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Review

Relevance of separation anxiety in the autism spectrum and related disorders

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SUMMARY

Symptoms of separation anxiety disorder (SAD) are common among individuals with autism spectrum disorder (ASD) or subthreshold manifestations of the autism spectrum, also known as autistic traits (ATs). However, studies focusing on the association between SAD and ASD are still limited, especially from a dimensional perspective, and even fewer are carried in the adult population. In elucidating the relationship between autism spectrum and separation anxiety, borderline personality disorder (BPD) and feeding and eating disorders (FED), often masking a female autism spectrum phenotype and associated with separation anxiety symptoms, could play an extremely significant role. Specifically, in the relationship between these psychopathological entities, the development of insecure attachment patterns in individuals with autism, possibly due to the known difficulties in communication and social interaction presented by the patient and his family context, could promote the development of SAD and other mental disorders in continuity, such as BPD and eating spectrum disorders. We believe that investigating the relationship between ATs and separation anxiety can clarify the pathogenesis of these two disorders interpreted in the full spectrum of their manifestations and promote understanding of their comorbidities in an integrated model of psychopathology.

Key words: separation anxiety, autism spectrum, attachment, borderline personality disorder, eating and feeding disorders

Introduction

Autism spectrum disorder (ASD) is a condition included in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) within the section of "Neurodevelopmental Disorders" and characterized by a pattern of repetitive behaviors, interests, and activities, associated with difficulties in communication and social interaction[1]. ASD is usually associated with several psychiatric comorbidities, with rates ranging from 70-75%[2] to 83%[3]. Recently, increasing literature has focused on subthreshold forms of ASD, known as (sub-threshold) autistic traits (ATs). ATs are symptoms, behaviors, and cognitive features similar in quality to those typical of ASD patients but do not reach the diagnostic threshold for a full-blown disorder[4]. ATs were first identified among parents and siblings of patients with ASD, where they have been conceptualized as a "broad autism phenotype"[5,6]. However, further studies stressed the presence of ATs in the general population, where they seem to be distributed in a continuum, particularly frequent in specific high-risk groups and clinical populations of patients with other kinds of mental disorders[7-10]. Several studies highlighted the impact that ATs might exert, also when sub-threshold, on quality of life, being a vulnerability factor for developing other psychiatric conditions, including suicidal thoughts and behaviors[4,10,11]. In this theoretical framework, some authors raised the hypothesis that psychiatric conditions should be better conceptualized as "globalopathies", associated with an altered whole-brain organization[12]. According to this hypothesis, a neurodevelopmental alteration may be found at the root of several men-

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tal disorders, whose localization, timing, and severity would interact with other biological and environmental factors in shaping the specific psychopathological trajectory[4]. Among the mental disorders most frequently associated with autism spectrum conditions are anxiety disorders (AD)[13]. The presence of AD in patients with ASD is of specific interest because it is associated with greater impairment in global functioning compared to ASD patients without AD comorbidity[14]. Competing anxiety symptoms may cause acute distress in individuals with ASD, amplify their nuclear symptoms, and cause the onset of aggressive and self-injurious behaviors[15]. Chan et al.[16] found that more than 70 percent of children with ASD met DSM-5 criteria for diagnosing an AD; among them, separation anxiety disorder (SAD) was one of the most frequent.

SAD is a mental disorder characterized by inappropriate, excessive, or abnormal fear or anxiety related to separation from attachment figures[1]. Although the disorder was traditionally associated with childhood, during the last decades, the scientific literature showed how SAD could also be present during adulthood, especially in individuals with other mental disorders, particularly panic disorder[17,18]. These findings led, since the DSM-5, to an alignment of SAD with all other anxiety disorders, extending the diagnosis into adulthood[19]. Adults with SAD are characterized by high levels of anxiety related to separation from major attachment figures (partners, children, parents), and fear of situations that may cause them to become distant or detached, resulting in the constant need to stay close to them and severely impairing social and work functioning[17]. Despite the reported increased prevalence of SAD among ASD individuals, studies that specifically evaluated the association between those two conditions are still very limited. This topic's data mainly comes from broader investigations of AD prevalence in ASD children or adolescents[16,20,21]. While the lack of focused investigations on the relationship between ASD and SAD may be partially ascribed to the reported lower interest of ASD individuals towards social and affective relationships[22], recent authors stressed how ASD subjects might be more likely to develop SAD symptoms due to their greater reliance on a caregiving environment[16]. From this viewpoint, the insistence on sameness and intolerance to change typical of ASD individuals may also imply more significant distress related to separation from caregivers and safe-perceived figures. In addition, considering that among neurotypical subjects, SAD symptoms may arise in the late infancy developmental stages, ASD people may show SAD signs later in life due to developmental delays[16].

Studies on the etiopathogenesis of adult SAD have consistently highlighted the fundamental role of attachment in the etiopathogenesis of the disorder[23]. Specifically, attachment theory asserts that early experiences of dyadic interactions with parents create relational expectations, feelings, and behaviors about oneself and others that become ingrained in the attachment system and influence subsequent social abilities[24]. Through the attachment system, young children can find comfort in being close to their caregivers during stressful situations. In older kids, attachment patterns center on the caregiver's unconditional availability and response, like that of a confidant, rather than the newborn needing to be physically close to them[25]. An unresolved insecure attachment style can therefore lead to the persistence, even in adulthood, of the need for closeness to the caregiver and to the onset of anxious and debilitating symptoms when separated from them[26,27].

Interestingly, various researches have highlighted specific ATs that are most predictive of insecure bonds. Indeed, historically it was believed that children diagnosed with ASD were incapable of developing selective attachment bonds with their caregivers[19]. In times, there has been conjecture regarding the connection between the attachment system capacity of children with ASD and their intersubjective challenges such as eye contact, turn-taking, conversation, joint attention, and other aspects of interpersonal relationships. In this framework, numerous studies have highlighted how the severity of social impairments is correlated with a greater likelihood of failing to form a secure attachment bond[28,29]. However, numerous authors have proposed that while ASD children's challenges with social communication and comprehension influence their quality of attachment, they do not completely prevent the development of attachment connections[30,31]. Simultaneously, many researches have shown how developmental delay, a frequent condition associated with ASD, is a well-established risk factor for insecure attachment[32]. Given the correlation between developmental delay and attachment quality, it is unclear whether it is the cognitive impairment or the severity of autistic symptoms to influences more the attachment process. Prior findings that suggested developmental delay was a better predictor of insecure attachment than the severity of autism symptoms[33-35] however, results of more recent studies are less consistent. In fact, recent studies have shown that, even after adjusting for variations in children's developmental levels, the intensity of autistic symptoms significantly predicted a less secure bond[36,37]. Moreover, attachment theory highlights the influence of the environment in which infants are raised on their neurological development. The degree of baby attachment is influenced by the caregiver's availability, attentiveness, and awareness of the emotional cues sent by the infant. According to the sensitivity-security theory, infants who receive

timely and appropriate care from their caregivers would develop more secure bonds[38,39]. The processes of this transmission center on the capacity of caregivers—as in reflective and mind-based parenting—to concentrate on both their own subjective experiences and those of the newborn[40-42]. In this framework, since the initial theories about the causes of autism, the caregiving environment has been highlighted in this context, especially in relation to the belief that caregivers are not meeting the emotional requirements of the infant[43,44]. While the stereotype of cold, uninvolved parents has long since been disproven, parents of ASD children are frequently shown to have high levels of autism symptoms, particularly deficiencies in socio-emotional reciprocity[5,6]. It is however crucial to stress that the interaction between a kid and their caregiver is a two-way street, with the child's actions influencing the parents' actions and vice versa. Simultaneously, studies looking into the caregiving environment of children with ASD have detailed the challenges of parenting an ASD child. These challenges are much greater for caregivers of ASD children than for those of typically developing children or children with other developmental disabilities, and they include higher stress levels and a higher risk of mental health issues for caregivers[45,46].

Given this premises, it can be suggested that the presence of elevated ATs, and in particular the known difficulties in communication and social interaction presented by the patient and his family context, may influence the attachment style developed by the subjects since the earliest stage, promoting the development of SAD and other mental disorders in continuity.

The link between ASD, SAD and Borderline Personality Disorder

One particularly important condition that over the time has been associated with both elevated ATs, SAD and altered attachment style is borderline personality disorder (BPD). According to the DSM-5-TR, BPD is a mental disorder characterized by impulsive behavior patterns and instability in affect, self-image, and interpersonal interactions[1]. Anxious attempts to prevent actual or perceived abandonment, unstable and intense interpersonal relationships, identity disorders, impulsivity, suicidality or self-mutilating behaviors, affective instability, persistent feelings of emptiness, intense and inappropriate anger, stress-related paranoia, or dissociative symptoms are the core symptoms reported by people with BPD[1].

In recent times, an increasing number of studies are describing symptomatologic overlaps and correlations between ASD and BPD[47]. Recent research has shown that individuals with BPD reported considerably higher results on tests assessing the existence of AT when compared to a non-clinical population[48,49]. Meanwhile, other researchers have proposed that some BPD patients may have undiagnosed ASD, or vice versa[50]. Furthermore, in light of these findings as well as the opposing and complementary gender predominance of the two disorders, some authors have proposed that BPD may occasionally be a manifestation of the female phenotype of high-functioning ASD[47,51]. In fact, more recent research has found substantial commonalities between the two illnesses despite their apparent variances. Specifically, there are some similarities between the two diseases, including a propensity for close and shallow connections – that may reflect the use of camouflaging strategies typical of ASD females[52,53]–, a high prevalence of self-harming activities, problems with verbal and nonverbal communication, social functioning, emotional regulation, and theory of mind[54-56]. Furthermore, individuals with ASD are more prone to encounter harassment, rejection, and other socially stressful or possibly traumatic events due to their social problems and impaired socioemotional reciprocity. This can lead to the development of trauma and stress-related symptoms[57]. Specifically, after experiencing traumatic events of a lesser severity than those specified in DSM-5 criteria A, these individuals with increased susceptibility may develop a unique form of post-traumatic stress disorder (PTSD), called complex PTSD (cPTSD), which is strikingly similar to the presentation of BPD[58,59].

People with BPD also frequently have insecure attachment styles, and many researches indicated that early attachment problems have a significant impact on the development of BPD[60-63]. In particular, studies have shown that fearful and/or preoccupied attachment patterns are the most common characteristics of people with BPD[64-66]. According to theory, every attachment style is linked to a particular pattern of maladaptive affect regulation and interpersonal behaviors, both of which raise the risk of unpleasant emotional experiences[67]. When taken as a whole, these patterns might be interpreted as defensive measures taken to manage relationships that are marked by rejection and inconsistency[68,69]. This interpretation aligns with theories that propose an invalidating childhood environment shapes the fundamental etiological mechanisms of BPD[70-72]. As a result, research confirms the association between the two, with 90% of BPD patients being classified as insecurely connected[73]. Theoretical ideas that insecure attachment could be a vulnerability element in the pathophysiology of BPD possibly fostered by the presence of high ATs, are supported by these epidemiological results.

To this date, the relationship between borderline personality disorder (BPD) and the separation anxiety spec-

trum has only been the subject of a small number of studies. As suggested by the "DSM-5 alternative model for personality disorders," BPD is characterized by the trait facet "Separation Insecurity" within the trait domain "Negative Affectivity," where separation insecurity is defined as "fears of rejection by - and/or separation from - significant others, associated with fears of excessive dependency and complete loss of autonomy"[19]. Several features seem to overlap between the SAD and BPD, including fear of abandonment, the experience of separation events, insecurity of separation, poor ability to establish object constancy, proximity, and distance, and feelings of loneliness[74]. Despite that, a conceptual difference has been pointed out between separation anxiety and BPD's fear of abandonment: while the first often occurs in stable relationships, and the feared separation is frequently perceived as external to the relationship dynamic, such as unexpected accidents or death, BPD subjects often experience fear of abandonment within a pattern of unstable relationships and impulsive tendencies[74,75]. On the other hand, several overlaps between SAD and BPD have been reported in terms of comorbidity[76] as well as of possible shared genetic, biological and environmental risk factors[74,77].

Some studies have shown co-diagnosis rates of BPD in adult patients with separation anxiety disorder up to 25%[76]. Conversely, in patients with BPD, anxiety disorders are a common comorbid condition. In support of the hypothesis of a longitudinal overlap of the two disorders, it has been highlighted how BPD clusters with panic-agoraphobic spectrum disorders in families, indicating common familial factors for both BPD and SAD[78]. Furthermore, common neurobiological alterations have been observed in the two disorders, such as variation within the serotonin transporter gene (5-HTT), which has been associated with both BPD[79,80] and anxiety disorders, panic and SAD[81,82]. Moreover, it has been proposed that oxytocin systemic genetic and epigenetic polymorphism plays a critical role in both anxiety and BPD[83,84] and that the interaction between borderline symptomatology, anxiety, and separation may also be significantly influenced by the brain-derived neurotrophic factor (BDNF) system[85,86]. When it comes to worrying that people will leave, element common of both disorders, whole-genome analyses (GWAS) have produced a promising signal on chromosome 5 corresponding to the gene locus for SERINC5, which encodes a protein involved in myelination[87,88]. This signal has led to the development of a novel biological hypothesis regarding separation-related anxiety in BPD. Lastly, research has demonstrated that a largely shared brain network malfunction between BPD and SAD reflects experiences of attachment trauma, loneliness, and separation anxiety[89,90].

From a dimensional point of view, taking into account the possible changes in symptoms and the trajectory of illness during the lifetime, it is also possible that the different patterns of reactions and fears related to separation between BPD and typical SAD descriptions may at least partially be explained by the history of traumatic experiences that typically characterize subjects with BPD, eventually affecting separation anxiety manifestations and promoting emotional and relational instability[74,91].

The link between ASD, SAD, and Anorexia Nervosa

It should be noted that an association between insecure attachment style and higher levels of separation anxiety has also been reported for eating disorders[92]. These findings are particularly interesting for a better understanding of the possible overlaps between SAD and autism spectrum symptoms, especially considering the increasing number of studies about female ASD phenotypes. Female presentations of autism spectrum conditions are reported to significantly differ from the typical male clinical pictures to which DSM-5 criteria are tailored, often leading to misdiagnoses among ASD women[57]. Females in the autism spectrum, with average or above average IQ, often show lower social impairment due to a greater awareness of their difficulties and a better ability to mask them with social camouflaging strategies[53]. In addition, restricted interests among females seem to be more people/animal-oriented and generally considered more socially acceptable than those typically reported among males, including activities such as spending time with animals, enjoying fiction, or focusing on food and diet[93].

In this framework, many studies support the hypothesis of a possible reconceptualization of some forms of anorexia nervosa (AN) as a female autism phenotype, also stressing among AN patients the presence of greater ATs and of Theory of Mind profiles similar to those typical of ASD subjects[94]. The evidence of a familiar aggregation for both conditions[95-97], along with the higher presence of certain typically ATs in AN patients and in tandem with abnormal eating behaviors in ASD patients, all contribute to the hypothesis of a potential correlation between AN and ASD. Since the initial research to investigate for this association, results showed how AN patients frequently had characteristics common to ASD, such as a compromised social life and an obsession on sameness[95]. The findings of multiple research that have examined the parallels between AN and ASD have strengthened the theory of a correlation between the two disorders throughout time. AN in particular is often associated with characteristics that are also typical

of the autistic spectrum, such as rigidity in set-shifting tasks and global processing, as well as increased attention to detail[98]. Alongside this, there is a lack of emotional processing ability, low emotional intelligence, significant social anhedonia, diminished emotional awareness, and a deficiency in the ability to attribute emotions to facial expressions[99-101]. Even Theory of Mind appears to be compromised in AN, particularly when it comes to complex tasks—a deficit that is one of the most significant characteristics of ASD[102].

Contextually, according to a recent meta-analysis, individuals with eating disorders, are reported to experience higher levels of attachment insecurity when compared to non-clinical controls[103]. In eating disorder populations, the prevalence of attachment insecurity varied from 70% to 100%[104-106]. Subjects with AN, bulimia nervosa, or binge eating disorder showed in several research a greater incidence of avoidant attachment style compared to anxious attachment style[104,107]. According to some authors, issues with early attachment and/or subsequent trauma may interfere with mentalization, which may subsequently alter affect regulation[108]. As of right now, it's possible that restrictive eating, purging, and bingeing are associated with either too under or over affect regulation[109]. Although the type of attachment insecurity is not always linked to a particular eating disorder diagnosis, attachment insecurity has been reported to be correlated with the intensity of eating disorder symptoms across diagnostic categories[110]. Specifically, body dissatisfaction and eating disorder psychopathology are positively correlated with the need for acceptance, an element of attachment anxiety[111-113]. Similarly, relationship obsession and abandonment fear, particularly when manifested as a desire for validation from others, can be particularly problematic attachment-related insecurities that increase the intensity of symptoms associated with eating disorders. Furthermore, one may become more susceptible to the detrimental effects of maladaptive perfectionism, negative affect, and alexithymia if they suffer from attachment anxiety or avoidance[114-116]. Such evidences support the hypothesis that insecure attachment could be a vulnerability element in the pathophysiology of eating disorders, possibly fostered by the presence of high ATs.

Despite the growing body of literature on the link between autism, eating disorders and attachment style, researches focusing on the correlation between eating disorders and SAD is still in its infancy. However, a recent study that compared woman with eating disorders with controls, described how women with eating disorders reported more severe symptoms of separation anxiety throughout life, extending the link between eating disorders and insecure attachment to also symptoms of separation anxiety[92].

Discussion

To date, research on the possibility that the presence of high ATs may influence the attachment style developed, promoting the development of SAD and other mental disorders in continuity, in particular BPD and eating disorders, is still in its infancy. ATs have long been shown to be a risk factor for the subsequent development of numerous psychiatric pathologies and transdiagnostic psychopathological dimensions such as rumination and suicidal ideation. In connection with these themes, there has been recent progress in describing the extent of suicidal risk in people with ASD, including large samples and using control groups and potential risk and protective factors. A large study involved 56.008 self-harm cases and 1.399.356 controls aged 10–19 years and reported that many diagnoses were associated with significantly higher rates of self-harm. Compared to controls, the risk of self-harm was significantly higher in attention-deficit/hyperactivity disorder (ADHD) (OR 3.3, 95% CI 3.1–3.4), anxiety disorder (OR 3.8, 95% CI 3.7–3.9), autism spectrum disorder (ASD) (OR 2.4, 95% CI 2.3–2.6), depression (OR 7.9, 95% CI 7.8–8.2), and eating disorders (OR 3.1, 95% CI 3.0–3.2)[117]. Theoretical frameworks have been developed for understanding increased suicidal risk in ASD that includes ASD-specific risk factors, such as those associated with reduced social communication abilities. Furthermore, more common risk factors for many mental disorders that although not specific of ASD are often found in autistic subjects, like depression, isolation, and rumination have been reported as relevant correlates of suicidality in ASD individuals[91]. Notwithstanding, separation anxiety and attachment patterns also deserve attention as potential risk factors for suicidality[118]. Individuals with ASD show marked attachment responsiveness within the strict circle of significant figures[119]. Proximal responsivity is the responsiveness to affective situations in a close social context, and peripheral responsivity is the responsiveness to affective situations that occur in a more detached context[120]. In a recent study, participants with ASD had significantly lower scores for peripheral responsivity but not for emotion contagion (the emotion contagion reflects the automaticity of mirroring the emotional states of others) or proximal responsivity[121]. In other words, ASD individuals seem particularly sensitive to emotional states within the family context, and factors threatening such family homeostasis may exacerbate separation anxiety reactions, including suicidality[122].

Closing the circle, children with ASD, as patients with SAD, BPD, or eating disorders, could also be at higher risk of developing insecure attachment patterns, eventually due to their difficulties in communication and social interactions and/or due to the presence of simi-

lar difficulties in parents with subthreshold ATs[123]. This factor may subsequently promote the development of SAD symptoms, constituting a further overlap not only between ASD and SAD, but also with BPD and eating disorders, which, in turn, often come together.

Conclusion

Considering the above-reported considerations, deepening the knowledge of the intertwined relationships between ASD and SAD may help clarify the psychopathological framework of both these conditions and their associated spectrum of manifestations, also allowing a better understanding of their patterns of comorbidity and eventually promoting a more comprehensive and integrated model.

To find out which combinations of environmental and personal factors are protective and risk factors for the development of attachment in people with ASD, more research is required. Further research is necessary to resolve conflicting data on the significance of developmental delay and the severity of autistic symptoms. Additionally, studies examining the connection between attachment style and particular autism symptoms should be conducted.

Studies examining the correlates of attachment in children with ASD and the function of attachment as a risk and protective factor for later development and shaping of psychopathological trajectory represent a significant vacuum in the field. Research on the relationship between attachment and behavior and emotional issues in usually developing individuals is well established; however, in persons with ASD, little is known about this relationship. Longitudinal research examining the effects of attachment in people with ASD over the life course, including educational outcomes, relationships with others, and mental health, constitute a substantial gap in the literature. In particular, it is advisable that research takes into account the triangular relationship between ATs, attachment style and symptoms of separation anxiety and disorders that have recently emerged as possible atypical manifestations of ASD, specific to the female gender, such as BPD and eating disorders, which in turn are frequently characterized by insecure attachment styles.

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The authors declare no conflicts of interest.

Ethical consideration

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Author's contributions

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