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MINIREVIEW

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Clinical characteristics, neuroimaging findings, and neuropsychological functioning in attention-deficit hyperactivity disorder: Sex differences

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Abstract

Recent clinical studies, in both children/adolescents and adults, have shown the extreme neuropsychological heterogeneity of attention-deficit hyperactivity disorder (ADHD): specific neuropsychological deficits have been found only in a minority of individuals, with no direct correlation between discrete cognitive performances and the trajectory of clinical symptoms. Deficits in specific neuropsychological functions may be common in ADHD, but nevertheless no cognitive or neuropsychological profile may fully explain the disorder. Sex differences in the ADHD presentation, both at a neuropsychological and clinical level, also contribute to this clinical and neuropsychological heterogeneity. At a neuropsychological level, females with ADHD may show greater working memory problems, poorer vocabulary skills and worse visual spatial reasoning. Structural and functional imaging study also show discrete differences across sex; however, the great majority of clinical studies mainly or exclusively include male participants with insufficient data to draw firm conclusions on sex differences within the disorder. Here, we report the recent literature data, discussing still open research questions about the clinical presentation, neuroimaging findings, and neuropsychological functioning in ADHD with a focus on the impact of sex differences—a deeper insight in these unresolved issues may have relevant clinical and therapeutic implications for tailored, effective, and long-lasting interventions.

KEYWORDS
attention-deficit hyperactivity disorder, executive function, girls, neuroimaging, sex differences

1 | INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity/impulsivity, or a combination of these symptoms (American Psychiatric Association, 2013). It is one of the most common and costly conditions, affecting approximately 6% of children (Polanczyk et al., 2007), associated with functional impairment, poor health-related quality of life (Coghill et al., 2017), and significantly increased mortality rates (Dalsgaard et al., 2015). The management of the disorder is based on a multimodal approach combining behavioral and pharmacological interventions (Zuddas & Carucci, 2020).

ADHD is an example of a valid clinical neuropsychiatric syndrome with marked heterogeneity across multiple levels of analysis,

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although, at the moment, its etiology and pathophysiology are incompletely understood. A growing body of evidence supports a model in which several genetic and environmental factors interact each other during prenatal and early postnatal periods, increasing the neurobiological predisposition to the disorder (Cortese & Coghill, 2018; Faraone & Larsson, 2019; Walton et al., 2017). This, in turn, leads to subtle alterations within several brain systems that result in different deficits in multiple neuropsychological domains. This model recognizes a high degree of pathogenetic heterogeneity in the ADHD population, with significant individual differences in the extent to which genetic, environmental, and neuro-pathophysiological processes are involved in the disorder (Cortese & Coghill, 2018).

Sex differences in the ADHD presentation, both at a neuropsychological and clinical level, also contribute to the clinical and neuropsychological heterogeneity of the disorder. The majority of the clinical studies, however, mainly or exclusively includes males, and clinicians rarely take into account sex influence on ADHD core features' presentation. Here, we discuss the recent literature data on the neuropsychological functioning of ADHD individuals focusing the impact of sex differences both at a clinical and a neuropsychological level. For a more in-depth analysis of the topic, we also considered sex differences in the results of the neuroimaging studies.

1.1 | Method

This narrative minireview has been conducted by search and "research" of the most relevant literature in the topic area, via keyword searches on relevant electronic databases (PubMed and Google Scholar). The single and combining keywords used for literature searching have been: "ADHD" (or "attention deficit/hyperactivity disorder"), "gender" (or "sex"), "clinical characteristics" (or "presentation"), "neuroimaging" (or "MRI"), "neuropsychological functioning" (or "executive functioning"). We included clinical studies, meta-analyses, and systematic reviews of the last 20 years (we included older papers if they had a historical value on the topic). We mostly selected articles dealing with developmental age.

The results of our search are divided into three sections: (1) ADHD clinical presentation; (2) neuroimaging; and (3) neuropsychological functioning. We briefly discuss each topic in ADHD individuals and then focus on sex differences. The main results are reported in Table 1.

2 | ADHD CLINICAL PRESENTATION

As other neurodevelopmental disorders, ADHD clinical presentation varies with age, with the associated functional impairment also varying from patient to patient. ADHD children are highly impaired in their social relationships, have more experiences of rejection by peers and a more pessimistic view of their social world (Grygiel et al., 2018); they are also at a significant risk for more behavioral, familial, and academic failures (Coghill et al., 2017). ADHD adolescents present earlier sexual activity, especially those with high levels of comorbid conduct disorder symptoms (Galera et al., 2010). In adulthood, ADHD is associated with worse educational, occupational, economic, and social outcomes, more divorces, and higher probability to be incarcerated (Ebejer et al., 2012; Klein et al., 2012).

Significance

Neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), are more frequently diagnosed in males, but the underlying reasons are not completely understood. Sex-specific characteristics may help to better understand different aspects of the disorder and may provide useful insights into the different neuropsychological functioning between the two sexes. Here we review sex differences in ADHD at different levels of analysis (clinical, neuropsychological, and neurofunctional) in order to improve clinicians' alertness, diagnostic accuracy, and therapeutic specificity for tailored, effective, and long-lasting interventions in both sexes.

ADHD comorbidities are also heterogeneous and they vary over the life-course: In childhood, oppositional defiant disorder and conduct disorder are more common, while in adolescence and adulthood, anxiety disorders, affective disorders, antisocial personality disorders, and substance abuse disorders are more frequent (Charach et al., 2011; Franke et al., 2018; Harstad et al., 2014). Adults with ADHD, especially when a psychiatric comorbidity is present, may also show more intense suicidal behavior than normally developed adults (Fitzgerald et al., 2019).

2.1 | Biological models for sex differences in ADHD

In most studies, clinical samples consist mainly of male participants: The DSM-5 diagnostic criteria have been developed and validated using mostly male samples. A "*male prototype of ADHD*" might have been therefore structured, making ADHD in girls underdiagnosed in clinical practice (Mowlem et al., 2019; Nussbaum, 2012).

Male to female sex ratio ranges from 2:1 to 10:1 (averages 4:1), with higher ratio in clinical samples; this difference results attenuated with age and, in adulthood, male to female ratio is nearly 1:1 (Faraone et al., 2015; Mowlem et al., 2019).

Interestingly, male to female prevalence ratio has not been accurately reported for subthreshold ADHD (presence of ADHD symptoms that do not fully meet all criteria) that appears equally prevalent in boys and girls in a large-scale community study (Hong et al., 2014).

The so called "*female protective effect model*" may explain the differences in prevalence by sex: According to this model, females would need greater exposure to genetic and environmental ADHD risk factors to develop full ADHD symptoms. In fact, one hypothesis is that females with ADHD are more likely to inherit few high-impact

TABLE 1 Main sex differences

	Males	Females	Experimental groups	Most relevant studies on the topic
Clinical presentation				
	More hyperactivity, externalizing problems, physical aggression, tic disorders, and motor coordination disorders	More inattention, internalizing problems, verbal aggression, poorer coping skills, language disorder, and lower IQ	Children, adolescents, and adults	Gaub and Carlson (1997)[a], Rucklidge (2010)[a], Nussbaum (2012)[a], Ottosen et al. (2019) Mowlem et al. (2019)
Neuroimaging	Males	Females		
Structural anomalies	SA reduction of right ACC and left medial PFC	SA reduction in PFC (dlPFC bilaterally, left latero-inferior PFC, right medial PFC, right OFC) and left ACC[b]	Children	Dirlikov et al. (2015)
Cortical	SA reduction in PMC[b]			
	WM abnormalities in motor regions (primary motor M1)[b]	WM abnormalities in prefrontal regions (medial OFC)[b]	Children	Jacobson et al. (2015)
Subcortical	Volumetric reductions in basal ganglia and amygdala	No volume or shape difference[b]	Children	Qiu et al. (2009), Seymour et al. (2017), Tang et al. (2019)
	Shape-localized abnormalities in the caudate, putamen, and globus pallidus[b]			
	Volume reduction in the caudate, globus pallidus, and thalamus[b]	Greater relative volume reduction in the caudate, globus pallidus, and thalamus[c]	Preschoolers	Rosch, Crocetti, et al. (2018)
	No ADHD-related sex differences		Children, adolescents, and adults	Hoogman et al. (2017)
Functional anomalies	Underactivation in networks involving frontal, temporal, cerebellar, occipital, and subcortical regions during *working memory* task		Adults	Valera et al. (2010)
	Negative correlation between *working memory* neural activity and *hyperactivity symptoms*[b]	Negative correlation between *working memory* neural activity and *inattentive symptoms*[b]		
	Underactivation of bilateral frontal and parietal areas	Underactivation of right inferior frontal and postcentral gyri, right cerebellum, right middle temporal gyrus, and left basal ganglia, during *forethought* task[b]	Adolescents	Poissant et al. (2016)
	Hyperactivation of amygdala and superior temporal gyrus, during *forethought* task[b]			
	Hypoactivation of fronto-striatal and frontoparietal networks, during *response inhibition* task *(SST)*[b]	Hypoactivation of fronto-striatal and frontoparietal networks, during *response inhibition* task *(SST)* similar to males	Adolescents	van Rooij et al. (2015)
	Anomalies in FC, between vmPFC, striatum, and amygdala[b]	Greater diagnostic effects of anomalies in FC, between vmPFC and striatum, and amygdala[c]	Children	Rosch, Mostofsky, et al. (2018)
		Atypical intrinsic FC between striatum and dlPFC: stronger positive FC with the ACC and negative FC with the dlPFC		

(Continues)

TABLE 1 (Continued)

	Males	Females	Experimental groups	Most relevant studies on the topic
Neuropsychological functioning	Males	Females		
Processing speed, working memory, and visual special reasoning	Poorer processing speed, and deficits in motor functioning[c]	Working memory weakness, poorer vocabulary skills, worse visual spatial reasoning[c]	Children, adolescents and adults	Rucklidge (2010), Nussbaum (2012)[a]
Sustained attention	More commission errors (impulsivity) during *CPT*[c]	No differences on omission errors (attention) during *CPT*[c]	Children	Hasson and Fine (2012)[a]
Inhibition	Greater impairment in inhibition skills[c]		Adolescents	Rucklidge (2006)
		Impaired response control on tasks with higher cognitive load[b]	Children	Seymour et al. (2016)
	Higher impairment during conscious, effortful response inhibition[b]		Children	O'Brien et al. (2010)
		Greater response inhibition deficits in adolescence[b]	Children and adolescents	DeRonda et al. (2021)
	Greater behavioral disinhibition (impaired inhibitory control on the *SST* and *GNG task)*[b,c]		Children	Patros et al. (2018)
Planning		Higher impairment in planning[c]	Children	O'Brien et al. (2010)
Working memory		Greater working memory deficits[b]	Adults	Schweitzer et al. (2006)
Delay discounting		Increased delay discounting[b,c]	Children	Rosch and Mostofsky (2016), Patros et al. (2018)
	No sex differences on delay gratification and temporal discounting tasks	Tend to prefer smaller immediate rewards[c]	Children and adults	Doidge et al. (2021)[a]
Motor overflow	More mirror overflow[b]		Children	MacNeil et al. (2011), Cole et al. (2008)
		Similar levels of excessive mirror overflow, but more variable tap times[b]	Children	Chen et al. (2021)

Abbreviations: ACC, anterior cingulate cortex; CPT, continuous performance test; dlPFC, dorso-lateral prefrontal cortex; FC, functional connectivity; GNG, go/no-go task; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PMC, primary motor cortex; SA, surface area; SST, Stop Signal Task; vmPFC, ventromedial prefrontal cortex; WM, white matter.

[a]Meta-analyses or reviews.

[b]Compared their sex-matched controls.

[c]Compared to opposite-sex subjects.

genes which are rare and therefore less frequently manifest ADHD. It is also possible that females with ADHD inherit the same genes but require greater exposure to environmental factors than males to clinically manifest the disorder (Taylor et al., 2016).

Molecular genetic research suggests an important role for sex chromosome genes: In the male brain, the sex determining region on the Y-chromosome seems to regulate dopamine biochemistry and function. In addition, this region plays a key role in regulating the function of specific genes expressed in the brain areas involved in motor control, reward, and attention, closely related to ADHD pathophysiology. Furthermore, females with only one X chromosome (Turner syndrome) are more susceptible to ADHD (Liedmeier et al., 2020; Loke et al., 2015). This may suggest that the additional X chromosome could protect female from developing ADHD (Greven et al., 2018). Klinefelter syndrome, in which males have an extra X chromosome (XXY), is associated with ADHD too, but, interestingly, such patients show mainly ADHD-inattentive symptoms, similar to that is observed in women with idiopathic ADHD. These results seem to suggest that the number of X chromosome may influence sexual dimorphism in the ADHD profile (Green et al., 2019).

Endocrine factors are also involved in the sex differences in ADHD prevalence. Androgenic hormones determine the dimorphic characteristics of the brain and regulate the distribution, receptor density, and activity of the dopaminergic, gabaergic, glutamatergic, and serotoninergic systems (Gillies et al., 2014; Waddell & McCarthy, 2012).

According to the "*evolutionary theory of sexual selection*" (Geary, 2010), males and females have a predisposition, determined by an evolutionary advantage, to develop different psychopathological features. This predisposition has not been fully understood but appears to have a genetic, epigenetic, and hormonal basis. Males appear to have a window of vulnerability in early developmental stages and therefore to be at an increased risk of earlier onset disorders such as ADHD; females seem more likely to develop psychopathological manifestations with prevalent onset in adolescence, such as internalizing disorders. Hormones play a crucial role in this trend: Prenatal exposure to high testosterone levels, as largely documented later in life in individuals with externalizing disorders, may modulate the dopaminergic transmission pathway, predisposing the subject to traits such as disinhibition and sensation seeking, which are often associated with externalizing spectrum psychopathologies (Martel, 2013). In fact, the exposure to higher levels of testosterone in utero may be related to a lower D2:D4 ratio, which, in turn, has been reported to correlate with more ADHD symptoms (Breedlove, 2010; Stevenson et al., 2007). In females, on the other hand, an increase in estrogen levels during puberty seems to interfere with serotonergic transmission and to predispose to traits such as negative emotionality and rumination, which, in the case of hormonal dysregulation, can be associated with internalizing disorders (Martel, 2013).

Interestingly, a correlation between estrogen hormones and dopamine D2 receptors in the striatum has been also investigated. In female puberty, the increase in estrogen levels correlates with an increase in these receptors. This may partly explain the narrowing of the gap in the male:female ratio in the transition from childhood to adulthood (Nussbaum, 2012).

Finally, stress hormones may also contribute to the sex differences in ADHD. Men, compared to women, seem to have a stronger activation of the adrenocorticotropic hormone and cortisol response to stress, suggesting a different, sex-dependent, HPA axis functioning: Stress hormones have downstream effects on the activity and sensitivity of the dopaminergic neurons in the prefrontal cortex and ventral striatum, two brain areas typically involved in ADHD (Gillies et al., 2014; Stephens et al., 2016).

2.2 | Sex differences in ADHD clinical presentation

Girls receiving a diagnosis of ADHD are more likely to be diagnosed with the predominantly inattentive presentation and are usually less hyperactive (Gaub & Carlson, 1997; Mowlem et al., 2019; Rucklidge, 2010). Contrary to ADHD males, who are prone to disruptive and aggressive behaviors (Gaub & Carlson, 1997; Mowlem et al., 2019; Rucklidge, 2010) and show more frequently comorbidity with tic disorders and motor coordination disorders (Ottosen et al., 2019), ADHD girls show poorer coping skills, less self-esteem, and more frequent comorbidities with language disorders and intellectual disability (Gaub & Carlson, 1997; Rucklidge, 2010). Moreover, females usually have higher ratings of internalizing problems, as anxiety and mood disorders, personality and eating disorders; they also have more self-reported self-harm and suicidal ideation (Gaub & Carlson, 1997; Mowlem et al., 2019; Nussbaum, 2012; Rucklidge, 2010). Criminality, violent crimes, and prison sentences have been found to be higher in men compared with women with ADHD, as well as psychopathic traits in non-incarcerated adults (Rucklidge, 2010). Some authors show that alcohol and drug abuse are also higher in ADHD men than in women (Rucklidge, 2010). However, in a large population study, when compared to males, ADHD females showed a stronger association with several comorbid disorders including oppositional defiant/conduct disorders (ratio of the hazard ratio HRR 1.97), autism spectrum disorders (HRR, 1.86), intellectual disability (HRR 1.79), personality disorders (HRR 1.23), suicidal behaviors (HRR 1.28), schizophrenia (HRR 1.21), and substance use disorders (HRR 1.21), thus identifying a more vulnerable group of patients and evidencing that females can be equally or even more impaired than males (Ottosen et al., 2019).

In terms of social functioning, differences have been found across sexes. Males behave more aggressively than girls, resulting in exclusion by peers. Girls are usually less physically, but more verbally aggressive; if compared with girls without ADHD, they are also more inclined to relational aggression, that is, to ruin or disrupt the victim's social relationships (Rucklidge, 2010). When compared to males, females also seem less aware of their dysfunctional behavior and tend to be bullied rather than bully (Novik et al., 2006).

Considering the different clinical presentation and comorbidities in males compared to females, it is likely that the behavior of ADHD females may be perceived as less problematic or disruptive

and therefore that their symptoms are more tolerated by teachers and parents. As a result, females may be diagnosed only when they show significantly more severe forms of ADHD or when they have a clinical presentation like males. Alternatively, they may come to clinical attention only when they transit into other diagnoses such as anxiety disorder or depression.

A recent population-based study has shown sex differences in parental perceptions of ADHD behaviors and impairment. In a sample of 283 children aged 7–12 years, ADHD females, when compared with ADHD males by the Parental Account of Childhood Symptoms (PACS), showed more emotional problems, lower scores on parental stress indicators, fewer conduct problems, fewer complaints at school due to hyperactivity, and higher prosocial scores. Interestingly, females are perceived by parents to be more socially adequate and less compromised, being able to mask the core ADHD symptoms. It is yet to be understood whether prosocial behavior may be a way of compensating for the cardinal clinical features of ADHD (Mowlem et al., 2019).

3 | NEUROIMAGING

3.1 | Neuroimaging data in ADHD individuals

Abnormalities in the prefrontal cortex and the interconnected subcortical structures including the caudate, putamen, globus pallidus, and cerebellum have been largely described in ADHD (Castellanos et al., 2002; Nakao et al., 2011; Valera et al., 2007).

Structural magnetic resonance imaging (MRI) studies show that individuals with ADHD have significantly smaller global gray matter volumes compared to healthy ones, smaller gray matter volumes in the caudate nucleus and in the right lentiform nucleus, and larger gray matter volumes in the left posterior cingulate cortex/precuneus, a crucial portion of the default mode network (DMN) (Nakao et al., 2011; Sonuga-Barke et al., 2016). Smaller volumes in the frontal regions and the striatum represents one of the central features of ADHD; interestingly, caudate, putamen, and globus pallidus are part of the fronto-striato-thalamo-cortical circuits essential for higher executive functions (Nakao et al., 2011).

Recently, the enhancing neuro imaging genetics through meta-analysis (ENIGMA)-ADHD working group analyzed brain imaging data from 1,713 participants with ADHD and 1,529 healthy controls from 23 sites (age range: 4–63 years; 66% males). Through a precise mega and meta-analysis, significantly smaller volumes of the amygdala, accumbens, caudate, hippocampus, putamen, and of the whole intracranial volume were found in the ADHD population. Compared to previous studies mainly indicating a unilateral caudate and putamen volumes reduction (Ellison-Wright et al., 2008), these alterations resulted bilateral rather than unilateral; furthermore, authors explored possible confounders related to clinical measures and found that the structural brain volume differences were not related to any comorbid disorders, medication effect, or ADHD symptoms severity, but could be exclusively inferred to the condition of ADHD itself (Hoogman et al., 2017).

Several studies also examined the morphology of different areas of the cerebral cortex evidencing a predominantly thinner cortex with reduced surface area. In ADHD children, a widespread reduction of cortical dimensions in the PFC, superior parietal cortex, and medial and anterior temporal regions have been reported, thus with less agreement on the precise location of change (Batty et al., 2010; Narr et al., 2009; Shaw et al., 2006; Sowell et al., 2003).

Furthermore, the same ENIGMA-ADHD working group, recently confirmed that children with ADHD showed a smaller surface area, mainly in frontal, temporal, and cingulate regions. Differences in the cortical thickness (i.e., thinner in ADHD children) were limited to the temporal pole and the fusiform gyrus (Hoogman et al., 2019). Compared to previous researches showing a greater cortical thinning in the regions implicated in attention and executive functioning in adult (Makris et al., 2007), in this study neither surface area nor thickness differences were found in the adolescent or adult population; furthermore no significant correlations were found between cortical alterations and either stimulant treatment or intelligence quotient (IQ) (Hoogman et al., 2019).

Results from functional MRI (fMRI) studies seem to delineate specific pattern in ADHD children and they further suggest specific neural correlates for ADHD subtypes: Compared to typically developing children (TDC), ADHD-inattentive (ADHD-I) children show connectivity differences in the prefrontal dorsolateral cortex and cerebellum, while ADHD-combined type (ADHD-C) children differ from TDC mainly in the medial prefrontal cortex, posterior parietal nodes of the default network, and also sensorimotor, visual, and cingulo-opercular systems (Fair et al., 2012).

In a recent meta-analysis of fMRI studies, when compared to control subjects, ADHD participants showed abnormal activation in the brain areas involved in motor control, interference inhibition, switching, attention, and timing, during different emotional and cognitive tasks (Rubia, 2018). ADHD children also showed an hypoactivation in the systems involved in executive functions (frontoparietal network) and attention (ventral attentional network). A significant hyperactivation in ADHD compared to control group was instead observed in the DMN. Reciprocal interrelation between DMN and brain areas involved in attentional processes and executive functions appears to be also functionally impaired (Cortese et al., 2012; Rubia, 2018).

In addition to impaired integrity and connectivity in the DMN, which lead to consequent lack of attention and mind wandering, ADHD individuals also show fronto-striatal and frontoparietal connections' deficits, with consequent impaired decision-making speed and efficiency; ventro-striatal connections' deficits, with consequent delay aversion; and impaired orbitofrontal connectivity, with consequent learning deficits (Sonuga-Barke et al., 2016).

3.2 | ADHD-related sex differences in neuroimaging data

As evidenced by Hoogman et al. (2017) within the ENIGMA study, a main effect of sex can be evidenced in the volumes of most of the

subcortical structures, apart from accumbens and caudate volumes, independently from the ADHD diagnosis. Longitudinal studies also show that brain development has different trajectories in girls and boys. Gray matter increase rate in the frontal lobe peaks at about 10.5 years in girls versus 11.5 years in boys, with males showing a more rapid increase during adolescence. A similar increase has been observed in parietal and temporal lobe volumes and in the caudate nucleus; total cerebral gray matter volume is 10% larger in males, but peaks much earlier in girls than boys (10.5 years vs. 14 years) (Mahone & Wodka, 2008; Nussbaum, 2012).

Alongside the well-known sex differences in brain structure and development (Kaczkurkin et al., 2019) and a large number of neuroimaging studies in those with ADHD, there is a growing literature investigating sex differences in cortical and subcortical morphology and in functional connectivity in children with ADHD.

In studies examining the *cortical morphology*, girls, but not boys, show an overall surface area (SA) reduction in the prefontal cortex (PFC), in particular in the dorsolateral PFC bilaterally, in the left latero-inferior PFC, in right medial PFC, in right orbitofrontal cortex (OFC), and in left anterior cingulate cortex (ACC). Boys, unlike girls, have a SA reduction only at the right ACC level and in the left medial PFC. Moreover boys, differently to girls, show an overall SA reduction in premotor cortex (PMC) (Dirlikov et al., 2015).

Similar results have been also found by Jacobson et al. (2015) who examined sex differences in motor/premotor and prefrontal white matter (WM) microstructure applying diffusion tensor imaging (DTI) in children (8–12 years) with ADHD. Boys showed WM abnormalities in the motor regions (specifically primary motor M1), which are crucial to the more basic aspects of motor response control, while girls showed WM abnormalities in the prefrontal regions (specifically medial OFC), which are responsible for top-down regulation of high-order emotional and behavioral responses.

Sex-related differences of *subcortical structures* have also been investigated. In a sample of 47 ADHD children (27 boys and 20 girls) and 66 controls (35 boy and, 31 girls) aged 8–12 years, the large deformation diffeomorphic metric mapping (LDDMM) was used to examine the effects of ADHD, sex, and their relationship with basal ganglia volume and shape. Boys with ADHD showed considerably smaller basal ganglia volumes compared to typically developing (TD) boys. Volume compression was seen bilaterally in the caudate head and body and in the anterior putamen as well as in the right ventral putamen and in the left anterior globus pallidus; conversely, posterior putamen was more pronounced in boys with ADHD than in TD ones. No volume or shape differences were evidenced in girls with ADHD (Qiu et al., 2009).

Also, in a study conducted in school-age children with and without ADHD, sexually dimorphic volumetric reductions and shape compressions in the bilateral globus pallidus and amygdala have been reported in boys with ADHD compared to TD boys, whereas no differences were found in any structure between ADHD and TD girls. Further correlational analyses showed that in ADHD boys, a localized expansion in the globus pallidus, putamen, and amygdala correlated with greater emotional dysregulation (Seymour et al., 2017).

Consistent with these findings, another study that examined basal ganglia morphology confirmed a reduced volume and shape abnormalities of the globus pallidus and putamen (within subregions of the putamen receiving projections from limbic, executive, and motor cortices) in boys, but not in girls, with ADHD. These basal ganglia anomalies appear to correlate with poorer response control, regardless of cognitive demand, exclusively among boys (Tang et al., 2019).

In contrast to the previous study (Tang et al., 2019) showing subcortical differences in ADHD boys, but not girls, only one study in *preschoolers* (4–5 years old), naïve to stimulant medication, showed a reduced volume of the caudate, globus pallidus, and thalamus among girls with ADHD compared to TD girls, whereas no significant differences were observed among boys (Rosch, Crocetti, et al., 2018).

Few neuroimaging studies have investigated sex differences in *functional connectivity* (FC) of fronto-striatal networks in children with ADHD.

A functional imaging study in adults with ADHD revealed significantly altered patterns of neural activity during a verbal working memory task for males but not for females: 23 ADHD males showed a significant underactivation in widespread networks involving frontal, temporal, cerebellar, occipital, and subcortical regions during working memory task; 21 ADHD females showed no impairment compared to same sex control subjects. Within the same study, a negative correlation between neural activity during the working memory task and the number of hyperactive symptoms was found in men, while in women, a similar correlation was found with the number of inattentive symptoms (Valera et al., 2010). These findings are in line with another study including only female ADHD adolescents evidencing no differences in working memory-related brain activation (Sheridan et al., 2007).

Similarly, a study comparing 23 ADHD adolescents with 21 healthy controls during the assessment of congruent or incongruent stories found that ADHD males had a bilateral frontoparietal (including premotor cortex and supplementary motor) area underactivation compared to controls with an hyperactivation of the amygdala and superior temporal gyrus. ADHD females had a more widespread underactivation pattern in right inferior frontal and postcentral gyri, right cerebellum (a region activated in response to temporally unexpected stimuli), right middle temporal gyrus, and left basal ganglia. This could be a potential explanation of several difficulties on female ability to predict "when" events are going to occur (Poissant et al., 2016). By contrast, an fMRI study examining the neural correlates of response inhibition in a large cohort of 185 adolescents with ADHD using the *Stop Task* found a hypoactivation in both frontal-striatal and frontal–parietal networks in ADHD participants and also in their unaffected siblings when compared to controls, with no sex differences (van Rooij et al., 2015). Furthermore, a large fMRI meta-analysis including a range of cool, hot EF and emotion processing tasks also found no sex differences in activation deficits (Cortese et al., 2012).

Another seminal study evidenced an association between a greater PFC SA and a greater reduction in ISV during a motivational

go/no-go (GNG) task (motivational contingencies present) in ADHD participants. This association was particularly evident, among boys with ADHD, at the right OFC level, and among the overall group of ADHD children, at the right medial PFC level, delineating a noticeable effect of sex (Rosch et al., 2015).

Finally, a recent study (Rosch, Mostofsky, et al., 2018) examined ADHD-related sex differences in fronto-subcortical FC and association with delay discounting and demonstrated, for the first time, fronto-subcortical functional networks anomalies in girls with ADHD. Children with ADHD showed, in fact, atypical FC between the ventromedial PFC and subcortical regions, including the striatum and amygdala, and the greatest diagnostic effect was found among girls. Furthermore, girls, but not boys, showed heightened delay discounting.

4 | NEUROPSYCHOLOGICAL FUNCTIONING

4.1 | ADHD and executive functions

In the past, causal models of ADHD tended to posit a single-core dysfunction and focused on a single aspect of functioning—a behavioral inhibition deficit. Barkley et al. conceptualized a theoretical model that linked inhibition to four executive neuropsychological functions (working memory, behavioral inhibition, regulation of motivation, and motor control) that appeared to depend on it for their effective execution (Barkley, 1997). Later, Willcutt et al. (2005) evidenced that ADHD is associated with weaknesses in several key EF domains; however, although EF weaknesses are significantly associated with ADHD, EF deficits appear per se not to be sufficient to cause ADHD in all subjects with the disorder. In fact, less than half of ADHD children exhibit significant impairment on a specific EF task (Nigg & Casey, 2005). According to a reconceptualization model of EF, between 16% and 51% of children with ADHD were classified as impaired in an individual measure, but only 10% of them showed deficits across all five domains of EF and 21% did not show impairment on any of the five measures (Castellanos et al., 2006).

ADHD is characterized by quite independent cognitive domains deficits with a significant heterogeneity from patient to patient: In a study including 83 ADHD boys compared with 66 healthy boys on a broad battery of six neuropsychological tasks, the ADHD group performed worse across all six domains, with larger effect size for delay aversion (0.82) and working memory (0.95); medium for impulsivity (0.61), decision-making (0.55), and timing (0.71); and small for response variability (0.37). The proportion of ADHD boys with a deficit on each factor was indeed moderate, ranging from 18% to 36%. A quarter of ADHD boys did not exhibit a deficit on any of the six factors, with almost all who did have at least one deficit showed it in no more than three factors (Coghill et al., 2014). Another study showed that ADHD children significantly differed from controls also on emotion regulation and recognition (Sjowall et al., 2013).

Aside from the classical "cold" EF (i.e., motor response inhibition, working memory, sustained attention, response variability, and cognitive switching), other mechanisms including the so called "hot" EF (i.e., motivational dysfunction, delay aversion, sensitivity to reward and punishment, and emotional processing) and response variability and cognitive processing speed (and alerting) have been increasingly investigated as they have been shown to play a significant role in the disorder (Willcutt et al., 2008). The importance of reinforcements and reward perception is in fact a key point in the ADHD pathophysiology (Castellanos et al., 2006). ADHD children are hypersensitive to the lengthening of the time intervals between action and reinforcement, finding it difficult waiting for reward (Kuntsi et al., 2001). This is consistent with the "delay aversion" model developed by Sonuga-Barke, which suggests that ADHD symptoms are a functional expression of a motivational style rather than the result of an altered regulatory system (the so called "*dual-pathway hypothesis*") (Karalunas & Huang-Pollock, 2011; Sonuga-Barke, 2003).

In 2010, the two-pathway model has been extended and revised into the "*three-way" model:* Deficit in temporal processing, mediated by cortico-cerebellar loop disturbance, constitutes a third important component of ADHD, along with cognitive and motivational deficits. ADHD individuals appear consistently compromised in three main temporal processing domains—motor timing, perceptual timing, and temporal prediction. Main deficits in ADHD have been found in the tasks of sensory-motor synchronization, duration discrimination, reproduction, and postponement (Sonuga-Barke et al., 2010).

It is also worth noting that individuals with ADHD have been reported to be greatly inconsistent in their performance on neurocognitive tasks (Klein et al., 2006), and increased response-time intrasubject variability (RT-ISV) has been consistently documented as a critical etiological feature of ADHD (Kofler et al., 2013). A meta-analytic review of 319 studies performed in children, adolescents, and adults confirmed a greater RT variability in ADHD compared to their TD control group (Hedges' $g = 0.76$ in children/adolescents; Kofler et al., 2013). In a later study including a sample of 53 TDC and 70 children with ADHD (6.8 to13.6 years of age), RT-ISV measured by Eriksen flanker task (EFT) and sustained attention to response task (SART) was statistically significantly higher in ADHD compared to TDC ($p < 0.001$). Moreover, average amplitude of each frequency was measured for the ADHD-impaired, ADHD-unimpaired, and TDC groups: RT fluctuations seemed to be specifically driven by the ADHD-impaired subset (Adamo et al., 2014).

4.2 | ADHD and executive functions: Sex differences

Problems in neurocognitive functioning have been reported both in males and females with ADHD (Nussbaum, 2012). Several studies in ADHD found more impulsive errors, poorer processing speed, and deficits in motor functioning in males compared to females (Hasson & Fine, 2012; Nussbaum, 2012; Rucklidge, 2010). In contrast, females with ADHD were found to show more working memory problems,

poorer vocabulary skills, less intellectual abilities, and worse visual spatial reasoning (Gaub & Carlson, 1997; Nussbaum, 2012; Rucklidge, 2010). However, the literature on the topic remains inconclusive with many studies evidencing no sex difference in executive functioning (Rucklidge, 2010; Sjowall et al., 2013).

Studies using the *continuous performance test (CPT)* in ADHD children evidenced that boys were more likely to commit commission errors compared to their female counterpart, while no omission differences were found between the two sexes (Hasson & Fine, 2012; Newcorn et al., 2001). It could indicate that inhibitory control, but not inattention, can be mediated by sex and that the relationship between sex and impulsivity is stronger than the one between sex and inattention. Similarly, adolescent males with ADHD appeared to be more impaired in inhibition skills than females (Rucklidge, 2006).

In adults, attentional skills appear also to be potentially influenced by sex. In a meta-analysis, including 25 neuropsychological studies comparing adults with ADHD and healthy controls, a strong linear association between the male sex and a poorer functioning on the *Stroop Color-Word Test* (a measure of focused attention and interference control) was found. Thus, adult females with ADHD seem to perform better than males on attention tasks (Balint et al., 2009).

Conversely, working memory has been found to be more impaired in adult ADHD women compared to their male counterpart. Across all examined groups (ADHD-combined or inattentive types and normal controls), adult males performed significantly better than females on specific working memory tasks, such as *letter-number sequencing* and *digit span* of the Wechsler scales and Paced Auditory Serial Addition Task (PASAT) *number correct* and *omissions errors* (Schweitzer et al., 2006).

In a sample of 56 ADHD children (26 females and 30 males) and 90 controls (42 females and 48 males) aged 8–13 years, girls and boys with ADHD showed *similar* patterns of deficit on tasks involving both working memory and response preparation; however, they showed *different* patterns of executive dysfunction on tasks related to planning and response inhibition, and girls, but not boys with ADHD, showed higher impairment in planning (O'Brien et al., 2010).

ADHD girls, compared to TD children, also show an impaired response control (higher commission error rate and higher tau RT-ISV) during a complex GNG task, suggesting that cognitive load influences response control in children with ADHD in a sexually dimorphic manner in a context of possible different neural maturational processes timing (Seymour et al., 2016). The expansion of this study, including 8- to 17-year-old children with ADHD ($n = 353$, 104 girls) and TD controls ($n = 241$, 86 girls) revealed less improvement in response inhibition with age resulting in greater deficits in adolescence in girls, consistently with the developmental lag model of ADHD (DeRonda et al., 2021).

During a motivational GNG task a lower ISV has been found in boys, but not in girls with ADHD, suggesting a motivational contingencies' influence on cognitive task performance, with consequent ISV improvement in boys (Rosch et al., 2015).

Boys with ADHD tend to manifest atypical motor development earlier and longer than do girls with ADHD (Mahone & Wodka, 2008). Not surprisingly, cognitive tasks that require speed represent an area of weakness for boys, but not necessarily for girls. This may be related to differences in basal ganglia development (Mahone & Wodka, 2008). Thus, in the classroom setting, boys with ADHD may have difficulties in graphomotor control and speed. In contrast, young girls with ADHD may not be as at risk under academic demand such as handwriting, or when are strictly guided by teachers to maintain their optimal level of alertness and attention. However, girls with ADHD may have more difficulties than control girls when involved in tasks requiring independent planning, particularly when the planning must be done mentally, for example without an immediate feedback (Mahone & Wodka, 2008).

Regarding the impact of sex on impairment in motor control, some studies have been consistent in highlighting that boys show more mirror overflow movements (i.e., synkinetic movements occurring symmetrically opposite of intentional movements) than girls across diagnosis (Cole et al., 2008; MacNeil et al., 2011) as well as in the ADHD population (Mostofsky et al., 2003). However, a recent study revealed similar levels of excessive mirror overflow in boys and girls with ADHD, with boys exhibiting more variable tap times compared to TD boys, while no diagnostic effect was observed in girls (Chen et al., 2021). These contrasting results are interpreted by the same authors due to a possibly age effect considering the broader age range (5–12 years) in this last study compared to the previous ones (about 8–12 years). Further research on motor abilities also suggest that motor overflow tend significantly to reduce through adolescence in ADHD boys, while dysrhythmia and slow speed may tend to persist, reflecting possible distinct underlying neurologic processes in the developmental trajectories (Crasta et al., 2021).

Elucidating sex differences in reward-based decision-making in ADHD, a study by Rosch and Mostofsky (2016) examined for the first time sex differences in delay discounting among children with ADHD-C, compared to TD controls, using two tasks—a classic "real-reward" discounting task and a novel "real-time" discounting task, during which participants experienced the delays and rewards associated with their choices in real time. The results confirmed that ADHD children show greater delay discounting. Further, in the latter task, only ADHD girls, but not boys, showed greater delay discounting compared to TD controls. The preference for immediate reward, according to the authors, may be explained by a possible diminished response to reward and a greater aversion to delay in girls with ADHD.

A recent study confirmed poorer performance on delay discounting (classic *delay discounting task* and *real-time discounting task*) and cognitive control tasks (*GNG task*, *spatial span task*, *Stop Signal Task*) in ADHD participants, compared to TD samples, and revealed ADHD-related sex differences. Specifically, girls and boys showed impaired inhibitory control on the *Stop Signal Task*, but only ADHD boys showed impaired inhibitory control on the *GNG task*. As noted by the authors, considering that these two tasks are respectively influenced by working memory and behavioral inhibition, boys with ADHD, compared to girls, exhibit greater behavioral disinhibition.

In addition, girls, but not boys, exhibited increased delay discounting (Patros et al., 2018).

Finally, a very recent meta-analysis by Doidge et al. (2021), on sex differences on delay gratification and temporal discounting tasks in both TD and ADHD samples, confirmed that females with ADHD were more likely to prefer smaller immediate rewards than males with ADHD. The authors argued that this difference could be explained by ADHD symptom severity differences; the presence of comorbid conditions; worse outcomes in coping abilities; internalizing distress, speech, and language; and difficulties with organization and social skills issues, at a greater rate than ADHD males.

5 | CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The data reported in this minireview indicate that ADHD is not a single pathophysiological entity. Growing evidence suggest the existence of different clinical presentations, variable functional impairment and different psychopathological and cognitive profiles. Sex differences appear to be a substantial contributor to the ADHD heterogeneity in clinical presentation and in the underlying neuropsychological substrates. At a neuropsychological level, differences between children with and without ADHD mainly occur in several domains such as EF, motivation, and time perception (Coghill et al., 2018; O'Neil et al., 2018); however no specific impairment is a necessary or sufficient cause of the disorder: Different clusters of neuropsychological weaknesses among individuals can lead to a large clinical heterogeneity.

Although in childhood and adolescence ADHD appears to affect mainly boys (Greven et al., 2018; Mowlem et al., 2019), this finding may be not realistic since a possible diagnostic bias due to the structuring of a "*male prototype of ADHD*" may lead to a diagnostic selection on the basis of the clinical presentation described in the DSMs for males (Mowlen et al., 2019; Nussbaum, 2012). Females with ADHD are more often inattentive rather than hyperactive and, generally, have more internalizing comorbidities. This leads girls to be perceived as less impaired by parents and teachers, and therefore they reach the attention of clinicians less frequently and at older age, although significant comorbidities may be more strongly associated with ADHD in females than in males: The presence of ADHD seems to be associated with a higher relative risk of having comorbid autism spectrum disorders, oppositional defiant/conduct disorders, intellectual disability, personality disorders, schizophrenia, substance abuse disorders, and suicidal behaviors in females than in males (Ottosen et al., 2019).

Sex-specific variance in brain neuroanatomy, circuits and neurocognition, have been identified within ADHD females presenting different trajectories in brain development, probably related to more working memory problems, poorer vocabulary skills, less intellectual abilities, worse visual spatial reasoning, and higher impairment in planning (Greven et al., 2018; Mahone & Wodka, 2008; Nussbaum, 2012; O'Brien et al., 2010; Rucklidge, 2010; Schweitzer et al., 2006). It should be considered, however, that only few studies have involved sufficiently large samples of females: Further studies are indeed needed to better characterize ADHD in females, in order to reduce the health gap between sexes (Mowlem et al., 2019; Nussbaum, 2012; Young et al., 2020).

The integration of a sex-sensitive perspective in all aspects of ADHD research is urgently needed also considering that efficacy and the adverse events of many therapeutic compounds can vary according to sex: This difference appears to be related to pharmacokinetic and pharmacodynamic properties, immunological and hormonal factors, and a general lower lean body mass in women (Rademaker, 2001; Yu et al., 2016; Zucker & Prendergast, 2020).

Based on the false hypothesis that men and women are identical, currently, medications are studied mainly in men and the data obtained about the clinical efficacy and the potential side effects are then extrapolated to women. A recent systematic review (Kok et al., 2020) examining the efficacy/effectiveness and adverse events of ADHD medications (stimulants and nonstimulants) in an ADHD population revealed a MPH stronger effect earlier in the day but also an earlier decline after a single administration, and therefore less improvement in the ADHD core symptoms during the day, in girls compared to boys. Girls and women also appeared to be more responsive to nonstimulants; data on adverse events were not conclusive due to limited findings (Kok et al., 2020).

In summary, from a precision medicine perspective, we should consider ADHD as not as a single neurobiological entity: A better characterization of ADHD children and adolescents' neuropsychological profile should allow to identify different subgroups that could receive a more specific clinical assessment and, therefore, more effective therapies. Greater efforts should be made to better investigate ADHD clinical presentation in females, and to better understand their underlying neuropsychological functioning. This aim should be achieved in order to develop tailored diagnostic protocols as well as personalized and effective therapeutic strategies and to improve the quality of care of girls with ADHD.

6 | STRENGTHS AND LIMITATIONS

This narrative minireview aims to review the state of art for sex differences in child and adolescent ADHD presentation at clinical, neuroimaging, and neuropsychological levels. We discussed with a combined, concise, and accessible way, the clinical, neurobiological (i.e., neuroimaging), and neuropsychological interplay in the disorder, which are usually considered separately: This unified approach may contribute to a better understanding of the sex difference observed in this disorder and in turn to design more effective, comprehensive sex-specific therapeutic strategies.

Our work also has some limitations. This paper was designed as comprehensive narrative minireview since a more systematic approach would probably need a separate paper for each section. Further efforts should be made in order to carry out a *series* of systematic reviews of these topics and clinical trials aimed at accurately exploring sex differences in developmental clinical samples finalized to the advance of this field of research.

CONFLICT OF INTEREST

SC had collaborations within projects from the European Union (7th Framework Program: PERS, ADDUCE, MATRICS) and as subinvestigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen Cilag, and Angelini. Travel support from Fidia Farmaceutici. CB had collaborations within projects from the European Union (7th Framework Program: PERS, MATRICS) and as subinvestigator in sponsored clinical trials by Lundbeck, Otsuka, Janssen Cilag, and Angelini. FD had collaborations as subinvestigator in clinical trial sponsored by Lundbeck and as independent rater in clinical trials sponsored by Servier. AG was in the advisory boards for Eli Lilly and Shire. She has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen, and Otsuka. She has been speaker for Novartis, Eli Lilly and Shire. AZ served in an advisory or consultancy role for Angelini, EduPharma, Servier, and Takeda. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier, and Shire. He received royalties from Giunti OS, Oxford University Press. The present work is unrelated to the above grants and relationships. CN and MB do not have any conflict of interests to declare.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.C. and A.Z.; *Writing – Original Draft*, S.C., C.N., and M.B.; *Writing – Review & Editing*, C.B., F.D., and A.G.; *Supervision*, A.G. and A.Z. All authors take responsibility for the final manuscript.

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