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Review article

The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children worldwide, and also the recognition of its persistence into adulthood is increasing. While ADHD in childhood is highly heritable and mostly driven by familial factors, during adulthood it appears to show a lower heritability, even if there is not total agreement on this yet. This disorder often co-occurs with many other conditions, which also vary across the different stages of development, and several studies have used the twin design to investigate these comorbidities, giving valuable insights into the origins of the observed co-occurrence. This review aims to summarize the main results of twin research, according to the following domains: individual traits, cognitive impairment, behavioral manifestations, clinical conditions and psychosocial risk factors. Individual features seem to play a role in this symptomatology and include personality traits such as negative emotionality, personality disorders and temperamental dimensions with a predominance of novelty seeking. At a lower level, ADHD is associated with both functional and anatomic brain characteristics. ADHD is also associated with some forms of cognitive impairment, such as sluggish cognitive tempo, and learning disabilities, with a specific predisposition to reading disability. In addition, ADHD is strongly associated with externalizing disorders such as conduct disorder and oppositional defiant disorder, and some behavioral outcomes, particularly substance use and abuse both in adolescence and adulthood. Moreover, ADHD symptoms often overlap with other psychological disorders, namely affective and internalizing disorders, as well as autism spectrum disorder and autistic-like traits in a wider sense. Notably, a genetic overlap has been found between asthma and ADHD, particularly with respect to hyperactivity/impulsivity dimensions. ADHD also appears to represent a risk factor for disordered eating, and, more specifically, for binge eating and bulimia nervosa. Finally, among psychosocial factors, an association has been proposed between childhood maltreatment and ADHD symptoms.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable childhood-onset neuro-developmental disorder, with heritability estimates of around 0.7, as revealed by family and twin studies (Faraone et al., 2005). ADHD affects up to 1 in 20 children in the USA (Faraone et al., 2003) and it is characterized by dimensions of hyperactivity/impulsivity (e.g. excessive fidgeting with hands or feets) and inattention (e.g. failing to listen when being spoken to directly), as well as deficits in executive functioning (e.g. difficulty in shifting attention or getting started on a task). To date, no single genetic risk factor has been identified, since ADHD is more likely to depend on the interaction between multiple genetic risk factors (Thapar et al., 2013). Many studies have pointed out the strong genetic component of ADHD symptoms (Biederman and Faraone, 2005), while common and specific genetic factors have been discovered for the two main dimensions of inattention and hyperactivity/impulsivity (Levy et al., 2001). In particular, twin studies have concluded that additive genetic effects explain up to 80 % of the variance in the ADHD phenotype (Albayrak et al., 2008; Thapar et al., 1999; for more information on ADHD: Ougrin et al., 2010; Matthews et al., 2014; Tarver et al., 2014; Luo et al., 2019).

The main purpose of the present narrative review is to provide an overview of the main twin research endeavours that have been undertaken to shed light on ADHD comorbidities, since the co-occurrence

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of other conditions among individuals with ADHD is very common. Over the years, the twin design has proven to be a popular and effective approach to unravel the association between complex traits or diseases, or between variously defined exposure factors and health outcomes. With diseases like ADHD that have a variable age of onset, an important aspect to be considered is the timing of events within the twin pair. If one does not account for diagnosis status at follow up, then the estimates can be biased, and comparisons across studies can be difficult. This aspect should be taken into consideration when trying to interpret the peculiar age-dependent heritability pattern of ADHD, with estimates picking in childhood and declining in adult ages. Relevant information regarding the timing of events could be provided by population-based registries of diagnoses, as is the case for cancer (Mucci and Hjelmborg, 2016).

More specifically, by comparing monozygotic (MZ) and dizygotic (DZ) 'cross-twin/cross-trait' correlations (i.e. between one trait or disease in a twin and another trait or disease in the co-twin), it is possible to assess if and to what extent an observed association is due to shared genetic and environmental aetiologies. This information can be particularly useful as it can encourage research efforts aimed to identify ('pleiotropic') genetic variants that confer susceptibility to multiple disorders (e.g. ADHD and comorbid syndromes) or environmental risk factors that are common across these disorders.

When the focus of research is to verify if an exposure is associated to a given health outcome, the 'discordant twin' design offers investigators the opportunity to contrast affected twins and unaffected cotwins under a unique matching scenario. In this situation, the groups under study are made optimally comparable with respect to relevant unmeasured factors such as genetic background and environmental early family experiences. Despite what may be suggested by common sense, the discordance between twins can arise from fetal life, since the intrauterine environment can be quite dissimilar because of the twin-to-twin transfusion syndrome. Therefore, if the targeted exposure differs within the case-cotwin dyads, then the exposure-outcome association is likely to be a real (not confounded) one, and causal inferences become possible.

Results coming from twin research are in many cases consistent with those of epidemiological studies, since twins appear to be comparable to singletons in the rate of psychiatric disorders as well as of behavioral/emotional problems - which comprise traits typically associated with ADHD (Simonoff et al., 1997; Moilanen et al., 1999). For instance, no significant differences between twins and singletons have been found in the development of attention problems from 6 to 12 years of age (Robbers et al., 2011). On the other hand, findings coming from twin samples should be interpreted carefully: twins are more likely to show lower birth weight compared to singletons, which is a risk factor for ADHD on its own (Bhutta et al., 2002; Pettersson et al., 2015). For what concerns comorbidities, Faraone and Larsson (2017) have pointed out that ADHD's polygenic liability (derived from a clinical sample) can predict ASD in a population sample (Martin et al., 2014), which is in line with conclusions coming from twin research (Ronald et al., 2014; Polderman et al., 2014).

This review represents an unprecedented effort to summarize available evidence from previous studies that, using the two above-mentioned strategies and within the limitations of the twin methodology, have provided some important clues on the origins of the comorbidity between ADHD and a wide spectrum of conditions across the cognitive, behavioral, personality, imaging and psychosocial fields.

2. Methods

The search of the papers included in this work was conducted from December 2018 to May 2019 on PubMed database, trying to avoid other review papers and redundancy of results. Inclusion criteria of primary references consisted of articles adopting twin methods and specifically focusing on ADHD and its comorbidities, whatever the nature of these latter. No constraints on the year of publication, language or employed methods were applied in order to allow for a thorough review of the literature, as complete as possible. No papers were systematically excluded from the discussion and the risk of bias was not assessed at all. The fact itself that authors were able to conduct a study with recruitment of twins and their characterization was sufficient to repute that description of what they found deserved to be mentioned here. The discussion of the papers was organized according to the following domains, which were preventively planned: individual traits, cognitive impairment, behavioral manifestations, clinical conditions and psychosocial risk factors.

The keywords used in the search were "twin study" OR "twins" AND "attention deficit hyperactivity disorder" OR "adhd" AND "comorbidity" OR "comorbid" AND "psychosocial risk" OR "asd" OR "autism spectrum disorder" OR "asthma" OR "allergic rhinitis" OR "atopic dermatitis" OR "anxiety" OR "depression" OR "affective problems" OR "bipolar disorder" OR "borderline personality" OR "conduct disorder" OR "cd" OR "oppositional defiant disorder" OR "odd" OR "eating disorder" OR "obsessive" OR "compulsiveness" OR "temperament" OR "stressful life events" OR "personality" OR "brain" OR "polymorphism" OR "reading disability" OR "cognitive deficit" OR "substance abuse" OR "externalizing disorder".

3. Individual traits

3.1. Personality traits

Personality features are known to be associated with psychopathology, though the relationship is thought to be bidirectional (Widiger et al., 1999). Most previous research on this issue focused on the hierarchical three-factor model of Negative Emotionality, Positive Emotionality and Constraint, referring to the Multidimensional Personality Questionnaire (Tellegen, 2000). ADHD is known to manifest with conduct disorder (CD) or autism spectrum disorder (ASD) in many cases: it follows that the establishment of a particular kind of personality trait pattern as a link between these conditions would shed light on the impact of individual's personality structure on such comorbidities.

Based on the results by Krueger et al. (2002), who found that personality structure relates to externalizing disorders, Cukrowicz et al. (2006) were the first to investigate which personality trait patterns correlate the most with externalizing disorders, in both children and adolescents. To do so, the authors tested, from a community sample, same-sex twins (both males or both females), who differed in their behavioral disorder presentation and were categorized as ADHD only, CD only and co-morbid CD-ADHD. Authors started from the hypotheses that ADHD only and CD only would have presented moderately high scores of Negative Emotionality and moderately low scores of Constraint, while the co-morbid CD-ADHD would have presented the most extreme personality profile. The study showed that a profile composed by low Constraint coupled with Negative Emotionality was associated with CD and ADHD only and with co-morbid CD-ADHD, the latter presenting the most extreme personality profile. The single diagnosis groups did not differ significantly between each other, while each group differed from the control group; therefore, this result may indicate a possible contribution of specific personality traits to the development and/or maintenance of CD and ADHD, although future research is needed to determine whether personality can be considered a co-occurring feature or a risk factor for psychopathology.

Negative emotionality is also referred to as Neuroticism, a moderately heritable personality trait from the "Big Five" which has been defined as the tendency to experience negative emotions (Matthews et al., 2003). Park et al. (2017) started from the point that neuroticism, with its characteristics of proneness to anxiety, sadness, fear, anger and stress, may play a role in the comorbidity between ADHD and ASD. In fact, neuroticism is the only trait from the Big Five to be consistently

associated with both ASD and ADHD, two conditions which commonly occur together. Based on an unselected population-based twin sample, authors run a trivariate twin analysis, which allowed to estimate the magnitude of genetic and environmental influences that mediate the phenotypic covariation between neuroticism, autistic and ADHD traits. Results showed that the variances of neuroticism, ASD and ADHD were significantly influenced by a common genetic factor, which may represent the susceptibility to emotionally negative states. The study also highlighted unique environmental factors related to all traits or only to ASD and ADHD traits, independent of neuroticism. Overall, these findings indicate that the genetic association between ASD and ADHD could be partially explained by etiological factors that are in common with neuroticism.

Research should further disambiguate such co-occurrence: in fact, if neuroticism or negative emotionality really represent a risk factor for ADHD and other comorbid conditions, such as ASD, it would be useful for prevention in subjects obtaining high scores on this personality dimension.

With a brief mention to personality disorders, previous research has already pointed out that children with ADHD are at increased risk for developing cluster B personality disorders in late adolescence (Miller et al., 2008), consisting of antisocial, borderline, histrionic, and narcissistic features. Noteworthy, ADHD shares similar features with Borderline Personality Disorder (BPD), such as poor affect regulation and impulse control. Since previous studies had focused on this comorbidity at a phenotypic level, Distel et al. (2011) adopted a bivariate genetic study in a population-based twin sample in order to determine if the co-occurrence of ADHD and BPD may be explained by common genetic and/or environmental etiology. Findings showed a high correlation between ADHD and BDP, which could be equally explained by additive genetic (49 %) and unique environmental factors (51 %). Therefore, these data suggest that the comorbidity between these disorders may depend on their shared etiology. To our knowledge, only one study has focused on Borderline Personality Disorder adopting twin methods: since a comorbidity has been mentioned with other personality disorders belonging to cluster B, further research deepening on such association is needed.

3.2. Temperamental dimensions

According to Cloninger's definition, temperament refers to individual biological profiles and patterns for response to external stimuli, which remain relatively stable throughout life and are substantially determined by genes (Cloninger et al., 1993). In his psychobiological model, Cloninger describes four aetiologically independent dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (PS). Many studies have addressed the issue of whether and to what extent these temperamental dimensions may be associated with ADHD. Merwood et al. (2013) used a large population-based twin sample to investigate the contribution of genetic and environmental factors to the association of ADHD symptoms - divided into inattention (IA) and hyperactivity / impulsivity (HI) dimensions - with Cloninger's temperament dimensions. Participants were asked to provide self-ratings of their temperament and their ADHD symptoms, and then environmental contributions to individual differences in behavior were estimated by examining similarities and differences within and across MZ and DZ twin pairs. The main results showed that IA and HI were both associated with NS, a dimension that indicates impulsivity and irritability, with shared genetic influences among these variables. Furthermore, there were differential associations of HA and PS with the two ADHD dimensions: genetic influences on IA were uniquely associated with HA, while PS correlated positively with HI and negatively with IA. These results suggest that NS may reflect a core component of combined type ADHD, but also that the two ADHD dimensions may be characterised by unique profiles of temperament. Since NS appears to be a specific feature of ADHD, interventions should stress on positive aspects associated with this temperamental dimension, such as curiosity and the wish to explore the unknown, thus improving also strengths rather than weaknesses of people with ADHD (Table 1).

In a comparison between ADHD and ASD, Kerekes et al. (2013) found out, in a population-based twin sample, that these two neurodevelopmental disorders, though often co-occurring, are specifically associated with two different temperament profiles. Authors confirmed previous results indicating that ADHD is associated with a high propensity for NS. In contrast, profiles of temperament in children with ASD were characterized by high HA and low RD. Further studies may stress on such differences, since ADHD and ASD have been also shown to often co-occur, despite these conditions are associated with different temperamental profiles. Kerekes et al. also discussed Cloninger's three character dimensions, which are supposed to be mostly influenced by culture and social learning. These comprise self-directedness, cooperativeness and self-transcendence. In both adults and children, ADHD and ASD have uniformly been associated with low scores on self-directedness and cooperativeness, indicating that the severity of these neurodevelopmental disorders is phenotypically linked to the risk for character immaturity. Even if further studies are required, this outcome may suggest a direction for the developing of interventions taking into account such character features, given their dependence on social learning.

3.3. Anatomic and functional brain abnormalities

Research based on MZ twins discordant for a given disorder reveals to be particularly useful to estimate environmental effects on brain-function relationships, since genetic influence is taken under control. A study from Castellanos et al. (2003) recruited a sample of nine pairs of MZ twins discordant for ADHD, who were subjected to anatomic magnetic resonance imaging (MRI) of the brain. Results showed that twin-twin differences could be observed in total caudate volume, while no differences were detected in frontal, parietal, temporal and occipital regions, in grey and white matter, and in cerebellum. Although this result is limited by the small sample size, it provides some support for current models of pathophysiology of ADHD that are based on prefrontal-striatal circuitry. Neuroanatomic data from Chen et al. (2018), who also studied MZ twins discordant for ADHD, revealed smaller right striatum and thalamus in the affected twin compared to the cotwin, while there were no differences in the volume of the cerebral cortex. Notably, the cerebellum turned out to be larger in the affected twin.

From a functional viewpoint, van 't Ent et al. (2009) investigated brain changes linked with ADHD, which could be ascribed to both genetic and environmental causes. In this case, functional magnetic resonance imaging (fMRI) was used in order to examine neural activation during performance of a Stroop task[1] and a flanker task[2], in MZ twins highly concordant or discordant for attention problems (AP). Among the entire sample, compared to those with low AP, children with high AP showed decreased activation in dorsolateral prefrontal, parietal and temporal brain regions, while there was an increased activation of premotor cortex and regions associated with visual selective attention processing. More specifically, results from the comparison between pairs of concordant twins with high and low scoring respectively suggested that AP of genetic origin was characterized by decreased activation of the left dorsolateral prefrontal cortex during the Stroop task

[1] In the Stroop task, subjects have to report the ink colour of written colour words. This task is commonly used for measuring cognitive functions of inhibition and interference (Stroop, 1935).

[2] In the Flanker task, a central target is presented along with two or more irrelevant flanker items, which can be congruent or incongruent. This task allows to assess reaction-time interferences and mental control mechanisms (Eriksen, 1995; Hübner and Töbel, 2019).

Table 1
Summary of main results on ADHD and comorbid conditions from twin research.

Comorbid conditions		Attention-Deficit / Hyperactivity Disorder (ADHD)
Individual traits	Personality traits	**Low Constraint** coupled with **Negative Emotionality** is associated with Conduct Disorder (CD) and ADHD only and with co-morbid CD-ADHD (Cukrowicz et al., 2006). Variances of Negative Emotionality, Autism Spectrum Disorder (ASD) and ADHD are significantly influenced by a **common genetic factor** (Park et al., 2017).
	Personality disorders	High correlation between ADHD and **Borderline Personality Disorder** can be equally explained by **additive genetic** (49%) and **unique environmental factors** (51%; Distel et al., 2011).
	Temperamental dimensions	ADHD is associated with **Novelty Seeking** (Kerekes et al., 2013), with **shared genetic influences**. Genetic influences on Inattention are uniquely associated with **Harm Avoidance**, while **Persistence** correlates positively with Hperactivity-Impulsivity and negatively with Inattention (Merwood et al., 2013).
	Character dimensions	Both ADHD and ASD are associated with low scores on **Self-Directedness** and **Cooperativeness**, with the risk of character immaturity (Kerekes et al., 2013).
Brain abnormalities	Anatomic brain abnormalities	In twins discordant for ADHD, twin-twin differences can be observed in **total caudate volume** (Castellanos et al., 2003) and there are also evidence of **smaller right striatum and thalamus** in the affected twin compared to the co-twin (Chen et al., 2018).
	Functional brain abnormalities	Children with high attention problems show decreased activation in **dorsolateral prefrontal, parietal and temporal brain regions**, while there is an increased activation of **premotor cortex** and regions associated with **visual selective attention processing** (van 't Ent et al., 2009). individuals with ADHD show less activation of regions belonging to the **frontoparietal network** when compared to both their co-twins and unrelated controls (Godinez et al., 2015).
Cognitive impairment	Executive function	Comorbidity between externalizing disorders (ADHD, CD and Oppositional Defiant Disorder) and **deficit in Executive Function** can be explained by **common genetic vulnerability** (Coolidge et al., 2000).
	Sluggish Cognitive Tempo (SCT)	Phenotypic correlation between **SCT** and Inattention problems is higher than that of SCT and Hyperactivity / Impulsivity problems and can be explained by **genetic component** (Moruzzi et al., 2014). ADHD dimensions and SCT are also characterized by temporal invariance and stability (Leopold et al., 2016).
	Reading Disability (RD)	Comorbidity between RD and ADHD, in particular for measures of Inattention and **orthographic coding** (Willcutt et al., 2007), can be explained by **common genes with pleiotropic effects** (Willcutt et al., 2001; Sheikhi et al., 2013; Wadsworth et al., 2016), whereas it is possibly mediated by measures of **slow processing speed** (Willcutt et al., 2010). ADHD symptoms may be considered a stronger predictor of reading difficulties than vice versa (Greven et al., 2012) and the association between RD and ADHD appears to be stronger in males than females (Willcutt and Pennington, 2000).
	Other learning disabilities	Comorbidity between ADHD, **reading comprehension** and **homework behavior** can be explained by **genetic influences**. **Non-shared environmental influences** overlap between homework behavior and full ADHD and ADHD Hyperactivity / Impulsivity models only, while the ADHD Inattention model shows **non-shared environmental influences** overlapping across both reading comprehension and homework behavior (Little et al., 2016). There are **phenotypic and genetic associations** between ADHD Inattention dimension and **mathematics ability** (Greven et al., 2014). The comorbidity between ADHD and **Developmental Dislexya** can be explained by **genes with pleiotropic effects** (Mascheretti et al., 2017).
Externalizing disorders	Conduct Disorder (CD)	Comorbidity between ADHD and **CD** may be the result of **common genetic and non-shared environmental influences** (Rhee et al., 2008; Thapar et al., 2001) and, in particular, **additive** rather than non-additive **genetic variance component**, although moderate correlation of **child-specific environmental factors** exists between the two disorders (Hur, 2015). Most of the covariance between CD and low verbal ability depends on influences also shared with ADHD (Smith et al., 2011).
	Oppositional Defiant Disorder (ODD)	Heritability of ADHD and **ODD** is higher in children who share the same classroom and, in some cases, the expression of a child's **genetic vulnerability** to ADHD and ODD appears to be modulated by the sex of the teacher (De Zeeuw et al., 2015). There is an important role of **shared environmental effects** when investigating the comorbidity between ADHD, ODD and CD (Burt et al., 2005).
Behavioral manifestations	Substance Use Disorder (SUD)	ADHD is associated with **all substance use and abuse** Capusan et al. (2016a), an outcome which can be explained by **shared genetic** and **environmental influences** rather than a specific causal role of ADHD (Elkins et al., 2007). More specifically, Hyperactivity / Impulsivity symptoms contribute to the initiation of all types of substance use and abuse and to **nicotine** and **cannabis** dependence, while Inattention symptoms contribute for **alcohol** initiation and nicotine dependence (Elkins et al., 2007). The relationship between adolescent ADHD and adult alcohol dependence is **genetically driven** (Derks et al., 2014) and mostly depends on **shared genetic liability** that these disorders have in common with adolescent externalizing behavior (Edwards & Kendler, 2012).
	Eating problems	The association between eating problems, ADHD and ASD can be accounted for by both **genetic and non-shared environmental influences** (Råstam et al., 2013). ADHD symptoms in adulthood are strongly associated with **binge-eating behavior**, **binge-eating disorder** (BED) and **bulimia nervosa** (BN), and most of this association in females can be explained by **shared genetic factors** Capusan et al. (2017).
Clinical conditions	Autism Spectrum Disorder (ASD)	DSM-IV combined and population-defined severe combined ADHD subtypes show the strongest association with **autistic symptoms of all domains** (Reiersen et al., 2007). **Repetitive and restrictive behaviors** (RRB) are more correlated with Hyperactivity / Impulsivity than Inattention, the latter being equally associated with both RRB and **social interaction and communication** dimensions of ASD (Ghirardi et al., 2018). Social-communication dimensions can explain most of the phenotypic and **genetic overlap** between the ADHD symptoms and ASD (Pinto et al., 2016) and most of this **genetic overlap** concerns **pragmatic language** (Taylor et al., 2014). The association between traits of ADHD at 8 years old and traits of ASD at 12 years old is strongest than the reverse association, thus suggesting a longitudinal relation between these disorders (Taylor et al., 2012).
	Affective problems	Symptoms of ADHD and affective problems show substantial **genetic overlap** and are partly due to **shared environmental influences** (Rydell et al., 2017). The association between ADHD and **depression** also depends

(*continued on next page*)

Table 1 (*continued*)

Comorbid conditions		Attention-Deficit / Hyperactivity Disorder (ADHD)
		on **non-shared environmental factors** (Piek et al., 2007). The severe combined ADHD subtype and the talkative subtype derived from population are significantly associated with possible **bipolar illness** (Reich et al., 2005).
	Anxiety	**Anxiety subtypes** are mostly associated with Inattention rather than Hyperactivity / Impulsivity, due to both **genetic and non-shared environmental influences**. **Social anxiety** in particular has a significant negative correlation with Hyperactivity / Impulsivity (Michelini et al., 2015). Children with combined ADHD show higher **separation anxiety** (SA) than non-ADHD co-twin and children with either Inattentive or combined ADHD have higher **generalized anxiety** (GA) than non-ADHD co-twin, with higher levels of GA and SA in combined ADHD children than inattentive ADHD ones (McDougall et al., 2006).
	Asthma	ADHD is more common among children with **asthma** than controls and asthma is associated with both symptoms of Hyperactivity / Impulsivity and Inattention and the combination of them. This comorbidity can be explained by the presence of a strong **genetic component**, but also by **environmental influences** (Holmberg et al., 2015). Childhood asthma predicts Hyperactivity / Impulsivity in adolescence, an association which can be partly imputable to **genetic influences** (Mogensen et al., 2011).
Psychosocial risk factors	Child maltreatment	**Childhood maltreatment** represents a risk for the development of ADHD symptoms, possibly due to a **shared genetic liability** (Dinkler et al., 2017). In children, the association within twin pairs between poly-victimization and ADHD symptoms can be accounted for by **genetic factors**; differently, in young adults such association appears to be partly **environmentally driven** (Stern et al., 2018). According to other results, the effects of maltreatment on ADHD scores are partially causal and could not be entirely explained by familial (genetic and/or environmental) confounding Capusan et al. (2016b)

and right parietal lobe during the flanker task. On the other hand, analyses of discordant MZ pairs suggested that AP due to non-shared environmental influences was characterized by decreased activation in left and right temporal lobe areas, but only during Stroop interference.

Godinez et al. (2015) investigated which alterations in neural activation, related to poor executive function, could be ascribed to ADHD-specific and familial effects respectively. Authors found less activation of regions belonging to the frontoparietal network in individuals with ADHD when compared to both their co-twins and unrelated controls. In contrast, similarities in brain activation in discordant MZ twins concerning the activity of anterior cingulate cortex, insula, amygdala, and orbitofrontal cortex were found. These findings may reflect an underlying familial risk for decreased reactive control and potential alterations in motivational and emotional processes, while the impairment of processes more specifically related to executive control and goal maintenance may reflect a risk factor for the development of a problem of clinical interest.

4. Cognitive impairment

4.1. Executive function deficit

Executive function (EF) comprises cognitive abilities such as response inhibition, cognitive flexibility, planning and response preparation, which may depend on activity in prefrontal areas of the brain. ADHD children, either with reading disability or not, can be considered at risk for deficits in EF (Reader et al., 1994). Genetic and environmental contributions to this comorbidity have been investigated by Coolidge et al. (2000) in a twin model where also conduct disorders (CD) and oppositional defiant disorders (ODD) comorbidities were taken into account. Authors found out that all traits had a genetic etiology, since all within-pair correlations for the MZ twin pairs were twice the DZ correlations, whereas no evidence of shared environmental influences was found. Results from the multivariate cross-trait analyses also found in genetic influences an explanation for co-morbidity between ADHD and CD, ODD, and EF. Namely, this outcome suggests that a genetic vulnerability, rather than shared environmental factors, may underlie both behavioral and cognitive problems which are common among children. It follows that the development of interventions should focus on the early detection of such genetic vulnerability in ADHD subjects, in order to maximize the chance to improve and compensate for any possible deficit concerning EF.

Sluggish cognitive tempo (SCT), defined by slow movements, tendency in daydreaming and staring, hypoactivity and sleepy behavior, is also associated with ADHD symptoms, in particular for what concerns inattention. The internal and external validity of this dimension and its relationship with DSM-IV ADHD have been investigated by Willcutt et al. (2014). Although SCT has been proposed as a candidate dimension to discriminate between ADHD predominantly inattentive type (ADHD-I) and combined type (ADHD-C), the study managed to provide support for both internal and external validity of this construct but levels of SCT could not distinguish between ADHD-I and ADHD-C, since they were strongly associated with both ADHD-C and ADHD-I.

The nature of the relationship between ADHD symptoms and SCT problems has also been investigated by Moruzzi et al. (2014), who aimed to disentangle the relative contribution of both environmental and genetic factors. Authors found that the phenotypic correlation between SCT and inattention problems was higher than that of SCT and hyperactivity / impulsivity problems. Genetic correlations between phenotypes were also significant and the genetic component could explain a significant part of all phenotypic correlations. On the whole, these results found genetic overlap between individual differences in all dimensions, which were also highly heritable. Notably, twins' differences in SCT could also be explained by environmental factors in a more prominent way than inattention and hyperactivity / impulsivity, thus indicating the existence of partially distinct patterns of etiological influences.

The developmental stability and temporal invariance of the association between SCT and ADHD has been examined by Leopold et al. (2016) in a longitudinal study in which twins were assessed across a ten-year span, from early childhood to adolescence. Results of linear comparisons showed that levels of hyperactivity tended to decrease with time, levels of SCT tended to increase and levels of inattention revealed to be generally stable, while latent simplex analyses showed a high developmental stability among these dimensions. Correlations between inattention, hyperactivity / impulsivity and SCT were stable and relatively high, but also less than 1.0, thus confirming that SCT is independent from over ADHD dimensions. On the whole, findings demonstrated the existence of temporal invariance and stability among ADHD dimensions and SCT.

To summarize, given its relationship with inattentiveness, SCT appears to be a useful dimension to discriminate between ADHD inattention problems and hyperactivity / impulsivity problems, also taking into account the significant genetic component that explains such phenotypic correlations and the developmental stability and temporal invariance of the comorbidity between SCT and ADHD.

4.2. Reading disability

Reading disability (RD) is a specific learning disability characterized by impairments in single words reading, reading fluency and reading comprehension. This developmental disorder often co-occurs with ADHD in both clinic-referred and community samples, whether individuals are initially selected either for ADHD or RD.

Researchers have proposed different hypotheses concerning the nature of the comorbidity between ADHD and RD. Although ADHD and RD are often comorbid and partially share common genetic influences, they seem to enter into opposite types of Gene x Environment interactions: bio-ecological for RD and diathesis-stress for ADHD. In this regard, Rosenberg et al. (2012) formulated a genetic hypothesis which assigns a role for these opposite interactions to specific genes rather than shared ones. Using a sample of MZ and DZ same-sex twin pairs and behavioral genetic methods, authors managed to replicate the presence of opposite GxE interactions with parental education in RD and dimension of inattention in ADHD (ADHD-I). Authors suggested that these opposite interactions may be due to non-shared proximal environments instead of non-shared genes, or maybe a combination of them: to this point, further research is needed.

An alternative explanation for the comorbidity between ADHD and RD is the non-random mating hypothesis: accordingly, the two disorders are transmitted independently in families since the mating between individuals with ADHD and RD is supposed to be higher than what would be expected by chance (Faraone et al., 1993). The validity of this hypothesis was tested by Friedman et al. (2003) in a community twin sample. Authors pointed out that, among parents of comorbid children, the correlation between mothers' RD symptoms and fathers' ADHD symptoms, and vice versa, was not significant. The study also indicated that the two disorders were not transmitted independently in the sample, thus supporting the notion of a shared familiality for RD and ADHD. On the whole, these findings provide evidence against the non-random mating hypothesis, while they support the hypothesis of a cosegregation of these two disorders.

Given the relationship between RD and ADHD, a twin study from Levy et al. (2011) addressed the issue whether RD is more common in children with ADHD and one mental disorder or in children with ADHD and multiple comorbid mental health disorders, compared with other children without such conditions. The study pointed out that RD was higher for children with ADHD and depression or anxiety disorder symptoms, and also that reading problems were more severe as the degree of ADHD comorbidities increased. In order to explain the compresence of both internalizing and externalizing phenotypes, the study suggested that this may be due to a poor maturation of neural circuits involved in the control or modulation of behavior, which are fundamental for the development of reading skills.

The association between RD and ADHD has also been investigated starting from the cognitive manifestations which are exhibited by individuals with both disorders. To this purpose, Willcutt et al. (2001) used a nonreferred twin sample divided into ADHD-only, RD-only, both RD and ADHD, and neither RD nor ADHD. Authors adopted measures of phoneme awareness (PA) and executive function (EF, divided into three dimensions: inhibition, set shifting and working memory), which are assumed to be the cognitive phenotypes of RD and ADHD respectively, in order to compare performance of individuals with both disorders. Notably, findings showed that the RD-only group exhibited significantly more ADHD symptoms than the control group, and similarly the ADHD-only group achieved a lower score in the reading test compared to the control group. Authors also ruled out the possibility that the co-occurrence of RD and ADHD could be confounded with severity, since individuals with both ADHD and RD did not exhibit more severe symptoms of individuals with RD or ADHD only. On the whole, these findings suggest that either disorder alone exhibits subclinical manifestations of the other. A partial double dissociation between ADHD and RD was observed in measures of inhibition and PA respectively. On the contrary, deficits in working memory and set shifting were observed in the ADHD + RD group, thus providing evidence against the phenocopy hypothesis. Data are conversely suggesting that individuals may be predisposed to both RD and ADHD due to common genes with pleiotropic effects, starting from the finding of significant bivariate heritability.

Since both ADHD and RD are complex disorders which cannot be attributed to a single cause, Willcutt et al. (2010) adopted neuropsychological and behavioral genetic methods in order to test multiple-deficit models of both disorders, in a sample of twins. Authors addressed the issue whether the susceptibility to ADHD and RD may be attributed to a subset of cognitive weaknesses, since comorbidity may derive from specific neuropsychological weakness caused, in turn, by common genetic influences. Results showed that RD is associated with deficits in phonological processing, verbal reasoning and naming speed, whereas ADHD is associated with weak response inhibition. The main outcome of the study showed that slow processing speed was due to common genetic risk factors which could explain the comorbidity between RD and ADHD, thus indicating that processing speed measures may be used in the investigation of the etiology of this comorbidity.

The etiology of comorbidity between RD and ADHD has also been investigated by Willcutt et al. (2007) in a population-based twin sample. These authors pointed out that approximately 40% of individuals of the sample with RD or ADHD also met criteria for the other disorder. Notably, the phenotypic relation between the disorders turned out to be stronger for measures of inattention and orthographic coding rather than hyperactivity / impulsivity and phoneme awareness. Conversely, the higher heritabilities were observed in the group with comorbid ADHD and RD than in the groups with ADHD or RD alone; this is consistent with at least a partly common genetic etiology, and also suggests that risk genes (for ADHD, RD and their comorbidity) may be more easily detectable in the comorbid group. Results from analyses showed indeed that the comorbidity was largely attributable to common genetic influences, thus suggesting the presence of pleiotropic genes which increase the risk for both disorders.

Another way to study ADHD, RD and their comorbidity consists in the adoption of latent class analysis (LCA), which allows to obtain a classification in subphenotypes based on naturally occurring clusters of symptoms. This tool was used by Sheikhi et al. (2013), who obtained nine latent classes, divided into three groups: three ADHD latent classes, three RD latent classes and two ADHD-RD comorbid latent classes. Notably, the latter comprised a "Predominantly Inattentive / RD" latent class, which confirms previous findings about shared genetic influences between ADHD inattentive subtype and RD. Moreover, the other latent class was "Combined / RD", which was characterized by a higher genetic factor than the others.

In addition to cross-sectional studies, ADHD-RD comorbidity has also been investigated with longitudinal methods by Greven et al. (2012), who used a population-based sample of around 7000 twin pairs from middle childhood (7–8 years of age) to early adolescence (11–12 years of age). Authors adopted the genetic cross-lagged model, in which stability paths pertaining to ADHD symptoms and reading resulted significant. The cross-lagged paths from ADHD symptoms to reading turned out to be more significant than the reverse path, in particular for what concerns inattentiveness. This last finding suggests that ADHD symptoms may be considered a predictor of reading difficulties rather than vice versa. The relationship between ADHD symptoms and reading was also largely attributable to shared genetic factors, which also revealed to be stable over time. The role of genetic influence was mostly significant for inattentiveness, whereas the association between hyperactivity / impulsivity and reading was due to both genetic and environmental influences.

Another longitudinal study by Wadsworth et al. (2016) aimed to replicate previous results which showed strong genetic influences on RD at the first assessment and also on RD and ADHD inattention dimension comorbidity at both initial and follow-up assessments

(Wadsworth et al., 2015). This study confirmed the role of genetic influences on both initial assessment and stability of RD and also emphasized the role of genes on ADHD inattention dimension and RD comorbidity, which was stronger than the comorbidity with ADHD hyperactivity / impulsivity dimension, whether it was detected contemporaneously or longitudinally.

Finally, also the existence of sex differences has to be mentioned. In a study based on a community twin sample, Willcutt and Pennington (2000) observed a significant sex-specific interaction on RD among ADHD symptoms: the association between RD and ADHD revealed to be stronger in males than females, even though also females with RD showed higher levels of externalizing behaviors than controls. On the whole, findings suggested that, among males, ADHD mediates between RD and other internalizing or externalizing psychopathology. An important methodological aspect is however that previous twin studies on the comorbidity between ADHD and RD did not account for diagnosis status at day of follow up in the analysis; this may have affected the results on the co-occurrence of these diseases.

To summarize, the co-occurrence of RD and ADHD is mostly explained by common genes with pleiotropic effects, with ADHD likely representing a predictor of RD rather than the opposite association. Accordingly, ADHD may represent a risk factor for the developing RD and the direction of such association should surely be taken into account in the development of intervention programs.

4.3. Other learning disabilities

As previously said, RD comprises deficits in reading comprehension, which are known to affect school achievements and are likely to enhance chances of dropping out of school. Given the common comorbidity between ADHD and reading comprehension, there are also evidences according to which homework behavior is associated with reading comprehension. In a twin study, Little et al. (2016) aimed to investigate to what extent the association between ADHD and homework behavior affects reading comprehension, while genetic and environmental influences were taken into account. Authors found genetic influences overlapping between ADHD, reading comprehension and homework behavior. Such a result has been partially explained by the presence of a common deficit in executive functions, and more specifically in working memory. No shared environmental influences were found among the three factors, but notably there was an overlap between homework behavior and reading comprehension that may be due to aspects of the home environment. Results also showed the presence of non-shared environmental influences overlapping between homework behavior and full ADHD and ADHD hyperactivity / impulsivity models only, while the ADHD inattention model showed non-shared environmental influences overlapping across both reading comprehension and homework behavior. These non-shared environmental factors may include, for instance, the time of the day in which a twin decides to do homework, thus emphasizing the impact of attentional mechanisms in the comorbidity between ADHD and both reading comprehension and homework behavior.

Another study by Greven et al. (2014) investigated the association between ADHD and mathematics ability, two conditions that are both genetically linked to reading and cognitive ability. Authors found phenotypic and genetic associations between ADHD inattentiveness and mathematics ability, which were significantly stronger than those between ADHD hyperactivity / impulsivity and mathematics ability. Notably, the main finding of the study pointed out significant genetic associations between inattentiveness and mathematics ability only, which were independent from hyperactivity / impulsivity, reading and cognitive ability: this intriguing finding indicates that those genes specifically associated with ADHD inattentiveness symptoms may also concur for mathematics ability.

Knowing the nature of the relationship between ADHD and different forms of learning disability is crucial for prevention and treatment, since some of the main negative psychosocial outcomes of ADHD concern bad academic performance and poor school achievement. Given the importance of gaining knowledge in a nowadays competitive world, ADHD can be seen as a source of social gap, with long term effects on socio-cultural level and thus affecting the overall quality of life.

The association between ADHD and Developmental Dislexya (DD), a neurodevelopmental disorder characterized by an impairment in reading acquisition, was investigated by Mascheretti et al. (2017) in a twin study that addressed the issue of possible pleiotropic effects of DD genes (DYX1C1, DCDC2, KIAA0319, ROBO1, and GRIN2B) and environmental factors (smoking during pregnancy, risk of miscarriage, birth weight, breastfeeding, parental age, socioeconomic status, and parental education) on ADHD traits. Findings showed that hyperactivity / impulsivity was associated with DCDC2, KIAA0319, smoke, and miscarriage, after controlling for reading traits, thus providing evidence of pleiotropic effects that may be responsible for ADHD-DD comorbidity. To our knowledge, only one study adopting the twin method has focused so far on the ADHD-DD comorbidity: future studies are warranted to disambiguate the exact nature of such association. Such kind of knowledge is needed to inform not only clinical diagnosis but also correct information to the general population. Communicating correct information for lay people, with a simplified yet still understandable language, is essential in order to improve chances of success for prevention and treatment.

5. Behavioral manifestations

5.1. Externalizing disorders

According to epidemiological and clinical samples, ADHD and conduct disorder (CD) appear to co-occur in 30–50 % of the cases (Angold et al., 1999; Biederman et al., 1991). The causes of this comorbidity have been investigated by Rhee et al. (2008), who showed the correlated risk factors model being the model that fitted the best with the data, thus supporting the hypothesis that the comorbidity between ADHD and CD may be the result of shared genetic and environmental influences.

Thapar et al. (2001) also investigated the origin of this comorbidity in a twin study. Here, the authors aimed to identify common genetic and environmental risk factors for both disorders, and also questioned if the subgroup of individuals with both ADHD and CD (ADHD + CD) could represent a genetically more sever variant of pure ADHD. Results from bivariate genetic analysis showed that the comorbidity was mostly explained by a common genetic risk factor, even though a common non-shared environmental factor also contributed to the overlap.

Despite these evidences, data also supported the notion of ADHD and CD as two distinct categories, since additional shared and non-shared environmental factors were specifically associated with CD only: this is in line with the notion stating that CD is associated with social adversity, while ADHD may be more correlated with neurodevelopmental problems. For what concerns the ADHD + CD subgroup, results from the liability-threshold model indicated that it represents a more severe variant of pure ADHD associated with higher genetic loading, without being influenced by symptom severity.

Another study from Hur (2015) aimed to disentangle the relative contribution of additive genetic effects and non-additive genetic effects in the covariation between ADHD and CD. This study managed to demonstrate that the comorbidity could be explained by an additive rather than non-additive genetic variance component, although moderate correlation of child-specific environmental factors existed between the two disorders. Conversely, non-additive genetic factors and child-specific environmental influences only affected dimensions of hyperactivity / impulsivity, while CD was influenced by shared environmental factors. These results indicate that genes that are specific to a disorder may also represent potential risk genes for the other, and the presence of child-specific environmental correlation suggests that

environmental intervention methods that are effective for a disorder may also be effective for the other.

Starting from the point that low verbal ability represents a risk factor for CD, Smith et al. (2011) addressed the issue whether this association may be due to the presence of comorbidity between ADHD and CD, thus indicating that common influences shared between CD and low verbal ability are also shared with ADHD. To do so, the variance of CD was first divided into the variance shared between ADHD and verbal ability and then into the variance shared with verbal ability after controlling for ADHD. Results showed a statistically significant negative correlation between verbal ability and both ADHD and CD: this outcome indicates that most of the covariance between CD and low verbal ability depends on influences also shared with ADHD, thus suggesting that low verbal ability is not a significant risk factor for CD after controlling for ADHD.

Among externalizing disorders, another condition which is often comorbid with ADHD is the oppositional defiant disorder (ODD), which may affect school achievement in children since it is characterized by hostile behavior towards figures with authority in particular. In a twin study, de Zeeuw et al. (2015) focused on the possible presence of Gene x Environment interactions that may moderate the heritability of teacher-rated ODD and ADHD behavior. Results showed that heritability of both disorders was higher in children who shared the same classroom compared to those who did not, thus suggesting that different behavior is elicited by different classroom environments. Notably, the expression of a child's genetic vulnerability to ADHD and ODD appeared to be modulated, in some cases, by the sex of the teacher, even if the direction of this effect was not consistent.

Given the comorbidity among ADHD, CD and ODD, which have been mostly proven to be genetically mediated, Burt et al. (2005) have pointed out the need of adopting a combined informant approach, in order to minimize the risk of a "rater bias" that typically derives from all single-informant ratings. Authors found that the comorbidity appeared to be more genetic in origin when considering only maternal or child informant-reports individually compared to when using a combined informant approach. This finding provides evidence supporting the role of shared environmental effects when investigating the comorbidity among externalizing disorders.

Associations between ADHD and externalizing disorders have also been investigated longitudinally by Kuja-Halkola et al. (2015), with the aim of understanding how these traits co-develop from childhood into early adulthood. Authors also decomposed the covariation between traits into stable and innovative sources, which were also divided into genetic and environmental in nature. Results showed that externalizing traits in middle childhood influenced ADHD-like traits in adolescence, which in turn influenced externalizing traits in early adulthood. This result was interpreted as ADHD-like traits in adolescence may contribute to increase externalizing tendencies later in adulthood. The correlation between the traits increased across age, and notably with a large contribution of genetic innovation sources: this outcome suggests that the pattern of co-development changes during development as new genetic factors emerge, thus implying the need of developmentally dynamic theories of this comorbidity.

To summarize, the relationship among externalizing disorders (ADHD, CD and ODD) can be explained by both genetic factors and shared as well as non-shared environmental influences, even though there is no total agreement between different studies. Future research is needed to achieve a stronger disentanglement of the relative contribution of genetic and environmental factors, in order to better understand the nature of these comorbidities and improve prevention and the development of intervention programs best suited to individuals with such vulnerability.

5.2. Substance use disorder

Substance use disorder (SUD) is a very common comorbidity among individuals with ADHD, both in adolescence and adulthood. The relationship between ADHD and adolescent substance initiation and abuse has been investigated in a prospective twin study by Elkins et al. (2007), whose aim was to disentangle the relative contribution of ADHD subtypes (i.e. IN and HI), sex differences and comorbid CD to adolescent initiation and abuse of tobacco, alcohol and marijuana. Authors found that HI symptoms contributed to the initiation of all types of substance abuse and to nicotine and cannabis dependence, while IN symptoms contribution disappeared when controlling for HI and CD, with the exception of alcohol initiation and nicotine dependence, with no differences between males and females. With regard to adult ADHD, Capusan et al. (2016a) used a large population-based twin sample in order to investigate the association between ADHD different subtypes and the abuse and possible preference for alcohol, nicotine and illicit drugs. According to results, ADHD symptoms, and mainly the comorbid subtype, were associated with an increased risk for SUD, regarding both single- and poly-substance use in both women and men. However, this study did not find evidence supporting the existence of preferences for any of the substance studied, thus suggesting that ADHD is associated with use and abuse of virtually all substances. Authors proposed that individuals with ADHD may use substances as self-medication, in order to alleviate their symptoms, without particular preferences but simply relying on the availability in the local culture and social pressure.

The association between ADHD symptoms and SUD was also investigated accounting for the presence of autism spectrum disorder (ASD) and autistic traits (AT), which are common among individuals with ADHD. To this purpose, De Alwis et al. (2014) considered a large general-population twin sample where liabilities for both ADHD and AT were assessed in order to investigate their combined influence on alcohol, cannabis and nicotine use and abuse. Results showed that regular substance abuse and SUD was associated with higher liability to both ADHD and AT. In particular, it is worth noticing that the relationship between ADHD, AT and alcohol involvement was mediated by the presence of AT, since this latter appeared to reverse the association with alcohol only, but not with nicotine and cannabis use. A possible explanation proposed by the authors is that individuals with high AT scores, due to their interpersonal difficulties, are less prone to engage in social contexts where alcohol consumption is encouraged. On the contrary, individuals with ADHD are more likely to associate with those specific individuals, among peers, who seek for sensations and often engage in risky behaviors. Higher AT scores were associated with alcohol dependence, possibly due to the common presence of repetitive behavior and interests in these individuals, which may facilitate the transition from use to abuse, once consumption has begun.

Another study by Elkins et al. (2018a) addressed the issue whether childhood ADHD may exert a causal influence on SUD in adolescence, specifically on alcohol and marijuana involvement, or whether this association may be due to shared propensities. To do so, authors combined prospective and twin difference designs in order to identify within-pair differences and also sex-specific moderation of effects. Even if higher degrees of childhood ADHD were associated with earlier alcohol and marijuana use in adolescence, results did not show differences within MZ pairs, thus suggesting that the association may be explained by shared genetic and environmental influences rather than a specific causal role of ADHD. Effects of sex were restricted to hyperactivity / impulsivity dimensions, with females with higher scores on these latter showing more alcohol consumption and marijuana-use frequency than males. Sex moderation of effects, in the association between ADHD and smoking, were also highlighted in another study by Elkins et al. (2018b), where prospective and twin difference designs were combined in a cohort of female adolescents with ADHD. Of course, opposite-sex twin pairs would represent a valuable setting to better investigate the issue of sex-moderation of effects; however, results showed higher levels of smoking risks for female adolescents with ADHD rather than males. A possible interpretation of this outcome is

that females are more vulnerable to social consequences of inattention, making them more prone to depression and anxiety and thus increasing their receptivity to nicotine's neurotoxic effects.

Another study by Quinn et al. (2016) adopted multivariate behavioral genetic methods on a prospective study of twins from childhood to adolescence, in order to evaluate how the association between ADHD and alcohol abuse is explained by genetic and environmental factors. Results showed that alcohol problems could be mostly explained by hyperactive / impulsive symptoms rather than inattentive symptoms, and this association was due to additive genetic influences. Nevertheless, this association was in large part attributable to common childhood externalizing genetic influences, thus suggesting that the association between these two conditions is largely imputable to a broader and genetically driven predisposition to externalizing problems in childhood. Also, the relationship between adolescent ADHD and adult alcohol dependence is genetically driven (Derks et al., 2014) and mostly depends on shared genetic liability that these disorders have in common with adolescent externalizing behavior; ADHD and alcohol dependence may well be seen as two evolutive steps of a same pathological picture, even if hyperactivity alone (i.e. without inattentive or externalizing dimensions) is also significantly correlated, genetically speaking, to alcohol problems in adulthood (Edwards and Kendler, 2012).

Substance abuse also exerts a negative effect on ADHD symptoms. Treur et al. (2015) adopted the discordant MZ co-twin design in order to explore effects of smoking on attention problems. Results showed that attention problems scores were higher in smokers compared to subjects who never smoked and smoking during adolescence turned out to be associated with higher attention problem scores lasting into adulthood.

To conclude, the existence of shared genetic liability and environmental influences explaining the co-occurrence of ADHD and different kinds of substance use and abuse, along with the longitudinal features of such association, has been pointed out in twin research. Substance abuse also seems to affect ADHD symptomatology, especially for what concerns attention problems. Hence, the co-occurrence of ADHD and substance use and abuse should be taken into account in order to early identify individuals at risk for both conditions and to develop intervention programs specifically suited for preventing the transition from the simple use and abuse to substance use dependence.

5.3. Eating problems

ADHD has been proven to represent a risk factor for the development of disordered eating at varying degrees, since eating problems are more common among children and adolescents with ADHD than the general population (Swanson et al., 2011), in particular for what concerns binge eating (Cortese et al., 2007). A possible explanation of this co-occurrence is that ADHD may share some neurobehavioral circuits with binge eating, such as those involved in response inhibition, emotion regulation and reward processing (Seymour et al., 2015). The longitudinal relationship of childhood and adolescenceinattention and hyperactivity / impulsivity symptoms, as well as the combination of them, with late adolescence eating problems has been investigated by Yilmaz et al. (2017) in a community-based cohort of twins assessed at 8–9, 13–14, and 16–17 years of age. Authors found that disordered eating in late adolescence was better explained by the combination of both inattention and hyperactivity / impulsivity throughout childhood and adolescence, even when controlling for body mass index and for anxiety and depression symptoms. Possible explanations were proposed for this outcome, indicating that impulsivity may contribute to disordered eating through inhibition difficulties, while inattention may imply a lack in the awareness concerning hunger and the food that has just been consumed.

Another study by Capusan et al. (2017) considered a large adult twin population to investigate the association between ADHD and binge-eating behavior, binge-eating disorder (BED) and bulimia nervosa (BN), also focusing on the relative contribution of genetic and environmental factors and of both hyperactivity / impulsivity and inattention symptom dimensions. Results showed that ADHD symptoms in adulthood were strongly associated with binge-eating behavior, BED and BN, and most of this association in females could be explained by shared genetic factors, while binge-eating behavior was less common in men. Small but significant genetic correlation was found between inattention symptoms and binge-eating behavior, while there was no evidence supporting specific genetic effects for hyperactivity / impulsivity.

Eating problems are also common among children with ASD, since neuropsychiatric disorders on the whole are commonly associated with eating problems (Bandini et al., 2010). Råstam et al. (2013) investigated the rate of eating problems in a large twin sample in which subjects were broken down by diagnoses of ADHD and ASD. Authors found the highest prevalence of eating problems among children with comorbid ADHD and ASD, and this association appeared to be accounted for by both genetic and non-shared environmental influences. More specifically, social interaction problems and eating problems were mostly associated in girls, while males showed a stronger association between eating problems and impulsivity and activity problems.

To summarize, genetic and non-shared environmental influences explain most of the association between ADHD, ASD and eating problems. A strong association has been observed between ADHD symptoms in adulthood and binge-eating behavior, BED and BN, thus suggesting the need of taking into account such comorbidity in prevention, diagnosis and treatment of individuals at greater risk.

6. Clinical conditions

6.1. Autism spectrum disorder (ASD)

The association between ADHD and ASD has emerged several times in the course of this dissertation, hence the following paragraphs will discuss this comorbidity in detail. Within the framework of studies considering the overlap between ASD and ADHD symptoms, Reiersen et al. (2007) aimed to assess whether ADHD diagnosed children selected from the general population of twins would present elevated levels of autistic traits. The study was based on both DSM-IV and population-based ADHD subtypes, the latter defined through latent-class analysis. Autistic traits were measured quantitatively with the Social Responsiveness Scale (SRS) and divided into three domains: Social Impairment, Communication Impairment and Stereotyped Behaviors. The main outcomes of this study not only demonstrated that autistic traits are common among children with ADHD selected from the general population, but also that different ADHD subtypes are associated with different levels of social impairments. In particular, DSM-IV combined and population-defined severe combined ADHD subtypes showed the strongest association with autistic symptoms of all domains. For what concerns the severe combined latent class, there was also a notable difference in the proportion of female subjects reaching the threshold compared to the male group.

In a perspective of providing new guidelines to the development of interventions, Ronald et al. (2014) aimed to ascertain if specific symptoms of ADHD and ASD usually occur together. Starting from a bottom-up approach, authors exploited a population-based cohort of twins which allowed them to distinguish between genetic and environmental sources of variance. It emerged that within-condition correlations tended to be stronger than cross-condition correlations, though all ASD and ADHD symptom domains correlated moderately. Among ADHD symptoms, inattention and impulsivity correlated more than hyperactivity with ASD symptoms. For what concerns ASD symptoms, the dimension of restricted repetitive behaviors and interests (RRBIs) significantly correlated with ADHD inattention and impulsivity. The study also highlighted etiological heterogeneity for both

ASD and ADHD, since all symptoms showed specific genetic and environmental influences. Therefore, these results indicate that features of both ASD and ADHD often naturally co-occur, without however representing a complete comorbidity. The ASD dimension of repetitive and restricted behavior and interests (referred to as ASDr) also turned out to be of particular significance in the linkage between ASD and ADHD in a study by Polderman et al. (2014), who investigated phenotypic, genetic and environmental association between DSM-V-based ASD and ADHD dimensions.

Noteworthy, deficits in executive functions characterize both ASD and ADHD and, among these, reaction time variability (RTV) has been referred to as a possible shared cognitive impairment between ADHD and ASD. Using a population-based twin sample, Pinto et al. (2016) aimed to investigate the genetic and phenotypic relationship between autistic-like traits (ALTs) symptom subscales (divided into social-communication and non-social subscales) and the two ADHD dimensions of inattention and hyperactivity / impulsivity in childhood. In this study, authors also investigated the association between ALTs and dimensions of deficit in executive functions, which are known to be present in ADHD, and the extent to which this shared cognitive impairment underlies the genetic risk shared between ADHD symptoms and ALTs. In contrast with previous results, it emerged that social-communication ALTs could explain most of the phenotypic and genetic overlap between the ADHD symptoms and ASD. RTV turned out to be phenotypically and genetically correlated with social-communication ALTs, thus indicating that it's not specific to ADHD symptoms. Noteworthy, RTV could explain a significant proportion of the genetic influence between inattention subdomain and social-communication ALTs, thus indicating that shared genetic risk factors contribute to RTV, inattention and social-communication ALTs, even if it's not possible to determine if a causal relationship is involved. Evidence for genetic overlap between communication difficulties of ASD and ADHD traits, in particular for what concerns pragmatic language, was also found by Taylor et al. (2014) in a population-based twin study that included, for the first time, individuals in the general population who displayed particularly extreme degrees of traits of both conditions. Authors emphasized the importance of taking a trait-specific approach rather than comparing the two phenotypes as a whole, in order to better understand their true relationship.

The association between ASD and ADHD traits, and their bidirectional causal relationship across development, has also been investigated longitudinally. The first study of this kind is by Taylor et al. (2012), who used cross-lagged modelling in a sample of twin pairs aged 8 and 12 years old. It emerged that the association between traits of ADHD at 8 years old and traits of ASD at 12 years old was strongest than the reverse association and it mostly concerned communication difficulties, thus indicating common language difficulties between these disorders.

Dimension-specificity of the overlap between ADHD and ASD was also highlighted by Ghirardi et al. (2018), who used a large population-based sample of adult twins to investigate phenotypic and aetiological overlap between ADHD specific trait dimensions, divided into hyperactivity / impulsivity (HI) and inattention (IA), and ASD specific trait dimensions, divided into repetitive and restrictive behaviors (RRBs) and social interaction and communication (SIC). They found that RRBs were more correlated with HI than IA, the latter being equally associated with both RRBs and SIC. In addition, the strongest genetic correlation was between HI and RRBs, while the weakest was between HI and SIC. Non-shared environmental influences turned out to be relevant risk factors for the overlap between ADHD and ASD in adults, since they accounted for half of the phenotypic correlations. These results confirm the need of a dimension-specific approach in the investigation of the overlap between ASD and ADHD.

To summarize, autistic traits are common among children with ADHD, even if different ADHD subtypes are associated with different levels of social impairments. Namely, combined ADHD subtypes show the strongest association with autistic symptoms of all domains, whereas ASD dimension of RRBs is more correlated with hyperactivity / impulsivity rather than inattention, and this latter is equally associated with RRBs and SIC. There's also a longitudinal pattern in the association of these disorders, with ADHD being a better predictor of ASD rather than the reverse association. On the whole, these data may be taken into account in prevention and in the development of intervention programs, also considering the different symptomatology of these conditions and its impact on treatment.

6.2. *Affective disorders and internalizing problems*

ADHD has been shown to co-occur with affective illness and internalizing problems (e.g. Butler et al., 2011; Jarrett and Ollendick, 2008). Using a classical twin design in preschool children, Rydell et al. (2017) addressed the issue whether ADHD symptoms and affective problems co-occur early in child development, and also aimed to investigate the potential genetic and environmental overlap between these two conditions. The study highlighted a substantial genetic overlap between symptoms for both subtypes of ADHD and affective problems, thus supporting the notion of a shared genetic liability of both conditions in young children. Also shared environmental influences turned out to be linked with the association between ADHD symptoms and affective problems, even if in a lesser extent than genetic influences. On the other hand, non-shared environmental influences were not significant in this study. These outcomes led to several explanations for the etiology of this comorbidity: maybe ADHD symptoms make individuals prone to experience more psychosocial impairment than controls, or there could be a common familial risk factor, of both genetic and environmental origin.

In order to identify non-genetic risk factors for affective problems, and in particular for depression, Piek et al. (2007) were able to rule out both genetic and shared environmental influences, since differences between MZ twins are only imputable to non-shared environmental factors. This study also investigated the effect of comorbid developmental coordination disorder (DCD), which often co-occurs with ADHD: the aim was also to understand the potential relationship between this comorbidity, usually referred to as deficits in attention, motor control and perception (DAMP; Gillberg, 1995), and depression. Among the results, twins with ADHD showed higher levels of depression compared to their non-ADHD co-twins, thus indicating that non-shared environmental factors can also exert an influence on this comorbidity. Also twins with DCD showed higher levels of depression compared to their co-twins without DCD, and noteworthy DAMP children showed increased levels of depressive symptomatology compared to ADHD only, DCD only, and no ADHD or DCD conditions. A possible explanation is that twins with ADHD experience unique environmental situations, such as relational difficulties and school failures, which make them more prone to develop depressive symptomatology than the co-twins, thus revealing the importance of taking into account also emotional problems during the evaluation and treatment of these individuals.

For what concerns pediatric bipolar disorder, Reich et al. (2005) examined the possible relationship with ADHD symptoms in a non-referred twin population aged 7 and 18 years: in particular, the study asked if there was an association between subthreshold or full criteria cases of mania and either DSM-IV or population-based subtypes of ADHD. Authors did not find any significant association of possible mania with DSM-IV ADHD subtypes, whereas severe combined subtype and the talkative subtype derived from population turned out to be significantly associated with possible bipolar illness.

Even if future studies are warranted to better disambiguate the relative contribution of genetic and environmental factors in the comorbidity between ADHD and affective illness, ADHD has turned out to be associated with depression and bipolar illness. Such association should surely be taken into account in prevention and diagnosis, since the presence of ADHD may be indicative of a liability for emotional

problems and vice versa, and it should also guide the development of intervention programs.

Even anxiety often co-occurs with ADHD, and like this latter, it is characterized by heterogeneity and can be disgregated into different subtypes. Michelini et al. (2015) used a sample of adolescent twins in order to examine the association between ADHD (divided into attention problems and hyperactivity / impulsivity) and anxiety subtypes, which included panic / agoraphobia, separation anxiety, social anxiety, physical injury fears, obsessive-compulsive symptoms and generalized anxiety symptoms (Spence, 1997). Authors found that anxiety subtypes were mostly associated with attention problems rather than hyperactivity / impulsivity, and the aetiological overlap between the former ones was due to both genetic and non-shared environmental influences. A possible explanation of this outcome is that anxious people tend to present attention biases towards threat stimuli, which may underlie their difficulty to shift attention from a target to another in an adaptive way. Notably, social anxiety had a significant negative correlation with hyperactivity / impulsivity, thus supporting data from other studies that found that anxiety is associated with a suppression of hyperactive behavior in ADHD youth (Pliszka, 1992).

The association between ADHD symptoms and internalizing disorders has also been investigated in a Chinese twin study by Chen et al. (2016), where three types of internalizing problems were taken into account: anxiety / depression, withdrawn and somatic complaints. Authors found out that the overlap between ADHD and the three internalizing problem dimensions was due to common genetic and shared environmental influences. Notably, the study found modest genetic influences compared to higher shared environmental influences on the three internalizing problems, a result which is in contrast with many studies conducted in Western populations: a possible explanation could come from the social context, since collectivism and the seeking of being similar to each other are common in Asian culture and may contribute to increase shared experiences among twins.

The attempt of investigating the relationship between ADHD and affective problems could also take into account the impact that the presence of the ADHD twin exerts on the non-ADHD co-twin. To this purpose, McDougall et al. (2006) examined the level of both generalized and separation anxiety of the non-ADHD twin in MZ twin pairs. It emerged that children with combined ADHD showed higher separation anxiety (SA) than non-ADHD co-twins, and children with either inattentive or combined ADHD had higher generalized anxiety (GA) than non-ADHD co-twins. Levels of GA and SA were higher in combined ADHD children than inattentive ADHD ones. For what concerns anxiety level in non-ADHD co-twins, results showed that co-twins of children with combined ADHD had higher levels of both GA and SA than co-twins of both non-ADHD and inattentive ADHD children. Even non-twin siblings who had one DZ brother or sister with ADHD were investigated. Analyses on this direction showed higher SA scores in siblings of children with combined ADHD than in controls, while lower levels of GA were found in siblings compared to co-twins. Siblings in the combined group showed the highest levels of all and much higher than siblings of either inattentive or control twins.

To summarize, anxiety subtypes are mostly associated with attention problems rather than hyperactivity / impulsivity dimensions of ADHD, because of genetic and non-shared environmental sources: for this reason, the assessment of anxiety disorders may be taken into account for prevention and in the development of intervention programs for such individuals.

6.3. Asthma

Asthma and ADHD are both chronic health conditions that have been shown to often co-occur, even if the nature of this association is not entirely clear yet.

Holmberg et al. (2015) investigated the relationship between these two conditions in a large twin cohort, focusing on the possibility that the association may be restricted only to hyperactivity / impulsivity (HI) or inattention (IN) symptoms of ADHD. The impact of possible confounding factors, such as asthma severity and asthma medication, was also taken into account. The results of this study indicated that ADHD was more common among children with asthma than controls, and asthma was associated with both symptoms of HI and IN and the combination of them. The degree of the association between the conditions was higher in respect of asthma severity, even if it was not influenced by asthma medication and other confounding factors, such as atopic eczema. The twin analysis showed a strong genetic component for asthma and ADHD for what concerns intraclass correlation. The cross-trait/cross-twin correlations turned out to be even higher in DZ twins, thus indicating the presence of environmental influence. On the whole, these outcomes suggest that asthma in childhood, and asthma severity in particular, exerts an influence on the possible development of ADHD symptoms.

While information about asthma and ADHD was collected at the same age in the previous study, the longitudinal relationship between childhood asthma and ADHD in adolescence was investigated by Mogensen et al. (2011) in a population-based twin study (from 8-9 to 13–14 years of age). Authors considered confounding factors and the possible influence of asthma medication, and like in the former study, distinguished between DSM-IV ADHD dimensions of HI and IN since these symptoms are characterized by different etiologies and outcomes. The results showed that parent-reported HI scores at age 13–14 were twofold higher for children diagnosed with asthma at age 8–9 than controls. On the other hand, childhood asthma did not predict IN in adolescence. Notably, the association between asthma and HI emerged to be partly due to genetic influences, thus suggesting a genetic overlap between these two phenotypes.

To summarize, asthma is common among individuals with ADHD and its severity can exert an influence on both hyperactivity / impulsivity and inattention dimensions, as well as the combination of them. Such comorbidity is explained by both genetic and environmental influences, and childhood asthma has been proposed as a potential predictor of hyperactivity / impulsivity in adolescence, mostly due to genetic factors. For this reason, even if further studies are warranted, the diagnosis of asthma should be taken into account in both prevention and treatment of ADHD.

7. Psychosocial risk factors

7.1. Childhood maltreatment

Child maltreatment (CM) has been pointed out as a crucial risk factor of environmental origin commonly linked to neurodevelopmental disorders (NDD) in general and, more specifically, to ADHD. Also, CM affects some neurocognitive functions that are strongly associated with ADHD: these include working memory, executive and emotional control (Gould et al., 2012), inhibitory network connectivity and response inhibition (Elton et al., 2014). Nevertheless, it is still unclear whether the association is causal or indicative of familial (either genetic or environmental) confounding.

In a study by Dinkler et al. (2017), a co-twin control design was adopted in order to assess whether CM is a risk factor for NDD when controlling for familial effects. Authors demonstrated that, on average, individuals who were maltreated early in development had a higher number of NDD than non-maltreated individuals. For what concerns ADHD, compared to their non-maltreated co-twins, male MZ twins who were maltreated had significantly more symptoms of ADHD, suggesting a risk effect of CM. On the co-twin control analysis, CM was associated with a small increase in symptoms of ADHD, although the origin of the association remained unclear. Authors concluded that the co-occurrence of CM with an increased load of NDD symptoms could be accounted for by a shared genetic liability, which increases both the risk of being maltreated and of having more co-occurring NDD. These

results are in line with previous research showing that common genetic factors largely account for the covariation of parent-child hostility and child ADHD symptoms (Lifford et al., 2009).

Capusan et al. (2016b) analysed a large population-based sample of adult twins in order to investigate if unmeasured genetic and environmental confounders underlie the association between various forms of CM and ADHD symptoms in adults. The authors used conditional linear regression (within twin-pair analysis) for the association between CM and adult ADHD symptoms, separately in DZ and MZ twin pairs discordant for the exposure to CM. The hypothesis is that, if the association between CM and ADHD in adults is mostly causal, it would be expected to be of similar magnitude in twins as individuals and within DZ and MZ discordant twin pairs. Results showed that all forms of CM were more common in the ADHD group compared to the non-ADHD group. Within twin-pair analyses indicated that the effects of maltreatment on ADHD scores were partially causal and could not be entirely explained by familial (genetic and/or environmental) confounding. Similar results emerged for different types of maltreatment as well as for hyperactive / impulsive and inattentive ADHD symptoms. Therefore, based on the finding that MZ twin-pair estimates remained significant, the study demonstrated that the association between CM and ADHD symptoms in adults is partly causal in nature and partly due to familial confounding.

Capusan et al. study was based on retrospective reports of childhood maltreatment, which are not exempt from biases (Reuben et al., 2016). Moreover, ADHD may be not only the outcome but also an early risk factor for maltreatment, with evocative Gene-Environment correlation (r_{GE}) representing a possible contributing mechanism. In order to overcome such threats to the validity of the experiment, Stern et al. (2018) used prospectively-collected measures from a longitudinal cohort of twins. Their study was intended to examine the association between ADHD and the exposure to abuse and neglect in childhood and adolescence, up to age 12 and at age 18. The associations between abuse / neglect and ADHD diagnosis were examined separately for childhood and young adulthood at first and then also the longitudinal associations were investigated. In addition, the authors also investigated twins' differences in abuse / neglect and ADHD to control for familial confounding. Among the results, for what concerns childhood, authors found that there was just a modest association within twin pairs between poly-victimization and ADHD symptoms. Such association was not significant when repeated with MZ twins only, indicating that it was accounted for by genetic factors. Differently, in young adults, a modest association between twins' difference scores on poly-victimization and difference scores on ADHD symptoms was found, and it remained significant when repeated with MZ twins only; this indicated that, at this age, the association was partly environmentally driven. Other results are those from concurrent analyses, which showed that abuse / neglect was strongly associated with ADHD not only in childhood, but also in young adulthood. Longitudinal analyses indicated that childhood abuse / neglect could not predict later ADHD symptoms. Finally, childhood ADHD was associated with later exposure to abuse / neglect when comorbid with conduct disorder. According to these results, ADHD may represent a risk factor for the later exposure to neglect and/or abuse, while there's a lack of evidences that could support the causal influence of CM on ADHD, an issue which requires further research.

To conclude, child maltreatment may represent a risk factor for the development of ADHD, but also ADHD symptoms in turn may be risk factors for the later exposure to neglect and/or abuse. Such association in children is possibly due to a shared genetic liability, while it appears to be partially accounted for by environmental influences in adulthood. There is no total agreement on the nature of such association, since also a causal relationship has been proposed, and further research is needed. Discovering the nature of the link between ADHD and maltreatment in childhood is fundamental for prevention and treatment, since children who experience abuse may be at risk for the development of ADHD symptomatology and vice versa.

8. Conclusion

8.1. Limitations

This narrative review surely presents a number of limitations, as it is simply conceived as a starting point for researchers and readers who are just looking for a summary on the state of the art of twin research about ADHD and its comorbidities. The style of writing is intended to report facts and results objectively and merely as they are: for such reasons, in many cases we abstained from providing results' interpretation and from formulation of new hypotheses: these may not reflect the scientific questions that motivated the authors of the original works. The search of papers, which was achieved through an extensive sieve of scientific literature, was not guided by any *a priori* theory, but was conducted with the only intention of providing an overview of twin research on ADHD and its comorbidities as complete as possible. A consequence of this approach is that the various ADHD traits taken into account are heterogeneous and poorly interrelated in many cases, yet consistent with the aim of providing a panoramic overview on the topic; the latter is strictly focused on the contribution made by twin research on ADHD comorbidities. Since this review is not intended to be systematic but rather narrative, no papers were systematically excluded from the discussion and the risk of bias was not assessed at all. It follows that the overrepresentation of particular authors was unintentional and possibly due to the major quantitative contribution of such authors to this field. Furthermore, as far as the method is concerned, no constraints on the year of publication, language or employed methods were applied in the selection of papers. Given all these limitations, this review may also represent a starting point for other review papers, which may be conducted more systematically. Specific aspects of ADHD comorbidities certainly deserve a deeper and targeted investigation.

8.2. Final remarks

Overall, papers reviewed here contribute to shed light on the nature of ADHD and other comorbid conditions. A common genetic liability exists between ADHD and many of its comorbidities, like the chance of being exposed to abuse and neglect in childhood, which represents a risk factor for the development of neurodevelopmental disorders in a broad sense. Common genetic factors also appear to exist among ADHD and personality traits of negative emotionality, temperamental novelty seeking and the risk of character immaturity. All these evidences could be useful in the treatment of these individuals, by taking into account the risk of child maltreatment and focusing on such individual traits to improve interventions. ADHD is also accompanied by specific functional and anatomic brain features that account for its phenotypic manifestations: for instance, less activation of the frontoparietal networks may explain typical impairments in executive control and goal maintenance. Autistic-like traits are common among individuals with ADHD, including both the dimensions of restricted repetitive behavior and interests and social-communications difficulties, with the presence of genetic overlap but also depending on non-shared environmental influences, according to different studies. Considering the link between ADHD and ASD is important since a longitudinal relationship between these disorders also exists, with ADHD traits being capable to better predict ASD traits later in development than the reverse association. Moreover, a genetic overlap exists between ADHD symptoms and affective problems such as depression and anxiety, these latter also being explained by non-shared environmental influences. ADHD also shares a strong genetic component with asthma in childhood, and with asthma severity in particular.

Common genes with pleiotropic effects, which appear to be stable over time, also exist between ADHD and reading disability, the former being a strong predictor of the latter. Moreover, many studies have shed light on a common genetic vulnerability between ADHD, mathematics ability, reading comprehension and cognitive problems. Specific genes

are also associated with ADHD inattentiveness symptoms and mathematics ability, which could influence homework behavior. The existence of all these common genetic liabilities surely should be taken into account when developing interventions, since these should be designed on the features of all these comorbid conditions.

ADHD often co-occurs with other externalizing disorders, such as CD and ODD, which could be explained by both shared genetic and environmental influences. Furthermore, the correlation between these traits appears to increase across age, from middle childhood to adolescence and to early adulthood, with a large contribution of genetic innovation sources. Even ADHD and substance use and abuse appear to share common genetic and environmental influences. In particular, the co-occurrence of alcohol problems and hyperactive / impulsive symptoms appears to be imputable to a broader and genetically driven predisposition to externalizing problems in childhood, and it also seems to last into adolescence and adulthood. Finally, shared genetic factors exist between ADHD and binge-eating behavior, BED and BN, mostly in adult females.

It is worth noticing that the list of traits that appear to co-occur with ADHD, despite its considerable length, does not imply that all comorbid traits are basically problem behaviors, but simply that there might be underlying mechanisms, often not yet known, that might explain this relationship. In particular, twin studies contributed mostly to highlight the genetic and environmental correlation between ADHD and comorbid traits, but in many cases this correlation still remains poorly understood and might well arise from influences that are not directly linkable to behavioral processes, including immune and epigenetic dysregulation. It is also possible that the observed correlation between ADHD and its comorbid traits is partly explained by shared environmental or interactive effects, which should be better explored in future twin studies.

Investigating the relative contribution of genetic and environmental influences on ADHD comorbidities is fundamental for prevention, diagnosis and treatment. In fact, genes that are specific for a disorder may also represent a risk factor for the other disorder, thus enabling to predict the possible consequences of a particular genotype, whereas experiences and environments that represent a risk factor for a disorder may also be a risk factor for the other. Furthermore, environmental interventions which turn out to be effective for a disorder may also be effective for the other comorbid condition, thus suggesting the importance of acting on the environment where individuals grow up. Twin studies are fundamental for the understanding of the relative contribution of genes and environment in ADHD comorbidities, thus allowing to improve chance of prevention, diagnosis accuracy and development of treatments. Novel directions of future studies are warranted not only to provide further details on genetic overlap and GxE interaction for the observed traits, but also to better exploit the matched twin design, for example by combination with Mendelian Randomization, so that important associations could be detected.

To conclude, twin research should also stress on strengths and positive aspects associated with ADHD, such as creativity and inventiveness, resilience and energy, entrepreneurship behavior, spontaneity and empathy. For instance, to our knowledge only one study has pointed out the existence of an association between hyperactivity symptoms of ADHD and self-employment in a population-based sample of adult twins, thus suggesting that ADHD may play a beneficial role on career choices (Verheul et al., 2016). These topics are poorly represented in literature, but they should be further investigated, since outcomes from twin studies may give life to interventions focusing on strengths rather than weaknesses of people with ADHD.

Declaration of Competing Interest

There is no conflict of interest to disclose.

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