with FHR, co-occurring ADHD is likely not the primary driver of the observed morphometric differences. Sensitivity analyses by Sugranyes et al. (2021) found no significant effect of ADHD on morphometric measures [171], suggesting that FHR for psychosis may independently shape the trajectory of brain morphometric changes, irrespective of ADHD.Together, these studies provide critical insights into the neurobiological underpinnings of familial risk for schizophrenia and bipolar disorder, highlighting both shared and distinct pathways that shape vulnerability to these conditions. Structural brain measures, particularly GMV, surface area, and cortical thickness, emerge as valuable markers for understanding and potentially mitigating risk in high-risk youth.

Hypotheses and objectives

As already discussed in previous sections, FHR for psychosis - on one hand - has been associated with a higher prevalence of ADHD, which also showed some different clinical characteristics. On the other hand, certain clinical and phenotypical features may be *transdiagnostic*, meaning a clinical diagnosis of ADHD could form part of common pathways originating from distinct psychopathological processes. Specifically, this may include: (1) a "common" ADHD diagnosis observed in children without familial history of psychosis, associated with overlapping genetic and environmental risk factors between ADHD and SZ and BD and (2) another phenotype which may be linked to the complex interplay of cognitive, affective, and prodromal positive or negative symptoms that can occur in children and adolescents at FHR for psychosis. In this case, these symptoms may reflect an early or prodromal form of SZ or BD that concurrently meets diagnostic criteria for ADHD. This possibility raises the question as to whether ADHD symptoms in FHR individuals may reflect underlying neurodevelopmental changes associated with the risk of developing affective or non-affective psychosis rather than a primary diagnosis of ADHD itself. A further option is the additive or interactive relationship between these two possibilities. However, direct comparisons on phenotype of youth with ADHD according to familial risk for psychosis are still lacking.

However, direct comparisons of the phenotype of youth with ADHD based on familial risk for psychosis are still lacking. To our knowledge, this study is the first to phenotype brain structure across these different neurodevelopmental conditions during childhood and adolescence— a critical yet insufficiently explored period of brain development. The aim of this study was to assess differences in brain cortical structures between three groups:

1. Children and adolescents with ADHD at FHR for psychosis,
2. Children and adolescents with ADHD without a family history of affective or non-affective psychotic disorders, and
3. Healthy controls with no familial history of psychosis.

The analysis will focus on structural neuroimaging similarities and differences to determine which brain cortical changes in familial high-risk individuals are associated with "common" ADHD and which be specific to ADHD diagnosis in the context of familial risk for psychosis.

Hypotheses

- **H1**: FHR-ADHD and ADHD controls will show overlapping results of reduced grey matter volume, surface area and cortical thickness compared to HC in some frontal and prefrontal regions.
- **H2**: FHR-ADHD will show some specific alteration in grey matter volume and surface area compared to ADHD controls in other specific regions such as the occipital lobe, suggesting a partially different phenotype for the co-presence of FHR and ADHD.

Objectives

- **O1**: to identify which brain regions show overlapping structural alterations between ADHD controls and FHR-ADHD when compared to HC.
- **O2**: To investigate which morphometric differences may be considered as specific neurophenotypes of FHR-ADHD compared to ADHD controls.

6. Materials and methods

6.1 Participants

This is a cross-sectional, observational study conducted in the Department of Child and Adolescent Psychiatry of the Hospital Clinic of Barcelona, Spain. The sample is formed by three groups of children and adolescents aged 6 to 17 years: children and adolescents with ADHD that are offspring of patients with SZ or BD (FHR-ADHD group); children and adolescents with ADHD without antecedents of BD or SZ in first-degree relatives (ADHD controls); children and adolescents without a psychiatric diagnosis and without a familial history of psychosis (healthy controls, HC). Individuals were included in the study if they underwent T1-weighted MRI scan, while they were excluded if they had intellectual disability, autism spectrum disorders, or a history of any severe neurological conditions or head injury with loss of consciousness.

Recruitment of individuals at FHR was performed systematically through parents: adults with a diagnosis of schizophrenia or bipolar disorder, visited in the Department of Adult Psychiatry of the Hospital Clinic Barcelona, with offspring aged 6-17 years, were invited to participate. In the case of children and adolescents diagnosed with ADHD (ADHD controls), recruitment was carried out through the outpatient services of the Department of Child and Adolescent Psychiatry of the Hospital Clínic of Barcelona. HC were recruited in the same geographical area as the patients with SZ and BD. The exclusion criterion for being in the HC group was having any current or lifetime diagnosis of a mental health disorder (axis I, DSM-5), while having a first- or second-degree relative SZ or BD was an exclusion criterion for being in any of the two control groups (*i.e.* ADHD control and HC). To minimize selection bias, control parents expressing interest in participation due to concerns about their child's academic performance or emotional and behavioral issues were excluded. Once the case or control was identified, and if the parents agreed to participate in the study, a member of the research team arranged a visit to conduct a clinical evaluation of the parents to confirm the presence of a SZ or BD diagnosis for the FHR-ADHD group. Parental exclusion criteria were intellectual disability, and drug or

medically induced psychosis or mania. The absence of a history of psychotic disorders among first- and second-degree relatives was assessed for the ADHD controls and HC groups. After this visit, the clinical and cognitive assessments of the children and adolescents were conducted by another team evaluator who was blinded to parents' diagnosis. Following the clinical assessments, the MRI scan was performed in a separate session. If during the clinical baseline evaluation, a control participant was diagnosed with ADHD - an exclusion criterion for the HC group and an inclusion criterion for ADHD control group - and none of the exclusion criteria for the ADHD control group were met, the individual was reclassified into the ADHD control group.

6.2 Demographic, clinical and cognitive assessment

Written informed consent was obtained from parents or legal guardians of every participant, as well as from participants aged 12 years or older. Families received compensation for their time and travel expenses. Parental clinical assessment was performed including a diagnostic interview using the SCID-I and SCID-II scales[174], a global assessment of functioning (GAF)[175], and an evaluation of substance use. All participants underwent a diagnostic evaluation with the K-SADS interview[176].

6.3 Image acquisition and processing

A high-resolution T1-weighted 3-dimensional magnetization-prepared rapid acquisition sequence was obtained on a 3-T Siemens Magnetom Trio Tim or a 3-T Siemens Magnetom PRISMA scanner at the Center for Image Diagnosis, Hospital Clinic of Barcelona. The imaging parameters were as follows: 240 sagittal slices, 2,300-ms repetition time, 3.00-ms echo time, 1-mm slice thickness, 900-ms inversion time, 394 × 240 mm field of view, 256 × 256 matrix size, and a 9° flip angle. To exclude potential underlying abnormalities, an axial T2-weighted structural image was acquired and reviewed by a neuroradiologist blinded to group assignments. Cortical thickness, volume, and surface area measurements were computed using the standard FreeSurfer 5.3.0 pipeline for each hemisphere and for the frontal, temporal, parietal, and occipital lobes[178,179]. Morphometric measures were further extracted for each parcellation based on the Desikan-Killiany atlas [179]. Preprocessing steps included motion

correction, normalization of non-uniform intensity, alignment to Montreal Neurological Institute stereotactic space, skull stripping, and identification of the pial surface. Visual quality control of cortical segmentations was conducted in accordance with ENIGMA guidelines[180]. The extracted measures were subsequently used for statistical comparisons between groups.

6.4 Statistical analysis of demographic characteristics

Descriptive statistics, including group means for age and sex percentages, were calculated to provide an overview of baseline demographic characteristics of the groups. To assess baseline differences in age between the groups, an analysis of variance (ANOVA) was conducted comparing mean age at baseline across the three study groups. A chi-square test of independence was used to examine differences in sex distribution across study groups.

All statistical analyses were conducted in RStudio, with relevant outputs extracted to support subsequent interpretation of findings.

6.5 Statistical analysis of neuroimaging measures

Morphometric measures of cortical thickness, grey matter volume, and surface area were harmonized using the ComBat method to account for scanner-related batch effects while preserving biological variability[181]. Scanner model was treated as the batch variable, with group, age, sex, and intracranial volume (for volume and surface area measures) included as covariates. Harmonization was performed separately for each category of morphometric measure to ensure comparability across participants and minimize site-related variability in subsequent analyses. This process was implemented using the neuroCombat package in R. Cross-sectional analyses were conducted using linear models to evaluate the effect of group membership on each morphometric measure. Cortical thickness, surface area, and grey matter volume served as outcome variables, with group as the primary predictor. For each morphometric measure, we included in the model morphometric values for hemispheres and for brain lobes; an analysis of parcellations was performed for those lobes which were found to be significant in the previous analysis. Age and sex were

included as covariates in all models, while intracranial volume was incorporated as an additional covariate for models examining grey matter volume and surface area. To account for multiple comparisons across measures, FDR correction was applied. Post-hoc group pairwise comparisons with Tukey correction were utilized when ANOVA revealed a significant group effect. For each significant pairwise comparison we extracted Cohen's d effect size.

7. Results

7.1 Demographic measures

Eighty-eight participants (female = 34.09%; mean age = 11.40 [95% CI: 10.75–12.06]) underwent clinical assessment and MRI scanning: FHR-ADHD (n = 32), ADHD (n = 25), and HC (n = 31). Four subjects recruited as HC were diagnosed with ADHD and were included in the ADHD group for meeting inclusion criteria and not satisfying exclusion criteria. Analysis of variance revealed no significant differences in mean age between groups (tab.1). Additionally, Pearson's chi-squared test found no significant differences in sex distribution across groups (tab.1).

Participants (n=88, F%=34)	**FHR-ADHD (n=32)**	**ADHD (n=25)**	**HC (n=31)**	**Statistics** (no significant pairwise comparisons found)
Female (%)	25%	36%	42%	chi=2.07; p=0.36
Age in years (mean, 95% CI)	11.7, [10.60 - 12.80]	11.3, [10.10 - 12.60]	11.2, [10.10 - 12.30]	F=0.18; p=0.84

Table 1

FHR = individuals at Familial High Risk

ADHD = attention deficit and hyperactivity disorder

HC = healthy controls

CI = confidence interval

7.2 Group comparison of brain structural measures: lobar metrics

We observed a significant group effect on morphometric measures in the occipital lobes. Specifically, significant group effects were found for left occipital surface area (p = 0.047,

FDR-adjusted p = 0.128) and for left occipital grey matter volume (p = 0.021, FDR-adjusted p = 0.129). Additionally, near-significant group effects were noted for right occipital grey matter volume (p = 0.057, FDR-adjusted p = 0.287), left frontal surface area (p = 0.050, FDR-adjusted p = 0.128) and total left hemisphere surface area (p = 0.055, FDR-adjusted p = 0.128). Pairwise comparisons revealed that the FHR-ADHD group exhibited decreased morphometric measures compared to the ADHD group, with significant or near-significant differences observed for left (p = 0.064) and right occipital surface area (p = 0.037, Cohen's d = 0.53) and for left (p = 0.035, Cohen's d = 0.64) and right occipital grey matter volume (p = 0.061).

	Group effect p-value	**FDR-adjusted p**	**Pairwise Comparisons with Directions**	**p value of comparison**	**effect size**
Left occipital SA	**0.0466581**	0.1283168	HC > FHR-ADHD	0.7359	
			ADHD > HC	0.2676	
			ADHD > FHR-ADHD	0.0637*	
Right occipital SA	0.05437227*	0.3806059	HC > FHR-ADHD	0.2399	
			ADHD > HC	0.5744	
			ADHD > FHR-ADHD	**0.0372**	0.531004
Left occipital GMV	**0.02165849**	0.1299509	HC > FHR-ADHD	0.5945	
			ADHD > HC	0.2566	
			ADHD > FHR-ADHD	**0.0354**	0.6417764
Right occipital GMV	**0.05690332**	0.2869511	HC > FHR-ADHD	0.2514	

			ADHD > HC	0.6862
			ADHD > FHR-ADHD	0.0837*
Left hemisphere SA	0.05499292*	0.1283168	HC > FHR-ADHD	0.5073
			HC > ADHD	0.8228
			ADHD > FHR-ADHD	0.8838
Left frontal SA	0.05002666*	0.1283168	HC > FHR-ADHD	0.2920
			HC > ADHD	0.5182
			ADHD > FHR-ADHD	0.9419

Table 2

FHR = individuals at Familial High Risk

ADHD = attention deficit and hyperactivity disorder

HC = healthy controls

FDR = false discovery rate

GMV = grey matter volume

SA = surface area

P<.05

*=p<.01

7.3 Group comparison of brain structural measures: cortical parcellations

Following the group effects observed in occipital lobe measures, we applied the linear model to analyze morphometric measures of individual parcellations within the occipital lobe (tab.3). There was a significant group effect for grey matter volume in the left pericalcarine region, consisting of a significant reduction in individuals in the FHR-ADHD group compared to individuals in the ADHD group, after pairwise comparisons. We also observed a significant group effect in the right pericalcarine grey matter volume, that remained significant after FDR correction, consisting of a significant reduction in individuals in the FHR-ADHD group compared to HC and a near-significant reduction in the FHR-ADHD group compared to individuals in the ADHD group. A significant group effect was found also in left lingual grey matter volume, with individuals in ADHD group showing significantly greater grey matter volumes than HC.

There were also near significant group effects in the left frontal surface area measures. When we applied the linear model to analyze the individual parcellations within the left frontal lobe, we found a significant group effect for left precentral grey matter volume and for left lateral orbito-frontal grey matter volume and surface area. Left lateral orbitofrontal grey matter volume and surface area of individuals with ADHD were found to be significantly decreased with respect to HC after pairwise comparisons, while no significant difference was found with the FHR-ADHD group. ADHD controls had, on the contrary, greater left frontal pole grey matter volumes than both FHR-ADHD (p = 0.033, Cohen's d = 0.78) and HC (p = 0.048 Cohen's d = 0.64).

	Group effect p-value	**FDR-adjusted p**	**Pairwise Comparisons**	**p value of comparison**	**effect size (Cohen's d)**
Left pericalcarine GMV	**0.01743084**	0.05536744*	HC > FHR_ADHD	0.1194	
			ADHD > HC	0.5827	
			ADHD > FHR_ADHD	**0.0143**	0.844653

Left lingual GMV	**0.02768372**	0.05536744*	FHR_ADHD > HC	0.5132	
			ADHD > HC	**0.0219**	0.620844
			ADHD > FHR_ADHD	0.2470	
Right pericalcarine GMV	0.0105907	**0.04236278**	**HC > FHR_ADHD**	**0.0132**	0.742467
			HC > ADHD	0.9255	
			ADHD > FHR_ADHD	0.0617*	
Left lateral orbitofrontal GMV	**0.0328**	0.1091964	HC > FHR_ADHD	0.7051	
			HC > ADHD	**0.0348**	0.504099
			FHR_ADHD > ADHD	0.1900	
Left lateral orbitofrontal SA	**0.024641**	0.1091964	HC > FHR_ADHD		
			HC > ADHD	**0.0275**	0.536370
			FHR_ADHD > ADHD		
Left frontal pole GMV	**0.01822144**	0.1091964	HC > FHR_ADHD	0.9785	
			ADHD > HC	**0.0479**	0.634730
			ADHD > FHR_ADHD	**0.0333**	0.774684

Left precentral GMV	**0.0312083**	0.1091964	HC > FHR_ADHD	0.1074
			HC > ADHD	0.3654
			ADHD > FHR_ADHD	0.7991

Table 3

FHR = individuals at Familial High Risk

ADHD = attention deficit and hyperactivity disorder

HC = healthy controls

FDR = false discovery rate

GMV = grey matter volume

SA = surface area

P<.05

*=p<.01

8. Discussion

We found significant reductions in left occipital lobe, left pericalcarine and left frontal pole measures in the individuals in the FHR-ADHD group compared to individuals in the ADHD group; we also found a reduction in right pericalcarine grey matter volume in individuals in the FHR-ADHD group compared to HC and significant structural differences in individuals in the ADHD group compared to HC in the left lingual, left lateral orbitofrontal and left frontal pole measures.

We found an effect of group in the **left occipital surface area** and **grey matter volume**, consisting of a **reduction** in mean measures in **FHR-ADHD** when **compared to the ADHD group** (fig.1). These findings in the occipital lobe can be interpreted in light of previous literature, which has linked anatomical and functional alterations in this region—primarily responsible for visual processing but also for other elaborate cognitive and perceptive functions—to the early development of psychotic illness in young adults at high risk for psychosis and in adult patients with schizophrenia, and to the severity of the psychotic illness[171,182–186]. In one sample of adolescents at FHR, baseline differences in occipital measures have not been replicated[187] but after a one-year follow-up a significant shrinkage of occipital surface area was observed[187]. These findings highlight that occipital morphometric measures can vary in FHR individuals and may potentially represent a marker of risk for transition to psychosis. It is therefore not surprising that in our sample, the FHR-ADHD group showed earlier alterations in the occipital lobe, one of the earliest developing cortical regions, as highlighted in previous studies[171]: early structural alterations in the occipital region may thus represent a marker of altered neurodevelopment that increases the risk of developing psychosis, particularly in children and adolescents where the burden of genetic and early neurodevelopmental factors is significant. In addition to that, these reductions of the occipital lobe measures might be of crucial importance in defining different specific neuro-phenotypes of ADHD depending on the presence or absence of FHR, being present in FHR-ADHD but not in ADHD alone[160].

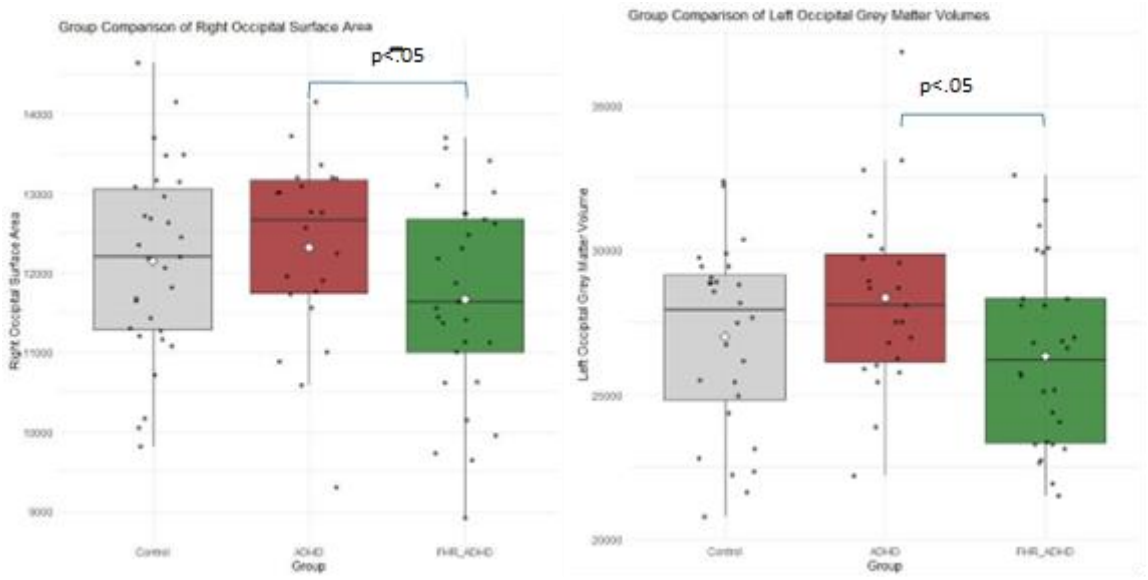


Fig.1

To our knowledge, this is the first study to identify specific differences in grey matter volume in the **pericalcarine regions** among HC, ADHD children and adolescents, and FHR-ADHD individuals. We found that **FHR-ADHD** individuals have **decreased grey matter volumes** in the **left** and **right** pericalcarine regions compared, **respectively,** to **ADHD individuals** and **HC**. The pericalcarine cortex represents the primary visual cortex[205], but it may also encompass higher cognitive functions beyond the primary processing of sensory stimuli[206]. In ADHD individuals, this region, especially in the right hemisphere, has been highlighted as an area of altered grey-white matter tissue contrast, which might indirectly indicate changes in cortical thickness and grey matter volume[207]. Additionally, nodal local efficiency in this area has been observed to increase, suggesting alterations in cortical local visual processing. These changes may also relate to an impaired ability to integrate top-down multisensory information with bottom-up stimuli, a proposed pathophysiological theory in ADHD[208]. Moreover, pericalcarine cortical thickness might also correlate with the severity of some ADHD symptoms[209], and with sensation-seeking and risky behaviors[210], traits that can be non-specifically linked to ADHD[211]; in conclusion, alterations in cortical volumes in fronto-temporal and temporo-occipital regions have been associated with different trends in response to methylphenidate in adult ADHD[212]: specifically, non-responders

exhibited a non-significant but observable trend towards lower regional volumes compared to responders.

While the possible role of alterations in the occipital areas, as discussed earlier in this section, has been partially studied in FHR individuals, significant reductions in pericalcarine morphometric measures in this population remain under-researched. Interestingly, reductions in left pericalcarine cortical thickness have been observed in individuals with first-episode schizophrenia compared to HC and FHR groups. However, the difference between HC and FHR groups was not significant[213]. In our sample of children and adolescents, decreased volumes in the left and right pericalcarine areas appear specific to the coexistence of FHR for psychosis and ADHD. Consequently, we hypothesize that when these two conditions co-occur, clinicians may consider a higher risk for developing severe mental illness if altered morphometry of the pericalcarine region is present; at the same time, the clinical ADHD syndrome and its symptoms may exhibit a suboptimal response to methylphenidate, necessitating cautious assessment of the efficacy and safety of this first-line medication. Interestingly, although not statistically significant, we observed different trends in the left and right pericalcarine regions. In the right hemisphere, ADHD individuals had mean pericalcarine volumes between the lower means of the FHR-ADHD group and the higher means of the HC group. In the left hemisphere, the ADHD group exhibited higher mean values, the FHR-ADHD group had the lowest, and the HC group had intermediate values. This finding aligns with previous observations of asymmetry in pericalcarine cortical thickness, where decreased values were noted in the right hemisphere compared to the left in adults with ADHD (Fig.2)[214]. Also, the significant differences between FHR-ADHD and ADHD controls observed in left pericalcarine volumes may not be replicated with statistical significance in the right hemisphere due to a small sample size and underpowered analysis.

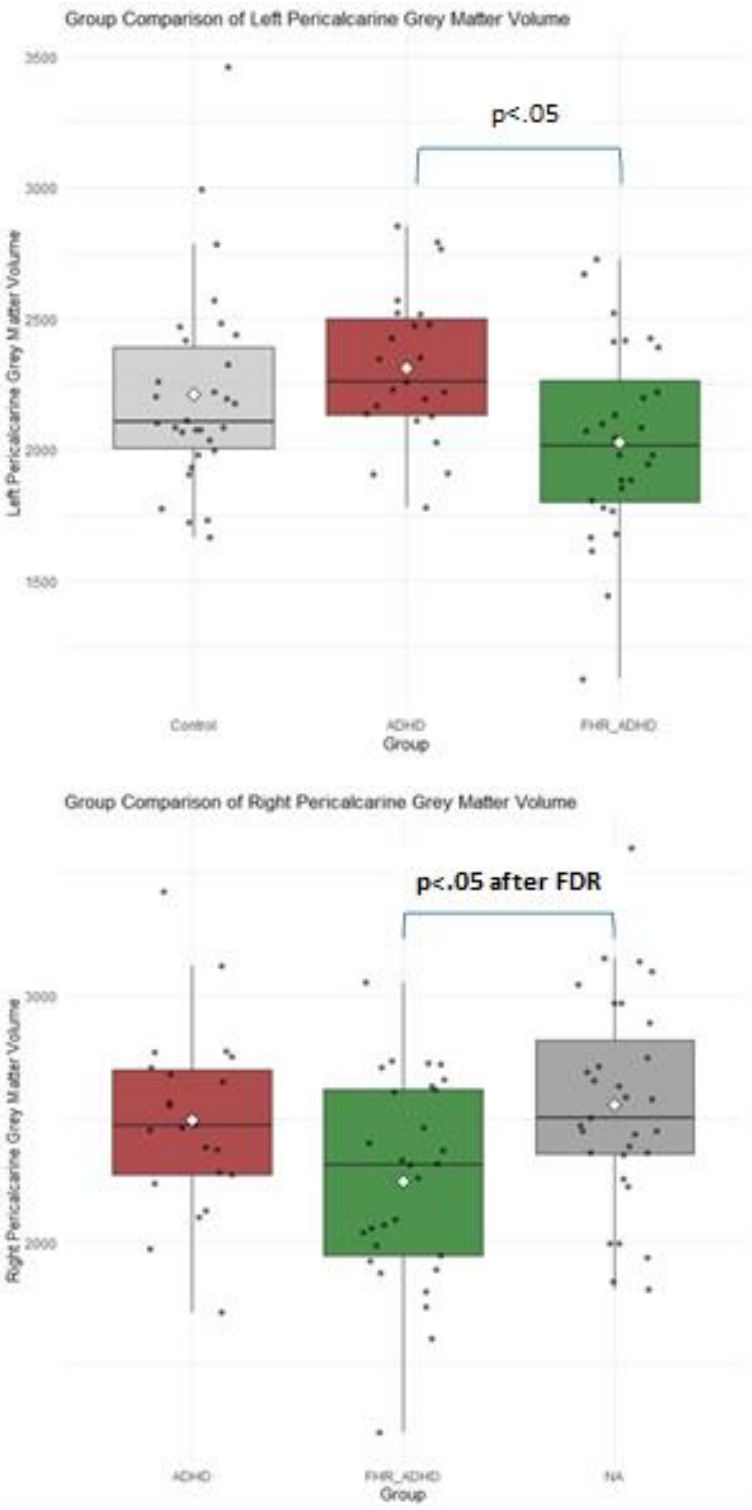


Fig.2

Curiously, individuals in the **ADHD** group had significantly **greater left lingual grey matter volumes** than **HC** (p = 0.022, Cohen's d = 0.62)(Fig.3), an uncommon finding in

ADHD samples. The lingual gyrus is a component of the occipito-temporal cortex functionally belonging to the visual cortex. The left occipito-temporal cortex is considered crucial for some cognitive tasks, such as basic associative learning of letter-speech sound correspondences and word identification and recognition in young individuals[215]. An increased grey matter volume of the left lingual gyrus has been associated with poorer inhibition functions in the Stroop color–word-interference task and better performance in tasks measuring divergent thinking in healthy young adults[216]. These cognitive alterations are consistent with those reported in ADHD individuals[217,218] and the correlation between increased lingual volumes and ADHD appears plausible. In addition to that, decreased lingual cortical folding has been found in youths at FHR who developed psychotic symptoms compared to those who did not[219] and has been related to poor treatment response in first episode psychoses.
The lingual gyrus has also been studied in adult Major Depressive Disorder in relation to antidepressant medications: increased lingual volumes predicted better antidepressant response, and antidepressants caused a volumetric reduction in the lingual gyrus in both responders and non-responders[220]. The trend of a non-significant decrease in left lingual volumes in FHR-ADHD compared to ADHD (Fig.3) might as well allow the speculation, even in the absence of causative and evidence-based explanations, that—at least in our sample—if Major Depressive Disorder were to occur in some ADHD and FHR-ADHD individuals, a better response to antidepressant medication might be predictable for the ADHD group compared to FHR-ADHD individuals.

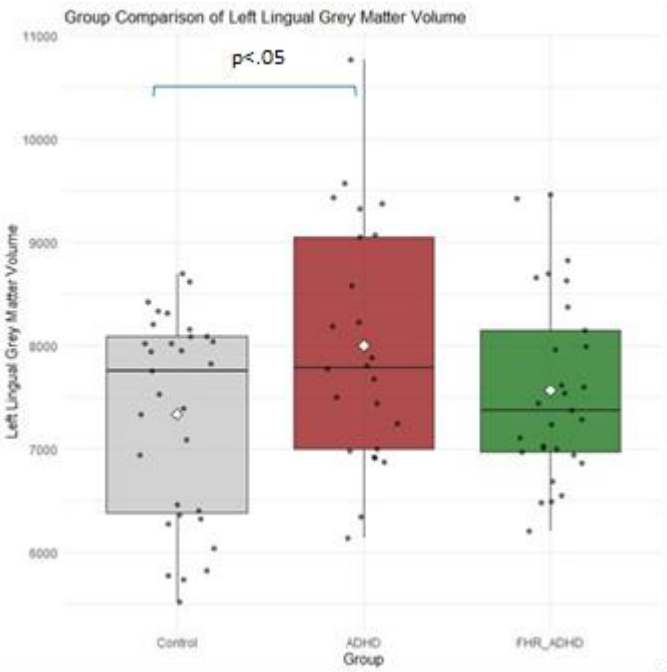


Fig.3

The group effect seen in **left precentral gyrus** grey matter volumes is in line with previous findings in ADHD[221,222]. The precentral gyrus is involved in fine motor control[223], sensorimotor mapping[223], and cognitive functions[224], playing a key role in higher functions such as attention, decision-making, response inhibition, and psychomotor activity, which can be altered in ADHD individuals[225]. For these reasons, it is considered one of the neuropathological markers of ADHD [221,226]. Interestingly, precentral gyrus grey matter volume is not usually affected in FHR children and adolescents, with altered findings limited to decreased cortical thickness[170]. However, grey matter volume alterations have been found in schizophrenic patients compared with both HC and FHR individuals[227]. The role of illness duration and medication is still unclear, but the precentral gyrus may be considered another possible brain region that is not affected at early developmental stages in every individual at FHR but could gain relevance with the onset of a mental disorder, especially if specific clinical characteristics, such as cognitive dysfunctions, can be observed. It is noteworthy that ADHD individuals exhibit a non-significant trend, with volumetric precentral measures falling between the highest mean values observed in HC and the lowest means in the ADHD-FHR group (see table 3 in Results section).

The finding of lower **left lateral orbitofrontal surface area and grey matter volume** measures in the ADHD group compared to controls aligns with previous literature[161,188,200] (Fig.4). The orbitofrontal cortex is an important region that controls many functions, such as emotional and motivational regulations and behaviors, decision-making, impulse control, and reward circuits. Alterations in its functions have been related to several neurodevelopmental, psychiatric, and neurodegenerative disorders [228–234]. However, as the orbitofrontal cortex is such an interconnected region—with association areas, limbic structures, and other prefrontal cortical regions—its morphological and functional alterations are often non-specific. Nevertheless, we were not able to replicate the findings of Zhu et al.[118], who found significant reductions in left lateral orbitofrontal surface area of BpO individuals with ADHD compared to ADHD offspring of healthy parents, without finding statistical significant differences between the two ADHD groups and HC: even in the absence of significant alterations in FHR with ADHD in our sample, we align with these findings highlighting that this area may serve as a marker of two different phenotypes between ADHD individuals at FHR or not at FHR, and would deserve further studies. We also cannot exclude the possibility that, with a larger sample, significant alterations might also be found in FHR-ADHD, as they exhibited a non-significant trend toward reduction—albeit smaller than that observed in the ADHD group—when compared to HC.

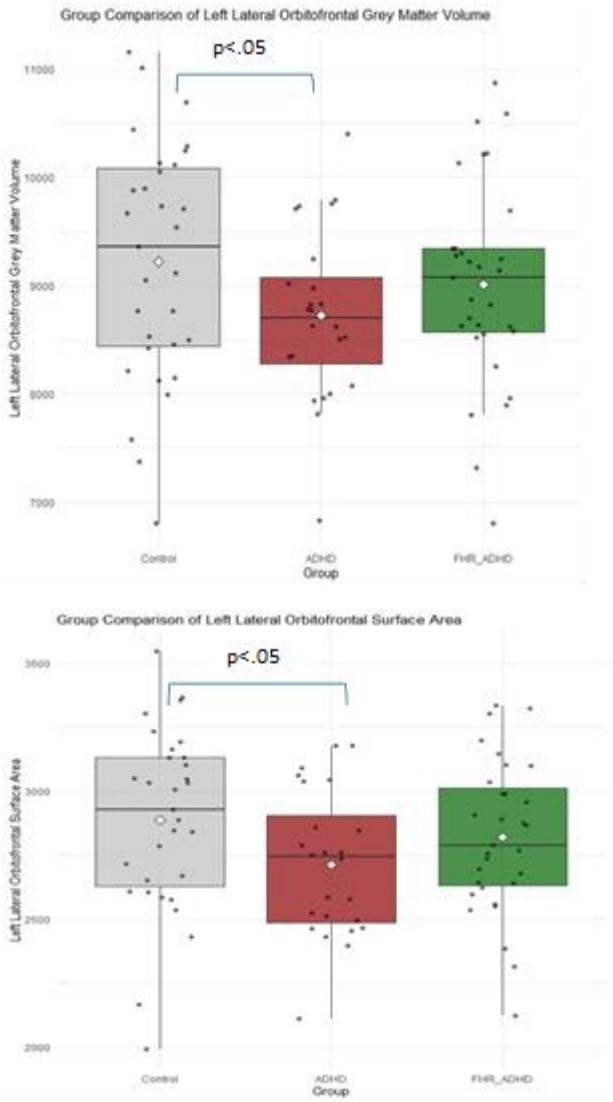


Fig.4

We found significantly **increased grey matter volumes in the left frontal pole** of individuals in the ADHD group compared to both the FHR-ADHD group and the HC group (Fig.5). The frontal pole subserves several functions, such as multitasking, social cognition, attention, and episodic memory, along with its interconnection with prefrontal, orbitofrontal, temporal, and somatosensory areas[235]. A decrease in its volume has been reported in adolescents aged around 17 years with ADHD and their unaffected siblings compared to HC[236] (mean age 17.2). However, in a younger sample of ADHD children aged around 9 years, an altered development of the frontal pole has been suggested[237]. The increase in grey matter volumes observed here may

represent an initial compensatory mechanism or a developmental delay, while at older ages, alterations in frontal pole volumes tend to normalize or reverse (i.e., become smaller than those of controls).
Another possible explanation might be that these data highlight a decreased grey matter volume in the left frontal pole of the FHR-ADHD group compared to the ADHD group and that, with a larger sample, we might observe a significant difference also between FHR-ADHD and HC. This possibility aligns with previous findings of decreased frontal pole volumes in FHR individuals, although significant results have been reported with opposite lateralization in the right frontal pole[238] and the differences between ADHD group and HC would remain unexplained. Even though these findings do not converge on a unifying and comprehensive theoretical explanation, they may represent another phenotypical difference distinguishing ADHD in FHR versus non-FHR individuals, warranting further research.

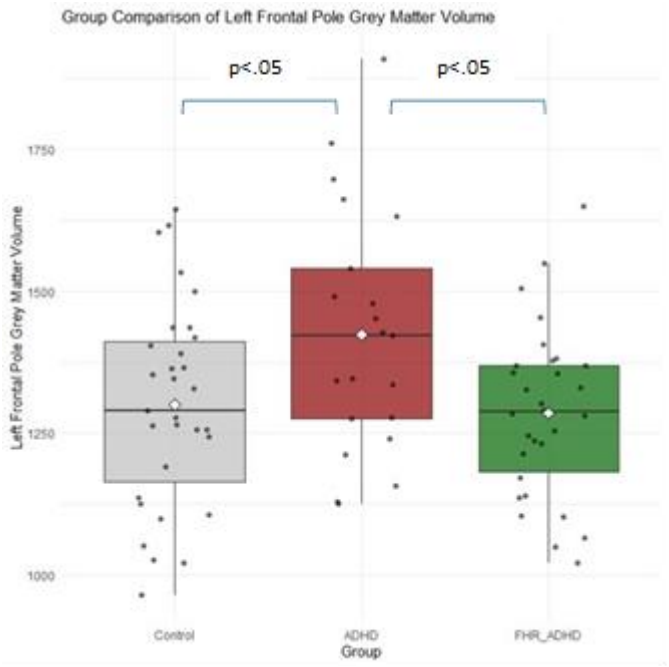


Fig.5

Although only near statistical significance, we observed a group effect in **the left frontal and total hemispheric surface areas**. The trend observed—with the FHR-ADHD group

showing reduced mean surface area values, HC exhibiting higher means, and individuals in the ADHD group presenting intermediate values (see tables 2 and 3 in Results section) —is consistent with previous findings of reduced frontal surface area in ADHD[187,188] and in FHR, where it has also been associated with the transition to psychosis[171,187,189].

Moreover, other studies have reported differences in frontal morphometric measures beyond surface area, such as grey matter volume, cortical thickness, and gyrification[163,185,190], suggesting an interrelatedness of different metrics in the same regions. Notably, in a study of individuals with ADHD, the effect was found to be limited to grey matter volume and cortical thickness after correcting for total intracranial volume, suggesting that alterations in surface area may, in some cases, significantly depend on total intracranial volume[188].

A reduction in left hemisphere surface area may align with other findings that emphasize brain dysfunctions lateralized to the left hemisphere, predominantly associated with cognitive, attentional, and linguistic functions[191–194]. However, findings regarding abnormal brain lateralization in ADHD remain inconclusive and somehow contradictory, warranting further in-depth investigation.

We did not find any significant group differences in cortical thickness measures. Cortical thickness has been proposed as one of the potential markers of ADHD in youth[160,195]. While alterations in cortical thickness have also been observed in symptomatic adults with ADHD[196], their effect sizes are generally smaller compared to measures such as surface area and tend to disappear during adolescence and adulthood[160].

Cortical thickness is known to peak at different—and early—neurodevelopmental stages across specific brain regions, followed by a linear or nonlinear decline with development and aging[197,198]. Although ADHD is characterized by delayed cortical development[198], including cortical thickness, the latest peaks—occurring in the prefrontal cortex—are observed at a median age of 10.5 years in ADHD youth[198], compared to age 8 or earlier in neurotypical individuals[197]. Consequently, it is reasonable to hypothesize that in samples with older mean ages—such as ours—

differences in cortical thickness may be less pronounced. Furthermore, previous studies have reported that the primary differences in the brains of individuals with ADHD are limited to grey matter volumes and surface areas[199,200].

In FHR samples, differences in cortical thickness are not usually found cross-sectionally[171,201], while cortical thinning over time has been related to the presence of ultra-high risk criteria in young adults[202], transition to psychosis in FHR samples[171,187], and illness in adult patients[187,203]. In the absence of a longitudinal follow-up of this sample it is only possible to speculate that cortical thinning might be a dynamic process that occurs around - and relates to - the onset of prodromal or psychotic symptoms rather than an early neurodevelopmental marker of illness detectable at young age and with cross-sectional analysis of FHR samples, which when present may also be driven by gender differences[204].

Neuroimaging Differences Between ADHD, FHR-ADHD, and HC

Comparison	Surface Area (SA)	Uncorrected p-value	Cohen's d	Grey Matter Volume (GMV)	Uncorrected p-value	Cohen's d
FHR-ADHD < ADHD	Right occipital SA*	0.0372	**0.53**	Left occipital GMV*	0.0354	**0.64**
				Left pericalcarine GMV*	0.0143	**0.84**
				Left frontal pole GMV*	0.0333	**0.77**
ADHD > HC	—	—	—	Left lingual GMV***	0.0219	**0.62**
				Left frontal pole GMV***	0.0479	**0.63**
HC > FHR-ADHD	—	—	—	Right pericalcarine GMV*	0.0132	**0.74**
HC > ADHD	Left lateral orbitofrontal SA**	0.0275	**0.54**	Left lateral orbitofrontal GMV**	0.0348	**0.50**

Table 4

Note: All p-values are uncorrected.

*= in ENIGMA studies of ADHD: no similar alterations in ADHD individuals vs controls in these regions

**= findings of ENIGMA studies of ADHD in these regions are replicated in our sample

***= ENIGMA studies of ADHD evidenced different alterations in these regions

8.1 Limitations

When interpreting the current results, several methodological limitations must be considered. First, the sample size may have been too small to detect subtle structural differences, some of which lost significance after correction for multiple comparisons in our study. A larger sample size would have allowed better differentiation between trends that represent non-significant variations within the normal distribution and those indicating genuine morphometric differences between groups. The limited sample size also precluded further subdivision, for example, by pubertal stage or parental diagnosis (SzO vs. BpO), which could have influenced brain structure and its trajectory in different ways. Second, while the aim of this study was to explore potential differences in ADHD according to the presence or absence of a familial high risk (FHR), the absence of a control group consisting of individuals with FHR but without ADHD limited the ability to determine which findings are specific to the coexistence of the two conditions versus those which characterise FHR individuals. As discussed, previous neuroimaging studies have identified differences between HC and individuals with ADHD or FHR that extend beyond cortical structural morphometry. Including additional measures such as subcortical volumes, gyrification, or functional MRI data, and exploring their relationships with clinical findings, could be a valuable future direction for better understanding similarities and differences among the studied groups. Another limitation is the cross-sectional design of the study. Although this design is useful for identifying associations between observed variables, a longitudinal study would allow for the assessment of the trajectory of morphometric values over time. This approach could also link these trajectories to critical elements of clinical progression, such as transition to schizophrenia, bipolar disorder, or other severe mental illnesses.

Despite these limitations, this study has notable strengths. First, the naturalistic recruitment of the FHR sample ensured a representative selection of real-world individuals, minimizing selection bias. Second, the blinded assessment reduced expectancy effects and confirmation bias, ensuring the objectivity of measurements. These assessments were conducted in a clinical setting, further enhancing diagnostic reliability and standardization of protocols. Moreover, the age range of the sample minimized potential confounders that often arise in studies with broader age gaps.

Additionally, the comparison between the FHR-ADHD group, the ADHD group, and the HC group allowed for the identification of both shared and unique differences among these groups—an analysis that, to our knowledge, had not been performed previously. Furthermore, all group differences were corrected for multiple comparisons, ensuring that significant results were not overestimated. The imaging acquisition, preprocessing, and analysis protocols used were validated, well-established, and consistently applied, with all data processing phases conducted by experienced professionals in an advanced medical center. Lastly, focusing on morphometric measures provided a significant and stable representation of brain structure, which may be less state-dependent than functional measures such as fMRI or EEG.

8.2 Conclusions

Taken together, our observations can lead to two different conclusions. First, it is possible to observe partially specific neurophenotypes of ADHD between individuals at FHR and those not at FHR. We identified specific differences between the two groups in the occipital region, including the left and right occipital lobes and the left pericalcarine lobule. Additionally, we found other morphometric alterations that appear specific to ADHD in the absence of FHR, namely in the orbitofrontal and lingual lobules, lateralized to the left hemisphere. Second, we observed trends in brain structural alterations in the right pericalcarine lobule that suggest a continuum. Specifically, these alterations were statistically significant in FHR-ADHD individuals, less pronounced and non-significant in ADHD individuals not at FHR, and absent in healthy controls (HC). This pattern suggests that alterations in this region are more marked when FHR and ADHD co-occur, while they may be only slightly present or absent in individuals with ADHD who are not at FHR or in those at FHR without ADHD.

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