De Francesco *et al. J Transl Genet Genom* 2024;8:102-18
DOI: 10.20517/jtgg.2023.51

Journal of Translational Genetics and Genomics

Review

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Exploring the comorbidity between internalizing/externalizing dimensions and cognitive disengagement syndrome through twin studies: a narrative review

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How to cite this article: De Francesco S, Amico C, De Giuli G, Giani L, Fagnani C, Medda E, Scaini S. Exploring the comorbidity between internalizing/externalizing dimensions and cognitive disengagement syndrome through twin studies: a narrative review. *J Transl Genet Genom* 2024;8:102-18. https://dx.doi.org/10.20517/jtgg.2023.51

Received: 14 Nov 2023 **First Decision:** 24 Jan 2024 **Revised:** 9 Feb 2024 **Accepted:** 5 Mar 2024 **Available online:** 27 Mar 2024

Academic Editor: Richard Frye **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Twin studies are cutting-edge design methodologies proper to behavioral genetics that aim to investigate how the interplay between genetic and environmental factors can concur to explain individual differences in psychopathology, temperamental traits, and behavior. This particular research design has been widely applied to the study of comorbidity between internalizing (INT) and externalizing (EXT) symptoms, especially in childhood and adolescence. Notably, the high co-occurrence of symptoms of both these diagnostic domains has led to the hypothesis that at their basis, there might be one single latent common susceptibility factor, namely p factor. Twin studies have contributed to marking a relevant turning point in this regard by highlighting the consistent genetic nature of this factor. In light of these premises, the present narrative review aims to outline the path for future twin studies in investigating the comorbidity between Cognitive Disengagement Syndrome (CDS) and INT-EXT disorders, examining the evidence supporting this need and its clinical implications. Since CDS has not been recognized as a stand-alone syndrome until very recently, research on this condition is still in its infancy and the etiological factors at the basis of its comorbidity with INT-EXT are still unclear. Being aware of the causal factors underneath the comorbidity between INT-EXT might pave the way for improving assessment diagnostic

procedures as well as setting up preventive interventions for CDS.

Keywords: Cognitive disengagement syndrome, internalizing disorders, externalizing disorders, twin studies, comorbidity

INTRODUCTION

For several decades now, the importance of behavioral genetics in the field of psychopathology research has been widely recognized, as it constitutes a unique investigative method that allows the analysis of genetic and environmental etiological factors underlying psychological disorders. Quantitative genetic studies, especially twin studies, are particularly applied in research on developmental psychopathology and have significantly contributed to enriching our current understanding of Internalizing and Externalizing symptoms. The terms Internalizing and Externalizing are used to refer to two groupings of behavioral, social, and emotional problems[1]. Internalizing (INT) symptoms are usually related to the self and underestimated by external raters as not effortlessly recognizable, while externalizing (EXT) symptoms generally occur in the interaction with the social environment[2].

Behavioral genetics, besides shedding light on the etiological factors of individual disorders belonging to each of these domains, has greatly enhanced our knowledge regarding the existence of a common susceptibility factor underlying the frequent comorbidity between these symptom's clusters. However, in the last two decades, interest has grown in a set of dysfunctional behaviors that cannot be categorized within the aforementioned domains. Since the late 80s, factor analysis studies have shown that some of these behaviors could be enclosed within a distinct condition originally termed Sluggish Cognitive Tempo (SCT)[3]. This condition refers to a set of developmentally inappropriate caregiver-reported behaviors and symptoms involving slowed-down cognitive processing speed, excessive daydreaming and mind-wandering, mental confusion/fogginess, task-unrelated thoughts, difficulty initiating and sustaining effort, low motivation, drowsiness, and marked hypoactivity that can impair a child's daily functioning in several domains[4]. The term SCT has recently been replaced with Cognitive Disengagement Syndrome (CDS[5]), which more accurately represents the nature of the syndrome and aligns more precisely with the current scientific understanding and terminology preferences. Given the nature of the features that characterize it, originally, CDS was considered a subgroup of Attention-Deficit/Hyperactivity Disorder (ADHD)[6,7]. ADHD is amongst the most pervasive psychological disorders affecting children in their schooling years. It is characterized by symptoms such as hyperactive behavior, impulsivity, and inability to sustain attention. Depending on which of these problems best characterizes the individual's symptomatic profile, they can be categorized into three different presentations: ADHD-I (predominantly inattentive type), ADHD-H (predominantly hyperactive-impulsive type), or ADHD-C (combined type)[8].

The recognition of CDS as a distinct nosological entity has gained significant scientific validity following a meta-analysis conducted by Hartman *et al.* in 2004, whose results indicated a clear differentiation between CDS and the inattentive subtype of ADHD[9]. Being a relatively young syndrome, twin research on CDS is still in its early stages but has already provided important insights, both confirming its differentiation from ADHD-I and identifying some common etiological factors with specific INT symptoms. However, despite the high rates of comorbidity between CDS and INT-EXT symptoms that have already been found in a growing body of literature, twin research on this topic still needs to be further deepened.

In light of the above, this review aims to discuss the potential significance of twin studies in highlighting the genetic and environmental basis of the co-occurrence between INT-EXT and CDS manifestations. After an

initial methodological overview of research designs in quantitative behavioral genetics, the characteristics of INT/EXT clusters and their contribution to the debate on categorical diagnostic systems versus dimensional approaches will be examined. Additionally, behavioral genetic evidence supporting the need for a dimensional approach to psychopathology will be presented. The review will then emphasize the contribution of twin designs in differentiating between ADHD and CDS. Finally, available data on the comorbidity between CDS and INT-EXT disorders will be reviewed, with a special focus on the results from the first twin studies addressing this issue, potentially offering valuable insights for clinical monitoring at both individual and familial levels.

Behavioral genetics: definition and historical overview

Behavioral genetics can be defined as a research field whose aim is to investigate how the interplay between genetic and environmental factors can concur to explain individual differences in psychopathology, temperament traits, and behavior[10].

Its roots can be traced back to the 1970s, when the hypothesis that behaviors and psychopathology could be influenced not only by environmental factors, but also by genetics, was postulated. Since then, more importance has been attributed to the genetic underpinnings of psychological traits and the concept of "genetic predisposition" was gradually introduced[11]. Therefore, during the 1980s, the contribution of the environment was almost completely excluded from the research on the etiopathogenesis of psychopathology, whereas the influence of genes on various phenotypes became its main focus[10]. However, when considered separately, neither genetics nor the environment was sufficient to explain the etiopathogenesis of psychopathology, as they each accounted for only up to 50% of the variance; hence, a more comprehensive perspective was needed. The roles of both "nature" and "nurture" started to be considered equally important in understanding and explaining individual differences in complex behavioral traits[10]. As a result, the current literature agrees that the phenotypic variance of specific traits is shaped by the constant interplay of genetic and environmental factors. For instance, exposure to given environments can be driven by biologically determined elements, whereas being exposed to certain environments may alter the genetic pathways through epigenetic changes[10]. Consequently, behavioral genetics has gradually started to adopt a bio-psycho-social approach, according to which psychopathology emerges from the interaction between the individual's biological features and the environment, which can represent alternatively a risk or a protective factor for the development of psychiatric disorders[12]. The growing interest in this field of research has progressively led to the development of disciplines, such as epigenetics and quantitative genetics, devoted to the implementation of increasingly effective methodologies for studying the etiological factors underlying psychological phenotypes.

Quantitative genetics

The main goal of quantitative genetics is to assess the interplay of genetic and environmental factors in shaping specific phenotypes. The overall genetic variance of a complex trait can be divided into three components: (A) genetics, (C) shared environment, and (E) unique environment[13]. Specifically, A denotes the contributions deriving from additive genetic effects (i.e., the sum of the effects from all gene variants influencing the trait independently). C stands for the shared environmental factors, encompassing influences common to twins within a family, especially during childhood and adolescence (e.g., parental behaviors, socioeconomic status of the family, the rearing environment, etc.) or shared in utero during the gestation (e.g., exposure to the same maternal hormones). Meanwhile, E represents unique environmental factors that account for influences specifically acting on an individual (infections, peer relationships, lifestyle, etc), and also includes measurement error[14]. The primary research designs employed to explore genetic and environmental influences on phenotypes are adoption and twin studies[15]. Adoption studies evaluate the genetic and environmental contributions to the similarities among family members in complex

traits by analyzing two main samples: dyads of parents and children who share the same genetic heritage but not the environment and, on the opposite, dyads that share the same environment but are not genetically related[11]. Despite having proved to be valuable in unraveling the genetic and environmental contribution to several behavioral traits, adoption studies have some significant limitations. Firstly, the samples collected may not always be representative of the general population: on the one hand, people who decide to give children up for adoption are often exposed to severe socioeconomic and environmental conditions, whereas on the other, in order to ensure the child wellbeing, in most western countries, adoptive families are selected through intense screening processes aimed at identifying future parents with great socioeconomic statuses and high levels of education, but these variables obviously cannot be controlled when assessing biological families[13].

Moreover, because of cultural changes such as the increase in the use of hormonal contraceptives, the decriminalization of abortion, and the increasing rates of occupied women, in the last decades, adoption rates have decreased significantly, making it increasingly difficult to retrieve this specific sample[10].

Twin studies also allow the detection of environmental contributions to phenotypes, but they certainly represent the best indicator to estimate the extent to which biology influences a trait, through the comparison between Monozygotic (MZ) and Dizygotic (DZ) twins[10,16]. MZ twins can also be referred to as identical twins as, by being conceived by the fertilization of a single zygote, they share 100% of their genetic heritage and are phenotypically identical. DZ twins are instead conceived by the fertilization of two different eggs and share only 50% of the genetic heritage, just as siblings born from different pregnancies. However, in twin studies, DZs constitute a better control group than siblings, as they are peers who have also shared the same intrauterine environment[17].

Twin studies

Twin studies evaluate correlations for a given trait between MZ and DZ twins by assuming that if the phenotype is mostly influenced by genetic variables, correlations between MZs will be higher than those between DZs[11]. However, these premises are valid only if the Equal Environments Assumption (EEA) is met. According to the EEA, MZ and DZ twins share to the same extent all environmental factors that are relevant for the phenotypic expression of the trait under study. If this requirement is not met, because of the supposedly increased shared environmental elements among MZ twins, the accuracy of their comparison with DZ twins would be jeopardized. This could result in an overestimation of the influence of genetic factors, as also noted by Fagnani *et al.*[18]. Historically, twin studies have been criticized for a possibly reduced representativeness, due to a higher rate of pre-term birth in twins compared to singletons. However, over the years, twins have been shown to provide a reliable picture of all traits of interest in bio-psycho-social research, including personality, psychopathology, and the attainment of motor development milestones[10]. The main statistical methods applied in twin studies are represented by the univariate and multivariate models, which can be used depending on the aim of the study. The former is used to address the genetic and environmental contributions to the variance of a single phenotype, whereas the latter is used when two or more phenotypes are considered[18]. In a univariate model, the intraclass correlation is calculated and compared between monozygotic (MZ) and dizygotic (DZ) twins, whereas in multivariate models, the cross-twin/cross-trait correlation is the main focus of the analysis, as it regards the comparison of two or more phenotypes observed in the two twins belonging to the same pair (e.g., anxiety as observed in twin 1 and anger observed in twin 2)[18]. Structural equation models (SEM) are employed to identify the contribution of genetic and environmental factors to phenotypic variance and covariance[14]. In these models, the considered phenotypes are included as observed variables, whereas A, C, and E are the latent variables considered. There are three main models useful for estimating the parameters: the Cholesky model, the Independent Pathway model, and the Common Pathway model. The Cholesky model [Figure 1]

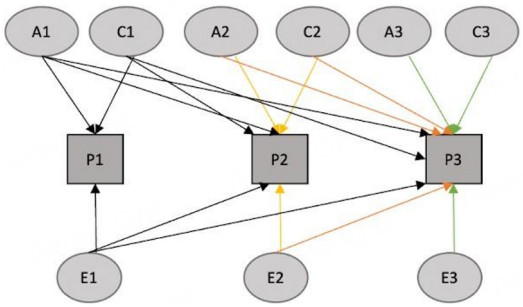

Figure 1. Multivariate Cholesky model. Observed variables are depicted in squares and latent variables in circles. A: Additive genetic factors; C: shared environmental factors; E: unique environmental factors.

posits that the correlations among the traits are influenced by both genetic and environmental factors[19,20]. In the case of n variables, the Cholesky decomposition involves n separate genetic and environmental factors: the first factor affects all traits, the second factor affects all traits except the first one, the third factor affects all traits except the first two, and so forth[21]. The Independent pathway model [Figure 2] suggests that shared genetic and environmental latent factors have a direct impact on all the traits being studied. These shared elements would influence the relationships among the traits, whereas a group of distinct hidden variables would be accountable for the unique variability in each trait[22]. Lastly, the Common Pathway model [Figure 3] posits that genetic and environmental influences contribute to a single common hidden variable ("Liability"), which in turn directly affects the observed traits. Furthermore, similarly to the previous model, this one also includes latent factors specific to each trait, which represent the unique components of variance that are not shared[23]. During the statistical analyses, all models are compared to each other through chi-square tests, and the selection of the best-fitting model is guided by the principle of parsimony. According to this principle, models with fewer latent variables are preferred over the more complete ones if they do not cause a significant worsening of fit to the data[23].

Internalizing and Externalizing Disorders

The terms Internalizing and Externalizing indicate two sets of behavioral, social, and emotional problems typical of childhood and adolescence[24]. These terms were first used by Thomas M. Achenbach with the purpose to aggregate, using a factor analysis, psychopathologies diagnosed in a sample of 600 youths aged between 4 and 15 years old. As a result, the authors were able to distinguish between disorders involving an impairment that is less visible from the outside and more intrapersonal, called Internalizing disorders, and disorders that significantly alter the interactions with peers and the surrounding environment, defined as Externalizing[1,2].

This division has gradually been adopted by the American Psychiatric Association[6]. The latest edition of the DSM-5 labels as "Internalizing" those disorders primarily characterized by depressed mood, physiological symptoms with their cognitive counterparts, and anxious symptoms[6]. Whereas disorders labeled as "Externalizing" are characterized by conduct disturbances, antisocial behaviors, impulse control difficulties, and a tendency towards substance abuse behaviors[6]. This distinction could promote the development of diagnostic approaches different from the purely categorical ones that clinical psychology has traditionally used, leaning towards an increasingly dimensional perspective[6]. However, it should be underlined that the existence and validation of these two broad categories do not aim at totally replacing the more conventional and current categorical approaches: while acknowledging the distinction between INT-EXT disorders, the DSM-5 continues to use labels to classify psychological distress into independent and separate diagnostic classes with specific symptomatology, pervasiveness, and duration[25]. However, the

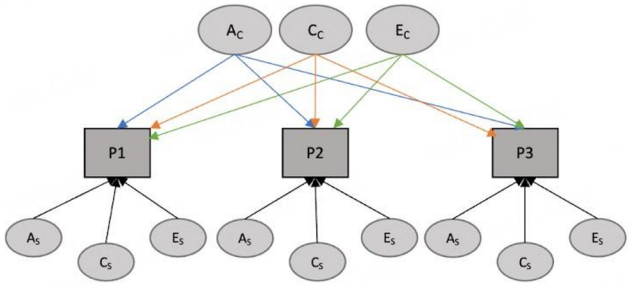

Figure 2. Independent pathway multivariate model. Observed variables are depicted in squares and latent variables in circles. Ac: Additive genetic factors common to the phenotypes; Cc: shared environmental factors common to the phenotypes; Ec: unique environmental factors common to the phenotypes. A: additive genetic factors specific to the phenotypes; C: shared environmental factors specific to the phenotypes; E: unique environmental factors specific to the phenotypes.

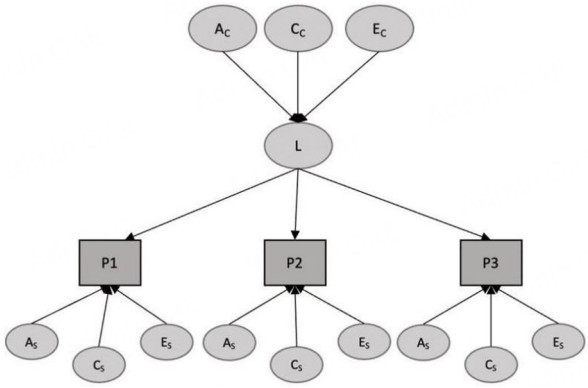

Figure 3. Common pathway model. Observed variables are depicted in squares and latent variables in circles. Ac: Additive genetic factors common to the phenotypes; Cc: shared environmental factors common to the phenotypes; Ec: unique environmental factors common to the phenotypes; A: additive genetic factors specific to the phenotypes; C: shared environmental factors specific to the phenotypes; E: unique environmental factors specific to the phenotypes; L: common latent susceptibility factor.

limitations of categorical classifications are not negligible, as they have often been the central reason for revisions and reeditions of the manuals. Caspi & Moffitt[26] emphasized how the existence of such a high number of diagnostic categories directly leads to high rates of comorbidity among the disorders themselves: the presence of transdiagnostic symptoms and the tendency to categorize psychopathology into specific labels mean that a significant portion of individuals diagnosed with one disorder may meet the criteria for the diagnosis of other conditions. The authors' proposal would be to adopt a more parsimonious approach to diagnosis, considering the distinction between INT-EXT disorders, which could further promote the development of dimensional psychodiagnostic approaches[26].

Adopting a dimensional perspective: the three factors model

As mentioned, one of the most discussed implications of the categorical approach regards the high comorbidity rates that can be found among different disorders. Research has shown that most people diagnosed with a psychiatric disorder would often match the criteria for at least another psychopathology[26]. These comorbidity rates make it necessary to evaluate the hypothesis that psychiatric disorders might be analyzed using a more parsimonious model able to aggregate the disorders into macro-categories, rather than identifying them as independent entities[26]. One of the first studies to introduce a new perspective on the existing taxonomic system was conducted by Krueger in 1999[27]. The research in question involved a confirmatory factor analysis, through which the comorbidity (and hence correlations) of the ten most common mental disorders (major depressive episode, panic disorder, dysthymia, social

phobia, agoraphobia, specific phobia, generalized anxiety disorder, substance abuse disorder, alcohol abuse disorder, and antisocial personality disorder) were examined. These disorders were identified through structured interviews based on the diagnostic criteria of the DSM-III-R, administered for the first time to a probabilistic sample, rather than exclusively to clinical cases[27]. Krueger's results highlighted that the structural model that was most able to explain the comorbidities between disorders was composed of three factors labeled as *Anxious-Misery*, *Fear*, and *Externalizing*[27]. Given the high correlation between the first two domains (r = 0.73), they were combined into a single variable called *Internalizing*[27]. Kendler *et al.* provided evidence for the replicability of the structural model from a genetic perspective[28]. In particular, they carried out a twin study on 5600 subjects considering the most common INT and EXT symptoms as phenotypes (e.g., Major Depression, Generalized Anxiety Disorder, Alcohol Dependence, Conduct Disorders, etc)[28]. Firstly, the inclusion of all of these symptoms in the model-fitting analysis at the same time has pointed out that the best-fitting model was an independent pathway with two strongly correlated common additive genetic factors, namely Ac1 and Ac2[28]. More specifically, Ac1 showed greater loadings on INT symptoms, while Ac2 on the EXT ones. In addition, they replicated the analyses focusing only on INT symptoms, finding that the best fit to the data was provided again by an Independent Pathway model with two common correlated genetic factors[28]. In this case, Ac1 had greater loadings on symptoms belonging to the "Anxious-Misery" domain (e.g., Depression and Generalized Anxiety Disorder), while Ac2 loaded on symptoms related to the "Fear" cluster (e.g., Animal and situational Phobia)[28]. Finally, in 2006, Krueger and Markon reviewed all the existing literature on susceptibility models for common mental disorders identified through the diagnostic criteria of the DSM, using population-based samples as their study subjects[29]. The results of this study, obtained through model-fitting analyses that compared the models reported in each study, once again provided evidence for the superior fit of the three-factor model to the data. This reaffirmed the division of INT into the categories of distress, commonly associated with a predisposition to major depression, dysthymia, and generalized anxiety disorder, and fear, which primarily encompasses more specific anxiety disorders[29].

Epidemiology of Internalizing and Externalizing Disorders

As far as epidemiology is concerned, during childhood and adolescence, the prevalence of the disorders attributed to these two categories is stated to be approximately 20%, with a tendency to endure in early adulthood, despite some substantial modifications[30]. In particular, lifetime estimates of major depressive disorder range from 23.2% to 43.3%, with an average onset between 11 and 14 years, whereas anxiety disorders, which are the most prevalent adult psychopathologies, show a prevalence range from 2% to 24% with a median rate of 8% in childhood and adolescence[31].

Specifically, when considering the epidemiology of anxiety disorder in youths, it has to be specified that Generalized Anxiety Disorder and Social Anxiety have the highest prevalence rates, whereas Panic Disorder and Obsessive Compulsive Disorders tend to be more prevalent in preadolescents and adolescents[32]. The worldwide prevalence of ADHD varies from 1.7% to 17.8%, with a median prevalence rate of 4%, while conduct disorder and oppositional defiant disorder prevalence fluctuates between 5% and 14%[32]. The prevalence of children exhibiting both INT-EXT symptoms shows a range of variation depending on the study population and geographic location. This variation extends from 2.4% in a British sample tracked from childhood into adolescence to 13.7% within the age group of 6 to 12 years in a Canadian cohort, and from 17.8% to 34.4% in a cross-sectional community sample of students spanning kindergarten through 12th grade in four U.S. states[33]. Prevalence rates appear to be strongly influenced by the gender assigned at birth: individuals assigned as male at birth (AMAB) show three times higher risk of developing conduct disorder than those assigned as female at birth (AFAB), whereas the difference is less clear when analyzing oppositional defiant disorder prevalence[32]. Studies indicate no significant variation in depression rates between genders during preadolescence; conversely, in adolescence and early adulthood, the prevalence of

depression becomes notably higher in females compared to males and remains stable in middle adulthood[32].

Overall, it can be stated that AMAB people are more at risk of developing EXT disorders, whereas INT symptoms are more prevalent in AFAB individuals[30]. The reasons for this distinction are not well understood yet. There seems to be a possible biological explanation related to the greater predisposition of AFAB individuals to develop INT disorders[33]; however, social factors underlying this distinction are certainly not to be overlooked. For example, within Western cultural contexts, a significant discrepancy can be observed in the ways emotions are allowed to be expressed by these two genders: AFAB individuals are encouraged from a young age to externalize emotions such as sadness and to experience them in a more introspective manner, while AMAB individuals are expected from childhood to primarily express emotions related to anger and markedly EXT symptomatology[33]. Regarding the incidence of disorders, in the last decade, there has been an increase in INT symptoms, especially during adolescence, in AFAB individuals[34]. More recent data also estimate a worsening of the mental health of AFAB adolescents following the COVID-19 pandemic: the social withdrawal resulting from infection prevention measures seems to have exacerbated latent INT symptoms, leading to an increase in symptomatic experiences among adolescents[35]. In particular, the World Health Organization indicated that the COVID-19 pandemic resulted in a global rise of approximately 27.6% in cases of major depressive disorder and a 25.6% increase in cases of anxiety disorders[36].

The contribution of twin studies in the analysis of developmental trajectories

Twin studies have been used to address the developmental trajectories of INT-EXT disorders and the latent factors responsible for symptoms' stability or changes through time. For example, Haberstick *et al.*[37] have implemented a longitudinal study through which they examined a sample of 382 twin pairs, aged between 7 and 12 years old, by observing annually the development of INT-EXT symptomatology[37]. By applying the Cholesky model, they were able to determine the extent to which shared genetic and environmental influences contributed to the modification of the symptoms in the transition between childhood and adolescence[37]. While EXT symptoms seemed to remain stable during the development of the subjects, the INT symptomatology tended to fluctuate significantly over time because of non-shared environmental experiences. Symptom stability within both INT and EXT disorders was mainly influenced by additive genetic factors transmitted from infancy to adolescence[37].

These results were confirmed by Hatoum *et al.*[38] through a longitudinal study that involved 408 twin pairs aged between 7 and 16 years[38]. To examine the temporal patterns of symptomatic manifestations, the authors applied a Latent Growth Model to the data[38]. This model includes the presence of two latent variables, namely the intercept (I) and the slope (S); the former represents the mean value of the phenotype under study, while the latter indicates its rate of change[39]. Each observed score at each measurement point is thus a linear function of these two parameters, along with the contribution of random error. In a sample from which genetic information can be derived, such as a twin sample, it is also possible to decompose the variance of variables I and S into genetic and environmental latent factors[39]. Through the application of this latest version of the Latent Growth Model, Hatoum *et al.* were able to observe that the intercept values, indicative of the stability of the curve over time, were highly heritable[38]. Genetic influences explained approximately 86% of the variance for INT symptoms and about 72% for EXT symptoms[38]. As for the variance values related to S, they found that the change in the trajectory of symptoms over time was not only due to unique environmental components (thus replicating the results of the previous study), but also to specific genetic factors linked to age[38].

The comorbidity between Internalizing and Externalizing disorders: the p factor

The high frequency of comorbidity rates among psychopathologies has progressively directed research towards a reformulation of their structural model, leading to a thorough reconceptualization of psychiatric disorders. They are no longer regarded as independent entities but rather as portions of a continuous diagnostic spectrum[40]. Furthermore, these epidemiological studies have revealed two different types of comorbidities depending on the experimental design adopted by researchers. Early studies have highlighted a type of comorbidity that faithfully adheres to its definition, meaning the co-occurrence of two or more disorders at the same time. Subsequent longitudinal studies, on the other hand, have allowed the identification of sequential comorbidity, indicating an individual's propensity to develop a specific disorder, as they exhibit signs of a pathological condition within the same diagnostic spectrum at the time of measurement[40]. The categories of INT and EXT seem to account for sequential comorbidity. It has been demonstrated that the portion of variance explained by these transdiagnostic factors is the one that remains stable throughout the lifespan, unlike the specific variance associated with each disorder, which would undergo more pronounced fluctuations over time[41]. Moreover, the estimation of co-occurrence between disorders from different domains has been examined over the years, both through cross-sectional studies and through longitudinal research designs. The former showed that the correlation coefficient between INT-EXT disorders was approximately 0.5, a substantial indicator of the coexistence of symptoms belonging to the two transdiagnostic factors at the time of data collection[42]. Furthermore, longitudinal studies have made it possible to observe the persistence of this correlation over time, thus delineating a pattern of comorbidity referred to as heterotypic. The discovery of this correlation between the overarching category of INT and EXT has led to the hypothesis that there may be a common underlying susceptibility for both transdiagnostic factors. This susceptibility is characterized by a broad set of common etiological factors that would act independently of those specifically associated with each disorder[40]. This hypothesis regarding the presence of a common latent factor underlying susceptibility to various disorders is not entirely new in the realm of the study of the mind. In fact, when tracing the history of psychometric research on intelligence, the hypothesis of the existence of a single overarching factor influencing each cognitive ability, known as the "g" factor, had already been proposed[26,40].

Specifically, as is well known, specific items within psychometric tests measuring Intelligence Quotient correspond to each of the abilities. While variations in scores on each subtest are attributed to specific factors, the correlation between various items is attributed to the "g" factor[26,40]. Likewise, by applying the same concept to the psychopathological domain, the correlation between various disorders is thought to be influenced by the "p" factor, a term first introduced in a study by Caspi *et al.* in 2014[40]. In this study, the authors confirmed the hierarchical structure of the model with the "p" factor at the top, even when incorporating a third symptom category alongside INT and EXT, namely Thought Disorders. These Thought Disorders were typically excluded in previous research because the symptoms associated with them were considered uncommon in the general population[40].

The contribution of twin studies in the analysis of the comorbidity patterns between Internalizing and Externalizing domains

Twin studies have given great support to the exploration of the underlying factors behind the frequent comorbidity between INT-EXT domains[43]. However, the literature exhibits significant variability in findings mainly for two reasons. First, results are greatly affected by the instruments used by the authors to assess the symptoms under study. For example, a finding that recurs throughout the twin study literature reveals that generally, when parent-report measures are used, there is an overestimation of genetic influences on the traits analyzed, a trend not found when self-report measures are used[2,44]. Secondly, estimates can also differ based on the age of the sample under consideration. It is known that human life encompasses various developmental stages, and the environmental context gradually changes. During

childhood, where the family environment predominates, shared experiences are expected to have a greater influence on behavior compared to adolescence or adulthood, where shared family experiences give their way to more individual ones[45]. An emblematic study that clearly exemplifies the mechanism just described is the one conducted by Gjone and Stevenson in 1997, one of the first twin studies investigating the nature of comorbidity between INT-EXT symptoms in childhood and adolescence. The analysis of the authors emphasized a strong contribution of the shared environment as the primary factor determining covariation among transdiagnostic factors, but also a consistent genetic influence that was more pronounced in the adolescent age group[45]. Despite the variability, one clear trend in subsequent twin studies examining this comorbidity pattern is the fundamental role played by genetics in its occurrence. For instance, a study by Cosgrove *et al.* on a twin sample aged 12 to 18 found a high correlation coefficient between the two macro-categories of symptoms (r = 0.72), which was due mostly to genetic and partially to unique environmental factors, explaining 62% and 38% of the shared variance, respectively[43]. As time passed and studies continued, twin research provided us with one of the most significant insights regarding the structure of latent variables underlying the frequent simultaneous occurrence of behavioral and emotional symptoms, indicating the presence of a unique genetic factor at the basis of this phenomenon[46,47]. These results are important as they substantially support the hypothesis of the existence of a single latent factor (the "p" factor) responsible for the latent susceptibility to INT-EXT symptoms. One particularly notable study in this regard was conducted by Allegrini's research group[48]. For the first time, they used twin analysis to determine the genetic architecture of the "p" factor itself, assessing also its stability across different childhood and adolescence age groups. The authors found that the model that best fitted their data was a Common Pathway Model, in which the heritability of the common latent variable was 50%-60%. This finding, despite the significant influence of specific genetic and environmental factors on each phenotype, was fundamental to further confirm the presence of a unique latent susceptibility factor, mainly genetic in nature, responsible for nearly all the symptomatic manifestations[48].

Cognitive Disengagement Syndrome (CDS) CDS: A subtype of ADHD or a distinct disorder?

Although initially emerging from studies assessing the dimensionality of ADHD, it is now evident that CDS symptoms are distinct, though closely associated, with the inattentive symptoms of ADHD[49,50]. The latest research tends towards the attribution of these symptoms to a specific diagnostic category with peculiarities that differ from ADHD. Firstly, the inattention typical of CDS would appear to have different characteristics from that of ADHD. In the first case, the inability to maintain attentive focus would be elicited by internal stimuli, more similar to rumination observed in Internalizing disorders, which would lead the individual to engage more frequently in "daydreaming" compared to the general population. Vice versa, the inattention typical of ADHD appears to be more strongly elicited by external stimuli originating from the environment[51,52]. Secondly, regarding potential pharmacotherapeutic intervention, it has been highlighted that the presence of CDS as the main subtype of ADHD appears to predict low adherence and limited effectiveness to methylphenidate treatment. This outcome would support the hypothesis that a distinction can be made between the CDS dimension and ADHD[53]. Finally, CDS and ADHD also exhibit different longitudinal stability. Vu *et al.*[54], through an assessment of CDS and ADHD symptomatology in a sample of subjects aged 6 to 12 years followed over a period of 7 years, highlighted how hyperactivity/impulsivity and inattention symptoms of ADHD tended to remain stable over time. In contrast, CDS symptomatology showed a declining trend with development, ultimately resulting in its absence in the final measurement, indicating lower longitudinal stability compared to the ADHD control group. According to the authors, this result suggests the actual existence of specific symptomatology associated with CDS, with which ADHD is often comorbid[54].

The comorbidity between CDS, Internalizing and Externalizing Disorders

To date, a growing body of research associates CDS with a variety of psychopathologies and functional impairments[50]. Particularly, the hypothesis that CDS defines a transdiagnostic symptomatology more closely associated with the INT Disorders dimension, rather than the EXT dimension and the diagnosis of ADHD, is widely endorsed[50,51]. The typical CDS symptoms indeed appear to be more strongly correlated with anxiety and depression compared to oppositional and aggressive behaviors[3,55-57]. Moreover, they demonstrate a greater association with suicidal risk, social withdrawal, and peer exclusion compared to ADHD[50,57-59] as well as sleep problems[58,60]. These findings offer a potential interpretation of the results obtained by Harrington & Waldman[60], which demonstrate a limited capacity of CDS symptoms in differentiating clinical presentations of ADHD. Skirbekk *et al.*[61] also conducted a study that investigated the relationship between CDS, ADHD, and Anxiety Disorders in a sample of 141 subjects aged between 7 and 13 years. Participants were divided into four groups based on the presence of ADHD alone, comorbidity between ADHD and Anxiety Disorders, the presence of Anxiety Disorders without comorbidity of ADHD, and the absence of pathology (control group)[61]. The results show higher CDS scores in the group with comorbidity between ADHD and Anxiety Disorders. However, the presence of a significant difference between the group with only Anxiety Disorders and the neurotypical controls suggests the hypothesis of an actual correlation between CDS and Anxiety Disorders, while controlling for comorbidity with ADHD[61]. These hypotheses are supported by the study of Fredrick *et al.* on the relationship between ADHD, CDS, mind-wandering, and rumination, highlighting that, when controlling for CDS, the association between mind-wandering and ADHD appears to decrease, while the association between CDS and mind-wandering remains constant even when controlling for ADHD[52]. A possible interpretation of these data seems to be that the strong correlation observed between ADHD and mind-wandering[62,63] may be mediated by symptoms associated with CDS[52]. Moreover, a significant relationship between ADHD and the tendency for rumination did not appear to emerge. Instead, this tendency seems to manifest prominently and hold particular significance within the symptomatology associated with CDS. According to the authors, this association may provide a foundation for further examination of the comorbidity between CDS and INT[52]. Furthermore, elevated levels of CDS appear to lead to emotional and social difficulties regardless of potential comorbidity with ADHD[54]. In this context, the disorder seems to be linked to an increase in anxious and depressive symptoms, as well as difficulties in the social domain[54,62]. Considering the possibility of defining CDS as a disorder characterized by INT symptoms, Sáez *et al.*[59] evaluated the hypothesis that information provided by parents and teachers might be only partial. Therefore, a more reliable assessment of the disorder may result from the analysis of symptoms reported by both parents and teachers, as well as by the individuals themselves. However, the most interesting finding of this study concerns the significant association between CDS, a tendency towards group isolation, and a preference for loneliness[59].

These factors seem to provide an explanation for the observed correlation between CDS and suicidal risk, which seems to persist even when controlling for ADHD and depressive symptoms[51,59]. The mechanisms underlying the social isolation associated with CDS remain unknown. On one hand, this could arise from the social difficulties related to attentional and emotional regulation deficits; on the other hand, it is equally possible that a preference for solitude makes it more difficult for individuals with CDS to engage in positive social interactions[59]. Although the hypothesis of a potential comorbidity between CDS and INT symptom classes is widely discussed in the literature[54,62,64], further studies are needed to delve into the relationship between these two categories of symptoms.

In contrast to INT symptoms, the relationship between EXT symptoms (such as inattention, hyperactivity, oppositionality, provocativeness, conduct problems, antisocial behavior, and substance use) and CDS is more contradictory. Indeed, several studies highlight that CDS is either positively/ negatively associated or

not associated with EXT behaviors when controlling for ADHD-Inattention[9,64-68]. Specifically, a recent report conducted by Becker *et al.*[69] highlighted that existing studies investigating the relationship between CDS and Externalizing disorders demonstrate the existence of significant, albeit small, associations between CDS and a range of EXT behaviors such as ADHD (across its three presentations), oppositional defiant disorder, and conduct disorder. However, the majority of these associations become non-significant or even negative when co-varying ADHD symptoms[49]. Furthermore, two large nationally representative surveys[4,70] have shown that the most common (and extensively studied) EXT disorder that tends to co-occur with CDS is ADHD. Epidemiological studies seem to demonstrate that in 25-40% of youths with ADHD[4,70,71] and in 46% of adults with ADHD[4], elevated symptoms of CDS coexist. More specifically, in the study conducted by Barkley *et al.*[4], more than half of the participants (59%) exhibited comorbidity patterns between CDS and ADHD, primarily with presentations of ADHD characterized by significant features of inattention, rather than the hyperactive-impulsive type. This aligns with previous studies that have explored this overlap in children[61,64,70] and adults[4]. These findings suggest that the relationship between CDS and ADHD represents a comorbidity between two distinct yet related disorders, rather than a categorization within a single common disorder[69,71].

Furthermore, this comorbidity appears to be associated with increased risks, characterized by the presence of more pronounced symptoms of both disorders compared to what is observable for each specific disorder alone, especially when compared to individuals with CDS only[69,71]. Moreover, examining the existing relationship between CDS and various psychopathological symptoms, some studies have demonstrated that CDS symptoms are strongly associated with Inattention and INT behaviors of ADHD compared to hyperactivity-impulsivity and EXT behaviors of ADHD[49]. While the association between CDS and internalization is robust and generally tends to persist even when controlling for ADHD symptoms, the association between CDS and impulsivity-hyperactivity or externalization often turns out to be non-significant or negative when controlling for ADHD inattention. Despite these findings, the etiology of each of these associations with CDS remains largely unknown and represents an important area for future research on the subject[49].

THE USE OF TWIN STUDY DESIGN TO ANALYZE THE ETIOLOGY OF THE COMORBIDITY BETWEEN CDS AND INTERNALIZING/EXTERNALIZING SYMPTOMS

Twin studies on CDS and Internalizing symptoms

As highlighted in the previous paragraphs, there is a large body of twin literature that has focused on analyzing the underlying causes of the covariance between symptoms belonging to the categories of INT-EXT disorders, which emphasizes the crucial role of genetics in the occurrence of this pattern[43,48,72]. Nevertheless, at present, there are very few twin studies that have been concerned with analyzing this pattern by including CDS within the research design. Regarding the co-occurrence of CDS with internalizing disorders, the only twin study that has been carried out so far is the one conducted by Scaini *et al.* in 2023[73]. More specifically, this work focused on the analysis of the underlying causes of comorbidity between CDS and various anxiety-related phenotypes in a sample of 400 pairs of Italian twins aged 8 to 18 years. From a preliminary analysis, the authors found a significant association between CDS and only two types of anxiety, namely somatic and generalized anxiety.

Therefore, they tested the goodness of fit to the data of the different multivariate models specific to the twin methodology, finding that the one with the best fit was a Common pathway model[73]. This model indicated that the associations between CDS and the two anxiety phenotypes were influenced by a unique latent susceptibility factor whose variance was, in turn, significantly determined by both genetic and environmental common factors.

The results of this work thus highlighted that although CDS and anxiety-related problems represent distinct phenomena at the clinical level, they possess many common etiological factors, consisting of both life experiences and biological predisposition[73].

Twin studies on CDS and Externalizing symptoms

To date, twin studies have mainly focused on the comorbidity between CDS and ADHD, whereas the genetic patterns underlying the co-occurrence between CDS and other EXT have not yet been analyzed. Moruzzi *et al.*[74] have investigated the relationship between CDS, Inattentive Problems (INP), and Hyperactivity-Impulsivity Problems (HIP) in a sample of 398 Italian twins aged 8 to 17 years, highlighting that these domains are correlated both genetically and environmentally, thus remaining distinct[74]. More specifically, in this case, the best-fitting twin model was a Cholesky model, which underlined that the covariation between CDS, INP, and HIP was influenced by additive genetic factors and non-shared environmental factors[74]. In particular, stronger correlations have been highlighted between CDS and INP compared to those between CDS and HIP. Given that genetic correlations between these phenotypes also appear to be significant, the co-occurrence of CDS and ADHD-INP may be attributable to genetic components[74]. Moreover, within the examined sample, symptomatology related to CDS exhibits the lowest heritability, suggesting the plausible influence of environmental factors in accounting for variances in CDS scores among twins, compared to those related to HIP. This underscores the presence of partially distinct etiological patterns between CDS and ADHD[74]. The CDS traits, HIP and INP, still appear to be correlated at both genetic and environmental levels, suggesting that they may share, to some extent, genetic underpinnings and environmental risk factors[74]. This result sustains the hypothesis that CDS might develop from partially different patterns of genetic influence and might be considered a distinct phenomenon, despite sharing some etiological factors with the main ADHD presentations[74]. Another twin study that has examined the relationship between CDS and ADHD is the one conducted by Leopold *et al.*[75]. The authors highlighted a trend of hyperactivity-related symptoms decreasing over time through a longitudinal twin study where phenotypes were measured over a span of 10 years. In contrast, CDS levels tended to increase in opposition to the inattentive symptoms' characteristic of ADHD, which exhibited greater stability. In the analyzed sample, the correlations between CDS and ADHD dimensions were high and stable but always below $r = 1.0$, further confirming the hypothesis that these two disorders would be distinguishable from each other, despite their frequent comorbidity[75]. These findings are consistent with the previously discussed literature about the genetic contribution to the comorbidity of CDS and INT and with the body of literature that emphasizes the need to differentiate between CDS and other psychopathological domains. However, more research is needed to further examine the genetic contributions to the comorbidity between CDS and other EXT domains.

CONCLUSIONS

There is a substantial need for further investigation into the etiology of CDS and its potential classification as a distinct disorder in forthcoming diagnostic manuals. The comorbidity between CDS and INT has been profusely investigated[54,62,64], to the extent that the identification of CDS symptoms as transdiagnostic dimensions of anxiety and depressive disorders has been hypothesized[51]. However, genetic evidence regarding the co-occurrence of CDS symptoms, INT and EXT disorders is limited[40]. Given the evidence of the significant contribution of twin studies in highlighting the genetic influence on the comorbidity between INT-EXT disorders[40], it is important to implement this investigation considering CDS as a distinct nosological entity. Despite the emergence of some evidence in this area[73,74], results provided so far by the existing literature are far from being fully conclusive. Up to now, research on this topic has highlighted that, although having some overlapping genetic pathways with both INT symptomatology and ADHD, CDS might be considered a unique syndrome with significant internal validity[69,70]. Furthermore, as stated above, more research is needed to address the comorbidity between CDS and other EXT disorders.

Future twin studies would be therefore necessary to further deepen the understanding of the comorbidity between CDS and the whole spectrum of INT-EXT symptoms. Overall, the evidence of latent susceptibility between CDS and INT disorders, as well as between CDS and EXT disorders, could be valuable in clinical settings, both for encouraging clinicians to assess and monitor symptomatic manifestations of INT and EXT problems when subjects come to clinical attention for CDS symptoms (and vice versa), and for implementing interventions aimed at modifying the environmental variance in the onset of symptomatology, such as parent-training protocols. Furthermore, evidence concerning the validity of CDS as a stand-alone syndrome would be pivotal in developing specific assessment scales. Up to now, CDS can only be assessed through the use of the *Child Behavior Checklist* (CBCL) developed by Achenbach[76]. This scale assesses CDS through a specific subscale, which includes items "13" is confused or seems to have their head in the clouds, "17" daydreams, gets lost in their thoughts, "80" stares into space, and "102" is not very active, slow in movements, not energetic'[77]. However, despite being useful at addressing the core features of CDS, this scale has some limitations. Firstly, it is composed of only four items, making it impossible to unravel the various dimensions of this syndrome, fully distinguishing it from ADHD, and to ensure great internal validity. Secondly, being a parent report, the CBCL tends to underestimate INT symptomatology while overestimating the EXT counterpart[2]. As literature[2] has shown that the best raters for INT symptoms in childhood and adolescence are the subjects themselves, developing specific self-reports would be pivotal in enhancing the diagnosis of CDS and developing specific treatments and protocols.

DECLARATIONS

Authors' contributions

Conceptualized the work and laid out the manuscript's structural framework: Scaini S and De Francesco S
Carried out the comprehensive literature review: Amico C, De Giuli G
Collaborated on the manuscript's writing: De Francesco S, Amico C, De Giuli G
Played a pivotal role in refining the initial draft through meticulous revision: Giani L
Contributed significantly to the revision of the second draft, particularly focusing on the sections concerning the methodological aspects: Fagnani C, Medda E
Took charge of the final draft revision, providing crucial insights for the article's conclusions: Scaini S
All authors approved the final version of the manuscript.

Availability of data and materials

Not applicable.

Financial support and sponsorship

Not applicable.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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