9 Anxiety Disorders in the Autism Spectrum: Update and Multi-Case–Control Study on Clinical Phenotypes

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9.1 Introduction

Anxiety disorders are nosographic pictures listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). They are characterized on cognitive, behavioral, and pathophysiological levels by an excessive perception of threat in lived situations. According to the DSM-5, fear is an emotional response to an impending danger, whereas anxiety is a preview of a future threat that is responsible for a state of tension and alertness in preparation for actual danger [1]. This condition may affect the general population and be present in numerous and heterogeneous clinical pictures (Table 9.1).

According to the DSM-5 [1], people with level 1 Autism have noticeable issues with communication and social skills. It may be difficult for them to maintain back-and-forth banter during a conversation, and they may find it hard to reach out and make new friends. People who receive a diagnosis of level 1 Autism require support, but often maintain a high quality of life with little support. During school-age, people with a previous diagnosis of Autism spectrum disorders (ASD) report a recurrent presence of anxiety and related worries, which suggests a one-to-one relationship between anxiety disorders and deficits in social skills [2]. Up to 80% of children with ASD also suffer from one or more anxiety disorders. In particular, separation anxiety disorder (SAD) has the highest rate of comorbidity with ASD (38%), followed by obsessive compulsive disorder (OCD) at 37%, generalized anxiety disorder (GAD) at 35%, and social phobia at 30% [3]. In turn, these disorders increase the seriousness of basic ASD phenomenology and may have consequences for social retreat, the sleep/wake rhythm, family interactions, and the ability to adapt to educational activities [3]. Use of specific semi-structured interviews and clinical

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Table 9.1 Anxiety disorders[a]

Disorder	Features
Agoraphobia	Fear or pronounced anxiety concerning two or more situations, such as use of public transport, facing open or closed spaces, standing in a queue or crowd, and spending time away alone
Generalized anxiety disorder	Anxiety or extreme worry (e.g., nervous expectation), shown for most days and at least for 6 months, regarding a significant number of events or activities (e.g., professional services or scholastic results)
Specific phobia	Fear or pronounced anxiety regarding an object or specific situation (e.g., heights, certain animals, seeing blood, flying)
Panic disorder	Presence of frequent and unexpected panic attacks. An attack comprises sudden onset of intense fear or annoyance which reaches a peak in a few minutes
Selective muteness	Constant incapacity of talking in specific social circumstances in which it is normally expected that a person would speak. For such people, it is possible to talk in other circumstances
Separation anxiety disorder	Fear or pronounced anxiety that is inappropriate for the developmental stage, which appears in circumstances of separation from individuals to whom a person is sentimentally close
Social anxiety disorder (social phobia)	Fear or pronounced anxiety related to one or more social contexts where an individual feels exposed to other people's possible judgment. Fear becomes more pronounced in contexts where social interactions are required, when a person feels like somebody is watching them or they are required to introduce themselves to peers

[a]Table prepared according to data obtained from the DSM-5. Obsessive compulsive disorder (OCD) is located beyond the "anxiety disorders" group in the DSM-5. Unlike in previous editions of the diagnostic manual, OCD is now presented as a separate category

questionnaires has revealed that parents' judgment of social anxiety is significantly higher compared with social anxiety reported by affected individuals. This discrepancy between judgments could be a characteristic phenomenon of ASD [4].

Adolescents with Asperger syndrome, which is a low-compromised form of Autism, show significant odds of having an anxiety disorder. This increased prevalence of anxiety may be attributable to higher cognitive functioning, which corresponds to greater awareness of the surrounding environment and therefore greater social involvement with peers [3]. Adolescents who perceive forms of separation anxiety in themselves may also present bizarre behaviors, such as a habit of storing objects for sensory comfort in situations where separation is predicted. This is a common phenomenon, especially in late adolescence, and intense distress is reported in the absence of these objects of comfort [5]. The disorder tends to disappear or considerably diminish after 40 years of age [2].

In this chapter, we examine how anxiety can have different gradients and nuances in clinical pictures of ASD, especially where there is comorbidity with Attention Deficit Hyperactivity Disorder (ADHD), Tourette's Syndrome (TS), or other conditions. We also examine various specifiers that can be useful elements for classifying anxiety disorders. Throughout the chapter, results of recent basic research on the topic are considered.

9.2 Epidemiological Aspects of Anxiety Disorder

Children with ASD have double the prevalence of anxiety disorders compared with children in the general population. They also present variability of anxiety disorders based on different types of ASD. On an epidemiological level, Van Steensel, Bögels, and Perrin identified at least 40% comorbid anxiety disorders in children and adolescents with ASD [6]. In fact, nearly 40% of these children and adolescents showed clinically high levels of anxiety or had an actual anxiety disorder. Specific phobia was the most common disorder (30% of individuals), followed by OCD (17%), social anxiety disorder and agoraphobia (about 17%), GAD (15%), SAD (9%), and panic disorder (almost 2%) [6]. A close relationship between the social environment and anxious symptomatology also emerged, especially regarding forms of level 1 ASD [6, 7]. Another study highlighted that there was a greater frequency of abuse in both school and family environments in children diagnosed with Asperger syndrome or non-verbal disorder, with an overall prevalence of such episodes of about 94% of the studied population [7]. In that study, three-quarters of the parents reported that their children suffered at least one episode of abuse from peers in the year of the investigation; there were reports of bullying (75% of cases), physical or verbal attacks (10%), and real aggression with references to genitalia (15%). Children with low social skills or a diagnosis of Asperger syndrome were the most frequent victims of episodes caused by peers [7].

Prevalence studies indicate that between 11% and 84% of children with ASD suffer significant impairment attributable to anxiety [8]. It has also been noted that depending on the position on the Autism Spectrum, anxiety disorders varied in the degree of impairment and frequency, with a higher prevalence in those with Asperger syndrome and PDD-NOS (pervasive developmental disorder-not otherwise specified). These two groups also suffered panic attacks and specific phobias. Anxiety disorders had a lower prevalence among those who had been diagnosed with ASD with higher clinical impairment [6, 8]. In addition, the problems related to anxiety were more common in those with Asperger syndrome than in actual ASD [8].

White et al. [8] reported that social phobia and OCD were rarely diagnosed in the ASD population. There was a general agreement among clinicians that these symptoms could be explained by ASD; however, new neurological research has considered these disorders as possible comorbidities, highlighting reciprocal relationships between anxiety, sensory overload, and impairment of social skills [8].

It is difficult to identify and measure the symptoms of anxiety disorders in ASD, especially in those with limited verbal skills [9]. It is therefore essential to identify behavioral variations in sleep, changes in appetite, or sudden increases in the expenditure of physical and mental energies. Currently, this is difficult because specific measurement questionnaires are lacking. There is no common agreement among the scientific community about the correct way to measure anxiety or mood disorders in individuals with ASD [9]. A common hypothesis is that patients who prefer ritual activities characterized by high repetition also present baseline levels of greater anxiety. However, no precise relationships between these variables have been demonstrated. In contrast, relationships between anxiety symptoms and behavioral

interferences mediated by recurrent provocative attitudes and negative automatic thoughts have been shown. However, behavioral interferences and automatic thoughts are largely variable and influenced by the environmental context. There may also be a particular frequency of gastrointestinal disorders and a reduced quality of sleep due to the occurrence of specific somatization disorders in individuals with ASD characterized by high levels of anxiety [6, 9, 10].

9.3 Possible Predisposing and Etiological Factors

In current clinical practice, it is often difficult to diagnose and distinguish anxiety disorders starting from the basic inventory of ASD symptoms. It is equally difficult to identify etiological and predisposing factors that are peculiar to ASD per se, but independent from those relating to anxiety disorders. Expressions of anxiety in pediatric age groups are essentially behavioral in nature and can therefore be erroneously traced back to comorbidities, such as oppositional defiant disorder or ADHD [9]. Conversely, in young adulthood, we find greater compensation strategies that tend to contain anxious expressions through strict or schematic adaptive reactions. In ASD cases that present with the onset of anxiety disorder during early childhood, the symptomatology of the two conditions often intensifies following their mutual enhancement [6]. It is therefore essential to extend future research to clearly identify clinical markers that could allow us to differentiate between pure ASD and comorbid ASD and anxiety disorders.

Specific consideration has been given to genetic factors and their etiological role in the expression of both ASD and anxiety disorders. In genetic research, studies on ASD and anxiety disorders follow different branches, although both disorders share some basic genetic factors [11]. Recent progress in molecular biology [12] has highlighted that ASD has a complex and elaborate genetic architecture in which inheritable genes are found [13]. Broadly, these consist of a thousand genes with marked locus heterogeneity [14] whose expression in clinical phenotypes follows complex polymorphisms that can also be determined by environmental epigenetic influences, as demonstrated by studies with monozygotic twins [15]. Many of these genes have yet to be defined with certainty. However, some could explain the alterations in social communicative skills, and others could be related to the development of narrow interests and stereotyped activities [16]. ASD is a polygenic disorder, which could be caused by directly responsible genes or by genes related to anxious manifestations with relative degrees of expression [17–19]. Today, an academic focus is considering factors predisposing gene expressions that vary according to existing environmental influences [20, 21]. It is widely known that there is a continuous mutual interaction between genetic and environmental elements [22]. Parents' social and educational factors and the patient's own behavioral profile could play a role in the expression of the clinical phenotype. As an example, some children with ASD favor selected living environments that require less empathy and social skills because of a profile lacking flexibility or reduced planning capability. However, the cognitive development of these children is

influenced by the environments that they chose [23]. Environmental interactions may explain the marked variance and direct repercussion on specific brain functions [24, 25].

A previous study [26] suggested there was a relationship between neuroimaging volumetric data and anxiety or depression scores reported by parents in a sample of children with ASD that were specifically recruited and underwent magnetic resonance imaging (MRI). Significant correlations between the volume of the right amygdala and anxious symptomatology were identified, highlighting static linear relationships. The study concluded that there were possible connections between anxiety/depression symptoms and right amygdala volume [26, 27]. Shen et al. [28] suggested that compared with controls, people with ASD show an increased volume of cerebrospinal fluid. In the cases they reported, a 15% increase in average fluid content was obtained after standardization of weight, age, and sex. Strong associations between this fluid increase and sleep disorders and deficits in non-verbal skills were reported that were possibly connected with an anxiety disorder. However, an above-average cerebrospinal fluid volume can be found in healthy children at risk for developing ASD. Shen et al. also noted a relative increase in head circumference among the ASD group compared with controls [28]. Further studies are required to determine if there is an etiopathological link between increased cerebrospinal fluid volume and volumetric data for the amygdala.

A recent hypothesis concerns the particular role played by environmental interactions that represent the basis of higher cognitive functions and social skills. The focus of underlying deficits in multisensory integration allows greater characterization and understanding of ASD. Alterations in multisensory processing and integration can be heterogeneous within the Autism Spectrum; specific identification will allow us to investigate the underlying foundations of the disorder and its variants [3]. Two abnormal functional profiles have been identified in relation to sensoriality in patients with ASD: hyper-sensory and hypo-sensory profiles. Forms with a sensoriality that can be evoked by slight stimuli or lower sensory thresholds may be associated with concomitant anxiety disorders, most likely related to sensory overload added to previous social discomfort. Therefore, in clinical forms characterized by hyper-sensoriality, aspects related to anxiety should be carefully monitored and specific therapeutic programs defined.

Another hypothesis linked the presence of ligamentous hyperlaxity to anxiety disorders. Recent studies have concluded that at least 70% of people with hyperlaxity also presented with an anxiety disorder, about 70% of people with anxiety disorder, and 62% with panic disorder also had generalized hyperlaxity syndrome [29]. Ligamentous hyperlaxity may represent a somatic component that shows a peculiar frequency in anxiety and irritable temperament disorders. The relationship between hyperlaxity and anxiety disorder has been considered in both the developmental stage and adulthood [30]. Some authors suggest that the presence of a central connectivity disorder is the source of both hyperlaxity and ASD, where at the same time, there is a reduction in long-range connectivity and an increase in short-range connectivity [31]. Other researchers have related hyperlaxity to alterations in motor coordination and proprioceptive sensitivity.

9.4 Specifiers Influencing Clinical Expression

Age: In the general pediatric population, primary school (age 6–10 years) is the period in which the onset of anxiety disorder symptoms is more frequent, and anxiety often manifests as associated with difficulties in social skills. In the presence of ASD, the onset of anxiety disorders tends to be delayed, particularly during middle school, reaching peak intensity in later years and stabilizing in adulthood [2]. In people with ASD, adolescence may also be undermined by bipolar disorder, which in this age group presents its most typical onset. Borderline personality disorder, especially the early onset forms, is also frequently comorbid with ASD [3]. It has been observed that in ASD the "age" factor may be directly correlated with the magnitude of anxiety symptoms. As patients' average age increases, an increasing level of anxiety and a higher frequency of anxiety disorders are observed [6]. Conversely, other anxious expressions, such as separation anxiety, present with a decreasing frequency with increasing chronological age [2, 6]. It is possible that the expression of anxiety at an earlier age manifests itself more through behavior, and the intensity of repetitive activities may be accentuated by the anxious component.

Intelligence quotient (IQ): A significant anxious component is often present in people with ASD with high clinical impairment and low IQ scores. Although not expressed verbally, this may be associated with behavioral stereotypies or irritability in situations of environmental perturbation. Even in forms of level 1 ASD with low impairment, the manifestations of anxiety may be predominant in various functional areas and greatly affect the individual's life. Detection of low IQ scores has been associated with expressions of anxiety that are more related to social contexts [6]. Anxiety linked to social contexts would be inversely proportional to the individual's social skills and assertiveness [32]. In school age, difficulties reported in social skills often lead to deterioration in interactions with peers. Furthermore, in forms of ASD with low clinical impairment, the inhomogeneity of the cognitive profile (i.e., evidence of bias between verbal IQ and non-verbal IQ) has a direct correlation with the basal level of anxiety. However, this is not observed in high-impairment clinical forms, where the greater homogeneity of the cognitive profile makes it more difficult for the person to implement adaptive skills according to their environment and develop more routinized and standardized living environments. In these conditions, simple modifications to the routine are sufficient to determine an accentuation of behavioral rigidity and provoke irritability or aggressive reactions, from which depressive outcomes can result.

In conditions where cognitive observation has documented discrepancy between verbal and non-verbal skills (i.e., higher performance in verbal skill tests than non-verbal skill tests), there is often an association with depression + anxious disorder. Longitudinal observations from a 6-year survey by Kim et al. [9] reported the development of significant anxiety and mood problems in subjects with a previous discrepancy in cognitive tests [9]. In the school setting, parents' previous finding of sustained levels of anxiety also had a predictive value in terms of worse school performance in teacher evaluations and related family repercussions (depression, findings of impaired affectivity). In contrast, low levels of anxiety were found to

have a predictive value in terms of better school performance independently of reported IQ values [8]. Similar observations allow us to hypothesize that the association with depression + anxious disorder in people with ASD may represent a negative prognostic indicator for the purpose of clinical development in childhood.

Sex: It is known that ASD has a significantly higher prevalence in males than females, with a male:female ratio of about 3:1 [33, 34]. However, it is estimated that in females, there may be a bias involving a sub-diagnosis of ASD in relation to sex-related factors. Females tend to have greater emotional empathy that results in the underestimation of clinical signs characteristic of ASD [35]. It is also known that in the general population, anxiety disorders typically present a high prevalence in females. In ASD, anxiety disorders have a female:male ratio of 3:2 [2].

Moreover, in people with ASD, anxiety disorders are associated with a high frequency of hoarding behaviors in different life contexts, especially among females [5]. In particular, the tendency to hoard is associated with forms of ASD comorbid with ADHD; this tendency may be characterized by difficulties in attention shift, self-regulation disorders, and spatiotemporal planning and organization deficits. This supports the hypothesis of a positive correlation between "pathological hoarding" and anxiety traits, obsessive-compulsive traits, and social impairments [5]. The inability to discard unnecessary objects may be directly proportional to the magnitude of ADHD symptoms detectable in the individual case and may lead to a distinct environmental disorder with disabling effects on daily life, particularly in domestic environments. Preliminary research data suggests that hoarding disorder presents a peculiar association with ASD and with the severity of symptoms such as anxiety/depression [5]. However, in males, anxiety disorder presents more contained hoarding behaviors and less pervasiveness.

9.5 Clinical Phenotypes and Possible Comorbidities

ASD presents a widely heterogeneous repertoire of clinical manifestations. It is known that anxiety may be a symptom inherent to ASD. There is a biunivocal relationship between the social communication deficits responsible for the basic condition and the adaptive alert and thoughts that it involves. True predominant phenotypes can be identified when the anxious symptomatology assumes characteristics such as becoming a group of specific symptoms that impact on clinical expression and have permanence over time. By excluding anxiety conditions that are a common reflection of ASD, we can identify anxious entities to create a comorbid disorder. The proposed interpretative model is based on three main variables: type, intensity, and duration of anxiety symptoms [6].

Various expressions of anxiety can be classified into three main frameworks: (1) social anxiety, (2) anxiety with phobias or excessive worries, and (3) anxiety with obsessive-compulsive traits or repetitive/ritualized behaviors. Varying individual degrees of expressiveness can be highlighted in each clinical picture, from forms limited in intensity and duration to forms with greater interference in daily activities. A clinical picture of comorbid anxiety disorder can be highlighted if four

criteria are met: (a) permanence over time (in the absence of transience), (b) pervasiveness, (c) impact on adaptive skills, and (d) refractory nature to treatments.

Corresponding comorbidities that can be identified are:

– ASD + SAD
– ASD + specific phobia disorder or panic attacks
– ASD + OCD with/without repetitive and ritualized behavior

Figure 9.1 presents a diagram of the three levels of ASD impairment according to the DSM-5, considering the most representative anxiety disorder in each level and taking into account both the condition in which anxiety is reflexively associated with the basic clinical picture, and that in which anxiety flows from a transitory state into permanence, interfering in different neurofunctional areas, thus configuring anxiety disorder comorbidity.

A close relationship between temperament and social anxiety can be highlighted in people with level 1 ASD. In those with temperaments characterized by high empathy, the degree of perception and awareness of others' judgments of behavior that deviates from normality is also more relevant. As the empathy of people with level 1 ASD increases, a linear increase in social anxiety can be observed, particularly in the first decades of life. In temperaments with reduced empathy, particularly in adolescence, there is often a tendency to underestimate or neglect social

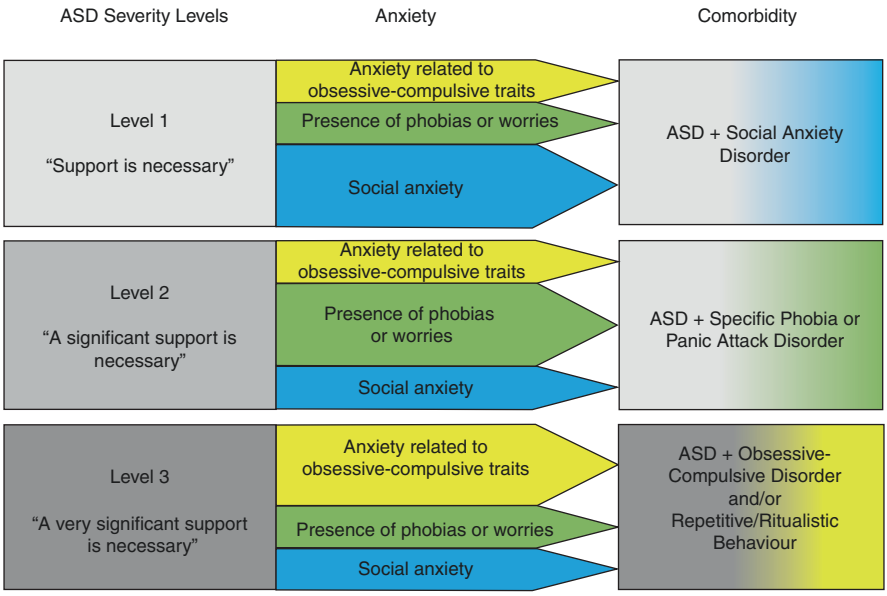


Fig. 9.1 On the left are the main diagnostic levels. At the center are clinical expression pictures with greater relative frequency, represented by the size of the colored arrows (arrow sizes are not statistically related to any data, but are purely explanatory of prevalence). On the right are anxiety disorders that take on a clinical picture of comorbidity

judgment on the part of other people. In addition, presence of the "anxiety disorder + depression" cluster may negatively influence the basic clinical picture, with deterioration in the executive functions and appearance of pathological avoidance. Psychiatric disorders with components of anxiety, obsessions, phobias, and alterations in sleep and mood are frequently found [36]. This phenomenon can be explained in relation to the secondary effects that involve the overlap of diagnostic criteria for different neuropsychiatric disorders described by the DSM-5 [1], even in level 1 forms. However, high levels of social anxiety are present in all of these different conditions. The ability to manage one's emotions is known to contribute to a greater degree of behavioral flexibility and more efficient ability to adapt responses to environmental feedback [32]. A greater awareness of discomfort and the adoption of adaptive compensations within daily occupations and interactions with peers over time [2, 8] are clinically important. As a person ages, a downward trend in social anxiety scores can usually be observed.

The diagnostic criteria for specific phobia/panic attacks are the same for individuals with or without ASD. However, it may be difficult to distinguish conditions in which the symptoms are indicative of an ASD diagnosis, or conditions in which they are due to a specific phobia or panic attack disorder diagnosis. Symptoms of phobia and anxiety are more common in people with ASD than in controls or syndromic children [8]. Factors such as cognitive and attentional deficits, and mood and behavior disorders may explain an altered perception of danger. In addition, in particular situations of risk, there may be a non-perception of danger, which is an indication of greater cognitive impairment; excessive fear can also be detected for common situations or objects in apparently calm situations [6]. For example, it is not clear how much food hyper-selectivity or rigidity toward certain foods can be explained in terms of taste, consistency, a specific phobia, or by the co-presence of several factors.

The presence of a specific phobia in ASD has greater relevance in forms that are the most cognitively compromised. According to parents' and teachers' reports, psychiatric clusters are often identified in ASD in relation to social phobia and specific phobias or to ritualistic and repetitive behavior that may or may not be associated with movement disorders (e.g., motor or vocal tics) [8]. A low cognitive profile may mask and make diagnosis of specific phobias difficult. Overall, specific phobia is the most frequent comorbidity among people with ASD, with a higher prevalence among females [37].

A restricted activity pattern and repetitive behavior is the most representative mode of anxiety disorder with obsessive-compulsive or repetitive-ritualistic traits in ASD. In highly compromised forms, this pattern supports or favors social isolation, as the expressions of anxiety have a predominantly behavioral character in these cases. Strong routines are often found with numerous and persistent daily rituals that support the chronicization of compulsive behavior. These phenomena can only partly be traced back to cognitive deficits that are an expression of ASD, but are explained in highly compromised forms through biunivocal enhancement between cognitive deficits and the poverty of behavioral expressions. It is difficult to differentiate behavioral patterns on an anxious basis compared with those linked to level 1

ASD. Careful observation can highlight an "anxious routine" pattern when it is more associated with changes in mood and irritability. Other elements that can be traced back to this expressive modality of anxiety include the tendency toward isolation and fixity toward common objects or environmental situations that can provide a feeling of reassurance and immutability, but in a way that determines interference by rituals in everyday life. In these cases, difficulty in separating from objects of little use is often reported. These characteristics compromise the level of adaptability to the environment and may lead to progressive difficulty in emotional regulation associated with resistance to change and the need for continuous reassurance [5].

9.6 Connectivity Disorders and Anxiety Disorders

Many studies have noted that some neurodevelopmental disorders can be described as an "abnormal connectivity spectrum disorder" (ACSD) based on the alterations observed at the neural connections network level. This group includes three developmental disorders: ASD, ADHD, and TS. These clinical conditions have extended overlapping and heterogeneity of clinical phenotypes. New evidence suggests that these disorders have significant similarities. For example, experimental studies have identified similarities in reduced long-range connectivity and high short-range connectivity in different brain areas [38]. This new perspective builds understanding about the severity of clinical manifestations through a gradient of altered connectivity. Supported by a neurobiological basis, these three conditions share common symptoms, such as social communication deficits, obsessive traits, Attention Deficit/Hyperactivity, and impulsivity. Diagnosis is usually formulated at preschool age and is more common in males, with deficits in functional and scholastic activity and significant behavioral, emotional, and psychosocial disorders. In cases where two of these disorders co-occur (e.g., ASD/ADHD), functional impairment in the quality of life is more evident than in individuals with a single diagnosis [3]. The co-presence of ASD/ADHD is a particular determinant of clinical levels of anxiety. In parental interviews, threshold scores were a negative predictor for the development of social skills deficits. Kim et al. [9] also found a significant correlation between social interaction difficulties and anxiety/mood disorders; the latter were not correlated with the development of language skills, which is a discriminating element of different ASD levels. Currently, the presence of anxiety disorders associated with depression in ASD is considered a major specifier of the comorbid clinical phenotype and no longer an emotional display of the underlying disorder. The specifier is analyzed through specific entries on structured parental questionnaires. Comorbid conditions are characterized by differences in cognition, motivation, and social awareness, as well as restricted interests and behavioral repetition. More aggressive and oppositional behavior has been documented in the presence of mixed conditions. In 45% of children with ASD, particularly in cases of ASD/ADHD, disruptive behavior disorder or oppositional provocative disorder may appear [39].

Epidemiologically, TS has higher comorbidity in people with ASD than in the general population; 4.6% of patients with TS also have a pervasive development

disorder. However, 22% of patients with ASD show motor tics or Tourette-like symptoms, possibly attributable to the common neurobiological basis that causes a synaptic imbalance overlap [3]. In most commonly used questionnaires, parents of children with ASD report a higher frequency of obsessive thoughts related to technologies (e.g., transport vehicles, television, or computers) than obsessive thoughts about social relationships (e.g., gossip, beliefs). In TS, the content of obsessive thoughts reported by parents is more related to sensory phenomena and, in particular, to passive perceptions of environmental stimuli or sensations related to voices or auditory stimuli [6]. Obvious deficits in social communication and pragmatic skills seem to be largely associated with symptoms of ADHD found in people with ASD [10].

Recent experimental evidence that documents a connectivity disorder is mainly from the neurophysiological and neuroradiological (functional MRI) domain. Clinical phenotypes that show similarities in neuropsychological attention, stereotyped behaviors, and reduced social skills profiles [38, 40] are part of the new set categorized as ACSD. Specific associations between connectivity alteration and cognitive performance alteration have also been documented in correlation with executive functions, attentive processes, and communication skills. In ACSD, connectivity anomalies are linked to white matter anomalies. This can be related to aberrances in afferent sensory pathways reaching the brain, with consequent difficulty in central elaboration [38]. In particular, neurodevelopmental disorders have focused on alterations of the frontal lobes (site of control and regulation of impulses), which leads to atypical regulation and modulation of information from the environment.

The co-presence of reduced long-range connectivity (frontoparietal areas and inter-hemispheric connection) and high short-range connectivity (occipital and orbital-frontal areas) was highlighted by electroencephalographic spectral analysis involving large numbers of people with ASD. Moreover, the same analysis in people with ADHD and TS showed close correlations with dysfunctional symptoms and difficulty in sensory motor modulation [41].

Neuroimaging studies have confirmed the altered connectivity hypothesis. Autism Brain Imaging Data Exchange (ABIDE) data [41] appear to confirm evidence of short-range hyper-connectivity in parietal sites and fibers directed to subcortical nuclei and evidence of long-range hypo-connectivity in cortical-connected or interhemispheric fibers [42, 43]. These experimental results remain of little known value today and need to be contextualized. MRI research has confirmed that in comparison with control subjects, signs of abnormal structural and functional connectivity can be attributed to microglial activation zones. Recently this phenomenon has been investigated on a cellular level, with the hypothesis that connectivity is related to oxidative or toxic-inflammatory stress on myelinated or long-axon fibers of large-caliber neurons (e.g., Purkinje cells). From this perspective, neuronal networks of the dopaminergic or serotoninergic type would be more susceptible as they are normally used to transmit messages over distance through continuous pruning and sprouting processes. Microglial interface areas, rich in glial–axonal junctions, may also be more susceptible because synaptic connections require greater energy expenditure. According to recent hypotheses, the organization of the network of connectome may not only be confined to cerebral nerve tissue, but may

involve other regulatory systems, such as the neuroendocrine and immune systems [44], that are modulated by peptidergic antigens and emotional or antigenic stressors. Molecules in continuous interchange through the blood–brain barrier can influence the activity of immunity cells by determining adaptive or defense responses to the surrounding environment [45, 46].

ACSD may therefore represent an interpretative model of the clinical heterogeneity of neurodevelopmental disorders. In particular, the literature indicates that the overlap among these disorders is high [38]. We have considered "anxiety" in relation to ASD and other two diagnostic categories (ADHD and TS) that belong to the same spectrum, with the aim of better characterizing the phenotypes [39, 47]. We conducted a study that examined anxiety disorders in three groups of patients (ASD, ADHD, and TS) who had received diagnoses according to the current diagnostic criteria.

The objectives of the study were to (1) verify the actual co-presence of anxiety symptoms in different diagnostic groups in relation to a control population and (2) establish how much anxiety coincides with internalizing or externalizing problems in the different clinical pictures. The study used the *Child Behavior Checklist* (CBCL), which is a standardized tool to identify emotional and behavioral problems in school-age children (age 6–18 years) [48].

Similar pictures to those discussed above can be found in the general population. However, the primary objective of our study was to verify if anxiety disorders can have specificity in neurodevelopmental disorders due to the presence of altered connectivity compared with control subjects. The secondary objective was to demonstrate whether there were associations between levels and types of anxiety with an evolution in an internalizing or externalizing way.

A nationwide survey in the United States found a greater presence of anxiety disorders in populations of children who showed neurological disorders than among their peers without this type of disorder [48]. That survey aimed to determine if there were higher levels of anxiety in populations with neuronal disorders, but did not delve into the way in which these symptoms occurred (i.e., externalizing or internalizing). The presentation of symptoms is important, as it can inform the design-specific treatments. However, another study showed that children with Autism tend to show a higher level of anxiety and internalizing symptoms, whereas children with ADHD showed more externalizing symptoms [49]. Although that study considered how the symptoms were presented, it did not consider TS.

Given the findings of the two studies mentioned above, we aimed to verify if anxiety disorders have specificity in neurodevelopmental disorders compared with control subjects on the basis of an altered connectivity model. We also aimed to demonstrate if there were associations between levels and types of anxiety with evolution of clinical problems.

9.7 Methods and Research Design

We analyzed anxiety disorders in three groups of patients who were diagnosed according to current clinical diagnostic scales. The standardized CBCL for school-age children (aged 6–18 years) was used to identify emotional and behavioral

problems [50]. The CBCL is a 118-item measure of parental perceptions of a child's emotional and behavioral functioning over the last 6 months and has sound psychometric properties [50]. The self-report questionnaire is completed by both parents and requires them to rate how true statements regarding the behavior of their child (in the last 6 months and currently) are on a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). There was no difference in administering the checklist to the different groups of patients.

The CBCL allows evaluation of behavioral problems through an "empirically derived" scale that provides information about different syndromic frameworks and a "DSM-oriented" scale that orients professionals toward diagnosis of some disorders according to DSM-5 criteria. The individual items are divided into groups and allow identification of eight clinical frameworks/syndromes: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. These frameworks were grouped according to their belonging to a clinical dimension into three main subscales that provide a dimensional and quantitative measurement of the framework itself: internalizing (anxious/depressed, withdrawn/depressed, somatic complaints), externalizing (rule-breaking behavior, aggressive behavior), and a third subscale representing neither one nor the other. Items for the anxious/depressed scale include *cries a lot, fears, fears school, fears doing bad, must be perfect, feels unloved, feels worthless, nervous/tense, fearful/anxious, feels too guilty, self-conscious, talks about suicide,* and *worries.* On the DSM-oriented scale, items relating to anxiety problems include *dependent, fears, fears school, fears doing bad, nervous/tense, nightmares, fearful/anxious, self-conscious,* and *worries.*

This exploratory study aimed to show the continuity between the different connectivity disorders and the way in which they generate an impact on daily life through the levels of anxiety experienced. With the aim of understanding and verifying similarities and differences in the manifestation of anxiety disorders in the three selected diagnostic groups, we conducted an observational multi-case–control study using four patient samples. Eligibility criteria were:

- A diagnosis of one of the three connectivity disorders (i.e., scores above the cut-off for ASD, ADHD, or TS)
- Aged 6–18 years (according to the CBCL validation scale)
- An IQ above 80
- Agreed to participate in the study

Patients with level 1 ASD were recruited to obtain a homogeneous group in terms of the cognitive profile. Patients with ADHD and TS were recruited according to current diagnostic criteria. In addition, a group of subjects without any diagnosis and with the same age range and IQ was recruited as a control group. At the beginning of the study, 34 patients with ASD (27 males, seven females), 33 with ADHD (28 males, five females), 33 with TS (27 males, six females), and 35 control subjects (15 males, 20 females) were recruited to obtain a sufficient sample size. There were 19 dropouts following the evaluation of the inclusion and exclusion criteria and CBCL testing. This resulted in the effective recruitment of 21 patients with ASD, 31

with ADHD, and 29 with TS. In total, 116 participants were recruited, 84 males and 32 females. Initially, we expected to have a similar number of females and males in each group, but early detection of ASD, ADHD, and TS in females in sufficient numbers at an early age is not yet achieved, as the general prevalence of these disorders is lower among females.

All tests were administered in the Child Neuropsychiatry Department of Verona University Hospital, in specific outpatient areas for neurodevelopmental disorders. The tests were conducted from January 1, 2018 to November 30, 2018 (Fig. 9.2).

Table 9.2 reports the demographic characteristics of the sample and means of the results for the clinical scales in the different groups.

Descriptive statistics were calculated as means and standard deviations for continuous normally distributed variables and median and inter quartile range (IQR) for non-normally distributed variables. Frequencies and percentages were used for categorical variables. To compare the means of the considered variables among the different groups, we used a one-way (case–control status) analysis of variance (ANOVA) and a two-way (case–control status and sex) ANOVA. Post hoc tests were also performed comparing each case status with the control group. For each group (case–control status), the mean adjusted by age was calculated. The analyses were not adjusted for age, as this variable was not clinically different among the groups. The selected threshold level for statistical significance was $p < 0.05$. All analyses were performed using Stata 14 (www.stata.com).

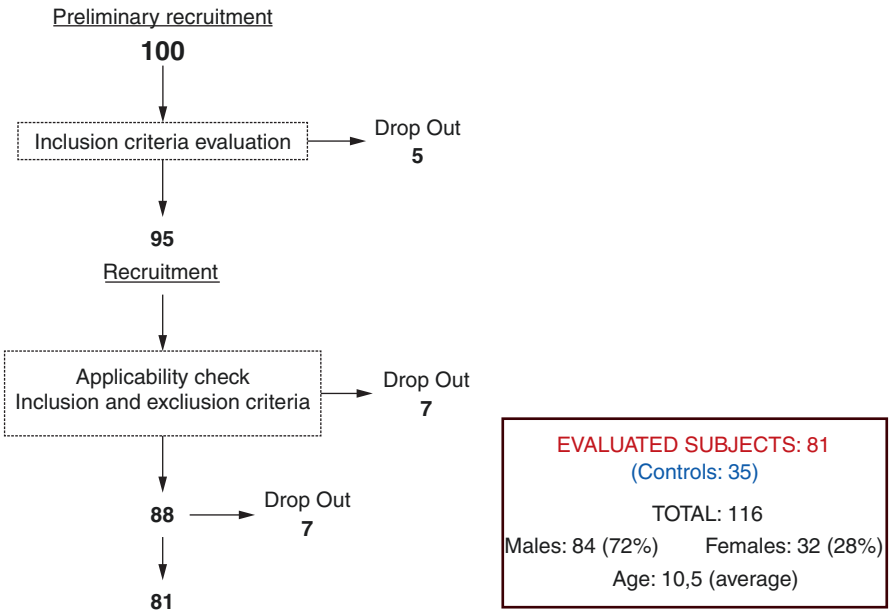


Fig. 9.2 Flowchart detailing the recruitment process, eligibility selection, and dropouts

Table 9.2 Sample characteristics

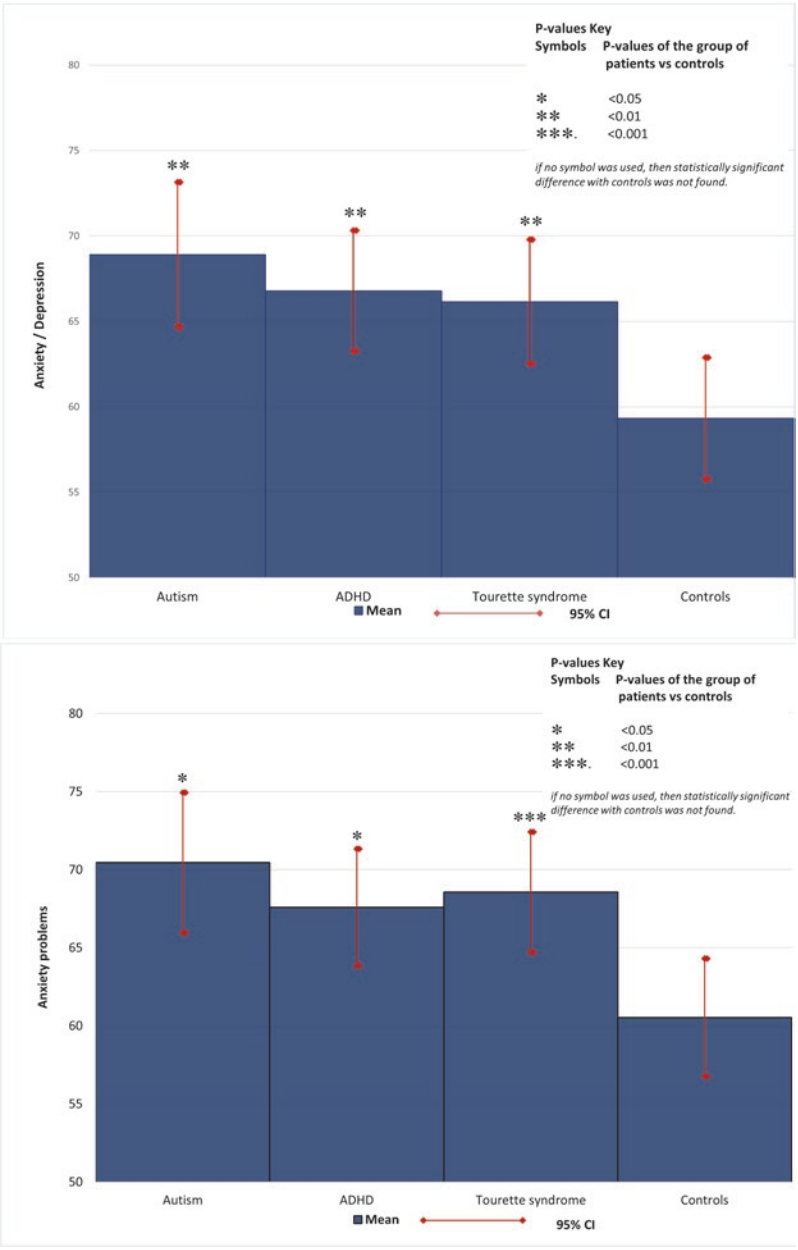
	ASD	Attention Deficit Hyperactivity Disorder	Tourette's Syndrome	Controls	
Patients, *n* (%)	21 (18.1)	31 (26.7)	29 (25.0)	35 (30.2)	
Variables					***p*-value**
	Mean (SD)				
Age, years	10.46 (2.16)	9.9 (2.13)	10.19 (1.92)	11.44 (2.34)	**0.026**
Sex					**<0.001**
Male	17 (81.0)	27 (87.1)	25 (86.2)	15 (42.9)	
Female	4 (19.0)	4 (12.9)	4 (13.8)	20 (57.1)	
Total IQ	93.75 (15.59)	95.29 (16.48)	94.04 (19.47)∗	105.47 (12.33)∗	**0.013**
CBCL scale					
	Median (IQR)				
Anxiety/ depression	70 (66–78)	69 (59–74)	66 (60–72)	57 (51–66)∗	**<0.001**
Anxiety disorders	70 (65–82)	70 (58–76)	67 (61–76)	57 (51–68)∗	**<0.001**
Internalizing problems	71 (68–74)	68 (58–73)	66 (61–71)	59 (54–66)∗	**<0.001**
	Mean (SD)				
Externalizing problems	60.48 (11.48)	63.26 (10.36)	60.62 (10.14)	53.26 (7.71)∗	**<0.001**

CBCL Child Behavior Checklist, *IQ* intelligence quotient, *SD* standard deviation
Note: In this table "Autism" means: level 1 Autism
Bar charts: *p*-values for the groups of patients vs. controls. ∗ <0.05
If there is no sign above the bar in any group, it means that there was no statistically significant difference between that group and the controls

9.8 Discussion of the Findings

In relation to the "anxiety/depression" and "anxiety problems" subscales, two representative graphs are shown below that present the scores recorded in the database. Comparison of the three diagnostic groups with the control group showed a significant difference confirming a functional profile that overlapped on the anxiety/depression axis. In Figure 9.3, we consider the scores for the CBCL subscale that considers symptoms of anxiety (e.g., school phobias, perfectionism, and devaluation of self) and depressive symptoms (e.g., guilt, excessive worry, crying, and excessive jealousy). As the group of symptoms reflected on this subscale is broad and heterogeneous, it may justify the significance in all three groups. Although the significant difference reached a slightly higher range in the ASD group, it confirmed a direct correlation between the type of disorder, underlying neurobiological conditions, and the extent of the manifestation, and resulted in extensive overlap in the three groups.

Figure 9.4 shows the distribution of scores for the CBCL "anxiety problems" subscale. In this case, it can be observed that the prevalence of anxiety problems was



Figs. 9.3 and 9.4 [In these Figures, "Autism" means level 1 Autism]: The values on the *y*-axis indicate the range of the *T* points within which the median scores obtained by the different reference samples fall in relation to the areas (anxiety/depression) or macro-areas (internalizing, externalizing) considered. Up to 65 *T* points, the score is considered standard, a score from 65 to 70 is considered borderline, and scores of 70 and above are considered clinically significant. Such scores may indicate specific problems in each area and provide indications on different syndromic frameworks. Sex-adjusted means and 95% confidence intervals for each group

higher in the three neurodevelopmental disorder groups compared with the control group. In particular, these anxiety problems were associated with self-belittlement, which is a typical repertoire for people with TS. In fact, the reduced fluidity of thought in this condition gives rise to awareness of its own limits, which is followed by either dysfunctional anxiety or addictive behaviors and actions conditioned by obsessive-compulsive traits (e.g., fixation with objects, especially technological objects) [48]. As mentioned in the "Clinical phenotypes and possible comorbidities" section, an anxiety disorder significantly interferes with children's daily school activities, with direct repercussions in different areas of life with psycho-social value.

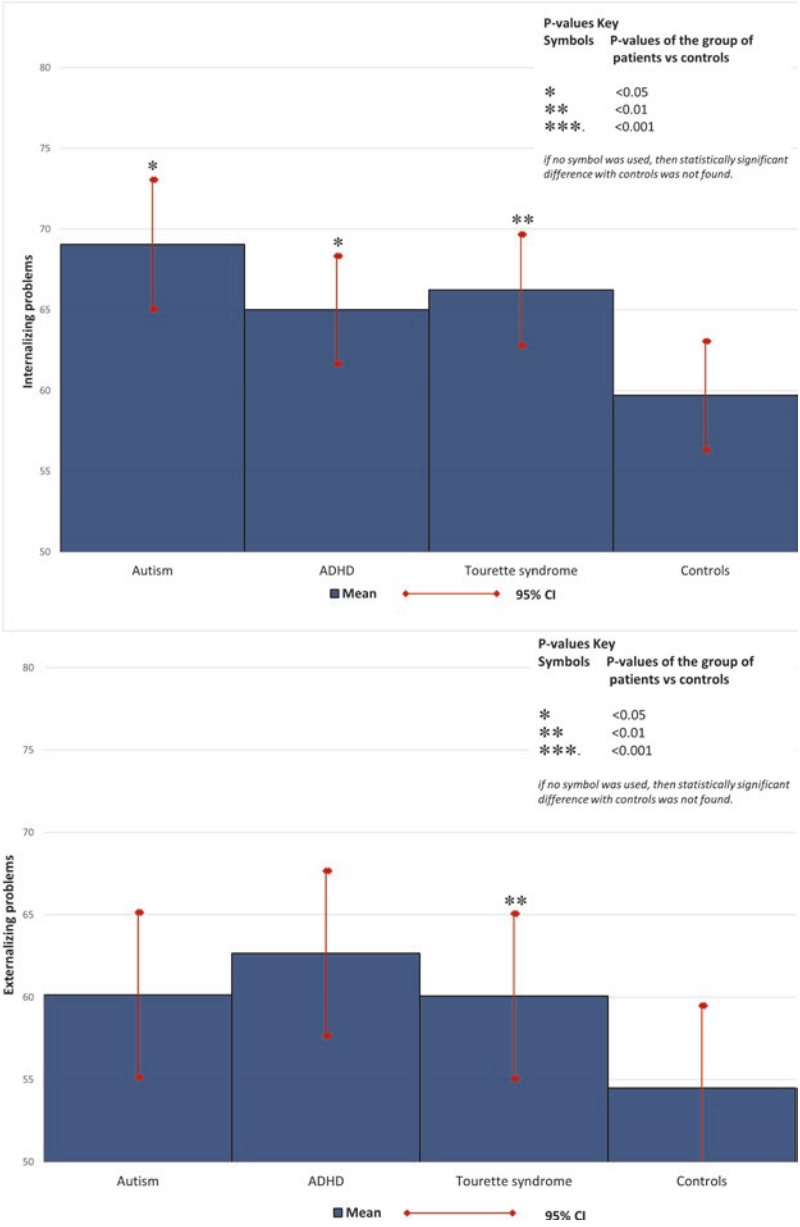
Anxiety disorders can present internalizing or externalizing profiles. In the first case, the disorder is associated with symptoms of inhibition and in the second with greater impulsivity. Our hypothesis was that depending on the type of comorbid clinical picture, anxiety can be managed with a turn toward withdrawal in some cases and a turn toward action in others. In ADHD, ASD, and TS, externalizing manifestations prevail in the presence of the impulsive component. What unites these two manifestations, which appear to be placed at the two extremes, is that both may be atypical reactions sustained by anxiety. In the first case, this assumes characteristics of inhibitory and conversional type, and in the second it assumes characteristics of short response latency or uncontrollable type, or a manifestation of an abnormal management of the response to environmental stressors. The internalizing and externalizing variants justify heterogeneous and overlapping manifestations within an abnormal connectivity disorders condition.

Specifically, in the ASD group, the internalizing component is supported by social anxiety, in which school and social phobia components are more prevalent than the obsessive component. In the TS group, the obsessive trait or reduced fluidity of thought and reduced tolerance of change that are typical of this condition penalize social empathy, thereby recovering social and school anxiety via another pathway. The presence of a significant difference in externalizing symptoms in the TS group may be a consequence of the percentage of patients that present a major component in overlap with ADHD, where the impulsive component prevails over the obsessive component [51].

The results of our study were consistent with those of other works, especially in that the average scores on the CBCL "anxiety problems" subscale were higher in the ASD and TS groups [48]. Furthermore, the average score related to "internalizing problems" was higher in the ASD group, and the average score related to "externalizing problems" was higher in the ADHD group [49, 52]. Comparisons between our analysis of "anxiety/depression" and "anxiety problems" subscale scores (with the three ACSD-related disorders as the reference) and other works are limited, as most of the previous studies considered only two of the three groups we examined (e.g., ASD and TS, or ASD and ADHD). Furthermore, anxiety problems in some previous studies were evaluated using different scales [49].

An important element of our study was the presence of high comorbidity; that is, those conditions in which ASD was associated with other neurodevelopmental disorders [53]. Approximately 30–50% of patients with ASD also show typical ADHD symptoms; conversely, 66% of patients with ADHD show characteristics of the Autism Spectrum [9]. The addition of two or more neurodevelopmental disorders may also significantly enhance the phenomenological expression of the underlying disorder,

especially in the condition of a simultaneous presence of "anxiety disorder" + "comorbidity of neurodevelopmental disorder" + "mood disorder" (Figs. 9.5 and 9.6).



Figs. 9.5 and 9.6 [In these Figures, "Autism" means level 1 Autism]: The values on the *y*-axis indicate the range of the *T* points within which the median of the scores obtained by the different reference samples fall in relation to the areas (anxiety/depression) or macro-areas (internalizing, externalizing) considered. Up to 65 *T* points the score is considered standard, a score from 65 to 70 is considered borderline, and scores of 70 and above are considered clinically significant. Such scores may indicate specific problems in each area and provide indications on different syndromic frameworks. Sex-adjusted means and 95% confidence intervals for each group

9.9 Criticism and Limitations of This Study

In our observational study, we found significantly higher levels of anxiety in the continuous group of neurodevelopmental disorders than in the control group. In addition, we observed some subtle differences between the different disorders. For example, the ASD group showed a significantly higher level of anxiety problems than the other groups. Regarding the form of presentation of symptoms, the groups of children with ASD and TS showed a higher level of internalizing symptoms. Those with ADHD also had a slightly higher level of internalizing symptoms than the control group, but lower than the ASD and TS groups. The TS group showed the highest prevalence of externalizing symptoms, with the ASD and ADHD groups having slightly lower levels. All three groups had a higher prevalence of externalizing symptoms than the control group, which was consistent with previous investigations.

A limitation of our study was that we considered the three diagnostic groups without identifying subdivisions between the pure conditions and comorbidities. The initial aim of our study was to consider overlapping conditions, based on the new definition of ACSD. However, from a diagnostic perspective, the current criteria satisfied the purposes of the definition and inclusion of subjects in the specific diagnostic frameworks. Another limitation was the use of structured interviews completed by parents rather than by patients themselves. A strength of this study was the specific definition of the priority clinical picture, despite the known levels of comorbidities. In particular, in the ASD group, we only selected patients who required low level of support (defined as level 1 according to the DSM-5) to obtain homogeneous samples for language and cognitive profiles.

Another limitation of this study was the number of participants. It is necessary to collect information from larger groups so that the trends are clearer and provide more useful information to determine appropriate support mechanisms for each case. However, only a small number of females were recruited in our study, partly because of the difficulty in early diagnosis in females. Many females with ASD receive a late diagnosis, making it difficult to include them in the studies of children and adolescents. A better system for the early detection of neurodiversity in females is recommended, especially during school age.

The identification of anxiety disorders in different diagnostic groups with the same cognitive and neurofunctional profile, as implemented in this study, allows us to observe how much the anxiety disorder itself, even in people with ASD, represents a condition that stands out and overlaps with the basic symptomatological core. Treatment for the anxiety disorder may also reduce the severity of the general picture, thus allowing a the individual to experience a better quality of life.

9.10 Therapeutic Perspectives

The treatment of anxiety disorders in ASD includes individualized approaches to cognitive-behavioral and pharmacological therapy [54]. Careful clinical observation with a multi-dimensional survey is required to provide a global reading of dysfunctional behaviors and obtain the best therapeutic results. Currently, there are

several tests that can be administered to parents, and extended to operators who work daily with the child. Although several questionnaires are used to detect anxiety disorders in people with ASD, few have been specifically defined for the Autism Spectrum [55].

Numerous studies have shown positive results with cognitive-behavioral therapy (CBT) [55–57]. In CBT, removal of anxiety stimuli and phobias is planned, taking care not to reinforce previous avoidance behaviors. A second phase is then scheduled where the patient is gradually exposed to feared stimuli and contexts, so that rituals or avoidance behaviors can be disfavored. CBT has shown particularly encouraging results in developing adaptive and spontaneous strategies for anxiety symptoms [56]. For anxiety management, three essential modalities are usually adopted: a psycho-educational approach, a cognitive approach, and an anxiety stimuli and phobic thoughts hierarchy approach.

The psycho-educational approach aims to make the patients more informed about the nature of their anxiety disorder, allowing them to obtain gradual and progressive adherence to the proposed therapeutic program. The cognitive approach favors restructuring thoughts, so that the patients can question their own fears and concerns. The third approach starts with the classification and hierarchization of phobic sources based on their anxiogenic properties, followed by gradual and repeated exposure of the patients to these sources to obtain spontaneous and natural reduction of anxiety symptoms. Better results are achieved in CBT when different protagonists are involved, for example, parents, educators, teachers, and other operators who are in close contact with the child with ASD. To achieve a more precise and stable clinical impact on the anxiety disorder over time, the program must be jointly established by a multidisciplinary team. In this way, control and reduction of anxiety can be obtained, promoting greater flexibility with regard to social dynamics. CBT results in an improvement of interactions and finding a modulation more in keeping with the frustrations and unexpected events imposed by daily life and usual conversations [56].

A meta-analysis by Ung et al. [55] also reported positive results of CBT, suggesting that future research on CBT should consider the differences between specific anxiety disorders in individuals with ASD and different pharmacological treatments in individual cases. In a review of patients treated with CBT, Warwick et al. [56] found percentages of positive responses up to 60% and showed that, in many cases, there was inconsistent discussion of the results obtained and questionable comparisons between the different studies. Those authors identified how results were sometimes reported separately based on the individual anxiety disorder and sometimes presented on the basis of anxiety disorders considered as part of a diagnostic group. Apparent differences or similarities in the results obtained can be derived from difficulties in comparing data sets [57]. Although in a majority of cases the responses to CBT were positive, the nature of this therapy requires a medium-long implementation time. In the presence of symptoms that are acute or need to be managed in the medium term, it may still be necessary to resort to traditional psychopharmacological treatments.

Drugs belonging to the selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor categories are at the forefront of psychopharmacological treatment for anxiety disorders. These drugs have proven efficacy for symptoms related to anxiety that cause functional impairment. These drugs have few secondary effects and are free of cardiotoxicity. As second-line drugs, benzodiazepines may be used in specific situations and are especially useful for treating acute GAD and depression-associated forms. The use of drugs from other categories (e.g., antipsychotics, beta-blockers) is rarely considered because of adverse effects on behavior. However, individual responses to these drugs should be carefully monitored by a specialized doctor, so that contraindications or side effects can be identified [56]. Common side effects are sleep abnormalities, anxious paradoxical reactions, or uncontrolled increases in appetite and body weight. Appropriate initial psycho-pharmacological treatment may allow more adequate participation in CBT programs or other possible therapeutic approaches for anxiety disorders in ASD.

9.11 Conclusion

Anxiety disorders affect a significant percentage of the ASD population, presenting predominant characteristics according to the levels of impairment reported by the DSM-5. An "anxiety" symptom, in relation to its gradient, could also represent a transient or reactive condition of the ASD framework or assume an increasingly specific connotation to the point of constituting a comorbid anxiety disorder. Comorbid anxiety disorders have been identified as social anxiety, anxiety with specific phobias or panic attacks, or anxiety with obsessive-compulsive or repetitive-ritualistic traits. The presence of a comorbid anxiety disorder affects the individual's clinical evolution.

It is important that the assessment process for people with ASD uses standardized tools that are shared by the scientific community and precociously recognizes the presence of comorbidity. The identification and management of these problems during the developmental stage could reduce the risk for developing chronicity in adulthood. Containment of the disabling effects of these conditions on individual life paths could eventually allow a better quality of life for individuals with ASD.

Considering the different clinical dimensions (e.g., level of impairment, type of anxiety disorder, presence of comorbidity, degree of empathy, and correlated capacity for emotional management), anxiety in people with ASD tends to show specific behavioral manifestations toward internalizing rather than externalizing problems. In level 1 Autism cases, it is more frequent to find worries and feelings of inadequacy, which are accentuated in social contexts.

Finally, the presence of overlap in ASD with other neurodevelopmental disorders, in addition to characterizing different phenotypic expressions, may sustain or accentuate the anxiety itself, justifying a more complete perspective, according to an ACSD model (Fig. 9.7).

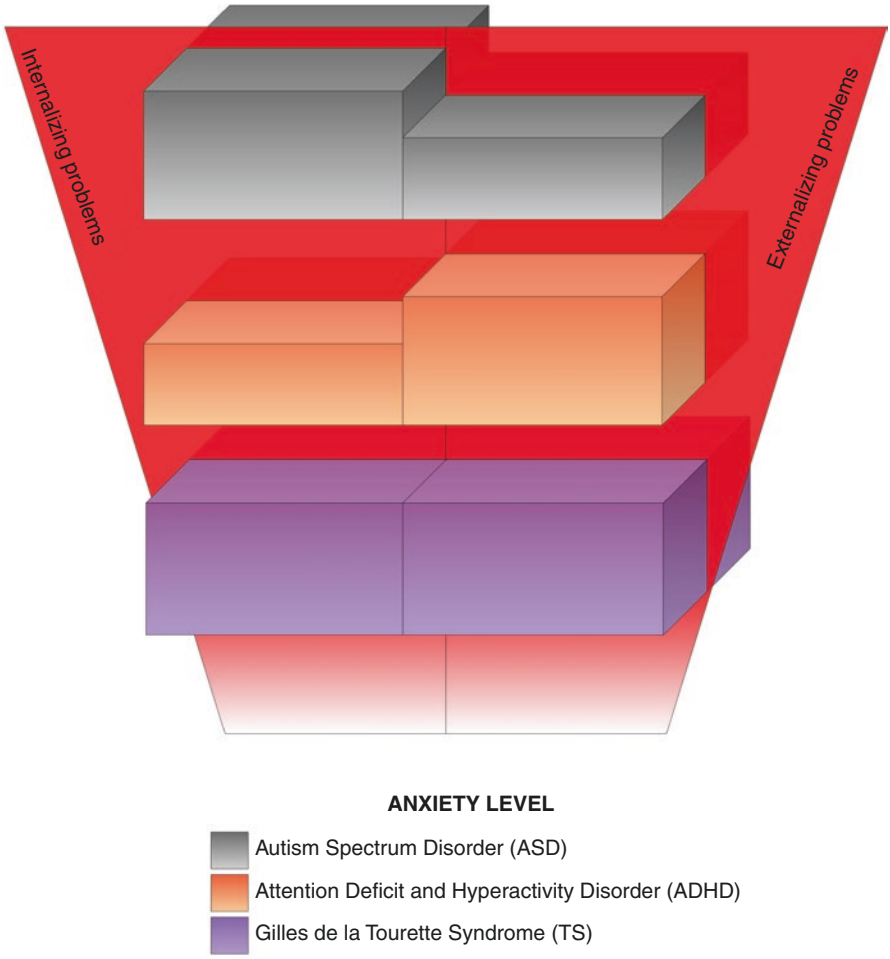


Fig. 9.7 Level of anxiety and predominance of internalizing/externalizing problems in relation to the disorders currently included in abnormal connectivity spectrum disorder (ACSD). Sizes and heights of the figures are not related to any data and are purely explanatory of level and predominance

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