The Adult Autism Subthreshold Spectrum (AdAS) model: a neurodevelopmental approach to mental disorders

Summary
A growing interest has been devoted to adult presentations of Autism Spectrum Disorders. This led to focus on comorbidity between ASD and other mental disorders, mainly (but not limited to) Borderline Personality Disorders, Post Traumatic Stress Disorders, Mood Disorders and Eating Disorders. The presence of any psychiatric comorbidity can mask ASD, in particular in subjects with no intellectual impairment. To address this psychopathological issue, studies adopting the AdAS questionnaire, an instrument with strong convergent validity with alternative dimensional measures of ASD and excellent internal consistency and test-retest reliability, able to detect subthreshold forms of ASD in adulthood, have been reviewed. Based on these evidences, the Subthreshold Autism Spectrum Model has been developed, which includes threshold-level manifestations but also mild/atypical symptoms of the disorder, gender-specific features, behavioral manifestations and personality traits associated with ASD. This model encompasses, although not coinciding with, the Broad Autism Phenotype. This is a subthreshold form of autism described in the context of the neurodevelopmental trajectory that – starting from autistic traits – might lead to the broad range of mental disorders. Therefore, the Adult Autism Spectrum can be considered a transnosographic dimension. This approach should help to detect individual features for certain autistic cognitive and behavioral patterns that may predispose to other mental disorders.

Key words
Autism Spectrum Disorder • DSM-5 • AdAS spectrum • Subthreshold autism spectrum

Introduction
Autism Spectrum Disorder (ASD) defines a group of early-onset neurodevelopmental conditions characterized by alterations in brain connectivity with cascading effects on neuropsychological functions. Core symptoms include difficulties in communication and repetitive, stereotyped behaviors. While etiopathogenesis of ASD is still unknown, there is a good evidence for genetic correlates. In particular, specific genetic mutations can be identified in about 20% of ASD cases and twin studies estimate an heritability between 64-91%, suggesting the interaction between heritable and environmental factors. These data confirm the seminal findings by Kanner and Asperger, which observed that both first and second degree relatives of children with “autistic disturbances of affective contacts” shared some features with their offspring, such as late speech, mild obsessiveness and lack of interest in human interactions. Furthermore, Asperger found that parents of autistic-like children report characteristics of pedantry, aloofness, social withdrawal and eccentricity. Considering the early onset of these disorders, few studies have been described the adult courses of ASD. In particular, the mild subtype is likely to be underestimated since for a long-time only autism with pervasive intel-
lectual and language disabilities as well with severe impairment in human interactions have been diagnosed 7. However, the interest on the milder forms and adult courses of disorder, previously labeled as Asperger's Disorder, has recently increased, with a focus on the high rates of comorbidity between these conditions and anxiety, mood, psychotic, trauma and stress related disorders. Moreover, the DSM-5 it introduced the diagnosis of ASD 18 with different levels of impairment. This radical change reflects the choice to classify psychopathology on the basis of both observable behavior and neurobiological measures, linking symptomatic manifestations with brain functioning 17.

The aim of this paper is to introduce a novel psychopathological model - the Subthreshold Autism Spectrum Model - broadening and redefining the dimensional approach introduced by the DSM-5. This model has been developed in the broader framework of an international Italy-USA research project (Spectrum Project), whose aim was to apply a Spectrum Model approach to mental disorders, giving relevance not only to proper criteria but also to subthreshold symptoms and signs, behavioral manifestations, atypical features, temperamental traits. This new approach has been proved to be quite accurate for understanding the clinical features, course and comorbidity of most mental disorders, and the continuity between general and clinical populations 9-10.

The AdAS questionnaire

The interest on a dimensional model for autism has considerably increased, since several authors highlighted the usefulness of such approach 11-13. Therefore, several psychometric instruments aiming to assess autistic symptoms as continuous dimensions have been developed 14-16. Manifestations of ASD may vary depending on different factors: severity of the autistic symptomatology, developmental level and age and this degree of intensity is reflected by the diagnostic category of Autism Spectrum Disorders 1. According to DSM-5, some individuals with severe ASD may completely lack spoken communication, while others may show normal speech with impaired use of language for reciprocal communication. Core diagnostic features are usually more evident during the developmental age, since interventions and acquired compensatory strategies may disguise several difficulties during adulthood. These factors defined the classical form of autism as a "disorder of childhood", although these do not reflect the variety of clinical practice. For example, an adult patient with ASD may show fluent language during clinical interview, with subtle impairment in eye contact, prosody, body posture and face expressivity. Therefore, patients with low level of cognitive impairments, when living in an environment matching their interests and skills, can report low level of impairment and can be underdiagnosed and undertreated. The ASD is usually recognized (and recognizable) during early childhood, although some individuals with ASD might seek clinical assistance only during adulthood with other diseases in comorbidity. In particular, this is frequently the case of patients with no language or intellectual impairment and high (or medium-high) levels of functioning. The prevalence of ASD is growing across all age groups, with a particular rise in the number of adult cases: this might be correlated to changes in diagnostic criteria as well as with greater awareness of autism 17-18.

Patients with ASD have a reduced coping ability to stressful life events and they are at higher risk to develop other psychiatric conditions, such as trauma and stress-related conditions besides mood, eating and anxiety disorders 19-26, but their relative good level of social and cognitive functioning can impact of help-seeking and diagnostic delay.

Comorbidity between ASD and other mental disorders has been described quite extensively, highlighting that other mental disorders in comorbidity in subjects with lower levels of cognitive impairments and mild symptoms 20,24-25,27-29 can hide ASD. The need to carefully evaluate the presence of autistic symptoms both in clinical samples and in the general population has often been stressed in literature since autistic traits may impact on the clinical presentation of other mental disorders and may be a risk factor for other disorders or towards suicidality 24,30.

Available instruments mostly assess ASD in a quantitative way, such as the Autism Spectrum Quotient (AQ) developed by Baron-Cohen 14-16. "Restricted and repetitive interests and behaviors" have been recognized as a core feature of ASD 1, although this dimension has been poorly evaluated in the existing questionnaires. Moreover, available questionnaires have been tailored on male patients with ASD. As a result, the profile of female patients with ASD has disappeared from the current nosography and from the range of detection of most instruments 31-35.

In order to address such limitations, the Adult Autism Subthreshold Spectrum (AdAS Spectrum) 38, a 160-items questionnaire for adult subjects with normal (or above normal) intelligence without language impairment, has been developed. In line with the Spectrum-Project 8-10 approach to psychopathology, the AdAS Spectrum refers not only to the core manifestations of the disorder, but also to the attenuated and atypical symptoms, the personality traits, and the behavioral manifestations that may be associated with ASD but that may also be present in...
subthreshold or partial forms. In developing the questionnaire, great attention was given to the female phenotypes of ASD as well as to the sensory reactivity area of symptoms. In the questionnaire, some gender-related manifestations have been included such as the tendency of female patients with ASD to mitigate social symptoms by imitation and by acting as someone socially successful. Another gender-related feature is the avoidance of social interactions and the preference in engaging in creative solitary activities, in spending time with pets, or enjoying fictional media. Moreover, female patients with ASD are usually able to recognize their own social difficulties, and consequently develop intense anxiety in social situations and avoidance behaviors, therefore, some social anxiety-like behavioral features have also been included in the questionnaire 36-37.

The questionnaire includes 160 items, grouped into seven domains allowing the evaluation of a wider spectrum of manifestations of autism. Items’ responses are binary (yes/no) and domain scores correspond to the sum of positive answers. The “Childhood/adolescence” domain includes symptoms related to early developmental phases (such as, being very quiet or unable to speak at all, avoiding eating or playing with other children or being teased or bullied). The “verbal communication” domain covers features of the speaking behavior, the preference for media communication, difficulties in participating in a conversation. The “non-verbal communication” domain explores difficulties in eye-contact and in physical contact, the presence of anger outbursts. The “empathy” domain explores impairment in understanding and interpreting facial expressions, intentions or thoughts, but also the presence of intense attachment to pets or objects. The “inflexibility and adherence to routine” domain includes difficulty in understanding the subtle aspects of verbal communication, insistence on sameness and habits, unwillingness to eliminate useless objects, tendency to follow specific procedures. The “restricted interests and rumination” domain includes the tendency of talking about few preferred topics and being fascinated by numbers, the incapacity to be concise, and the tendency to waste time over details, to lose track of time and to take refuge in day-dreaming. The “hyper/hypo-reactivity to sensory input” domain explores the tendency to over- or under-react to stimuli such as textures, smells, noises, temperature and pain.

The AdAS Spectrum questionnaire – although evaluating the presence of features belonging to ASD psychopathology – it has not been developed as a diagnostic instrument. It aims to assess the presence/absence of a broad variety of clinical manifestations associated with ASD or that can be present in individuals not fulfilling the diagnostic threshold. The duration, the clustering and the severity of criterion symptoms, mandatory to make a diagnosis according to the DSM-5, cannot be defined using the AdAS Spectrum questionnaire. However, this assessment tool allows to define, assess and evaluate, together with the typical aspects of ASD, a wider area of clinical and non-clinical manifestations, with a specific focus to some gender-specific elements 39.

In its validation study, the AdAS Spectrum questionnaire was administered to subjects endorsing at least one DSM-5 ASD symptom criterion, patients with Feeding and Eating Disorders (FED) and healthy controls. The AdAS Spectrum questionnaire has an excellent internal consistency, a good test–retest reliability, and a strong convergent validity. Although performing differently among the three groups, the questionnaire showed a good sensitivity in identifying subjects expressing either a full or a partial phenotype (i.e., only one symptom criterion) of ASD 39.

**Toward the adult autism subthreshold spectrum: ASD, Borderline Personality Disorder and Post-Traumatic Stress Disorder**

Several studies highlighted a certain degree of resemblances between ASD and Borderline Personality Disorder (BPD) 40. Core symptoms of BPD do not seem to be closely related to those of ASD, being mainly characterized by impulsivity with a pattern of instability of interpersonal relationships, of self-image, and of affects. Stressful situations and difficulties in managing anger may elicit anticonservative behaviors, such as threat and self-injuring, suicidal thoughts and behaviors 1. However, ASD and BPD might show a significant overlap when considering patients with ASD and lack of cognitive impairment. In fact, impairments in social functioning, miscommunications, incorrectly assumed intentions and emotionally outbursts, which are core features of ASD, are frequently observed in patients with BPD as well. On the other hand, the focus on emotive actions and the establishment of intense relationships and superficial friendships, typical features of BPD, might also be observed in ASD presentations. The similarities between the two disorders also involve neurocognitive functioning: neuropsychological studies targeting the recognition of facial emotions and prosody have found that both subjects with ASD and BPD show similar difficulties in Theory of Mind tasks and in understanding emotions 40-44. The relationship between ASD and BPD addresses also the trauma and stress related psychopathology. Subjects with ASD suffering from chronic exposure to traumatic events may develop a peculiar post-traumatic phenotype known as Complex PTSD (cPTSD), characterized by emotional liability, long-term instability in in-
terpersonal relationships, unstable self-perception and maladaptive behaviors, substance abuse and self-injuring. Due to this peculiar clinical presentation, these subjects might be misdiagnosed as BPD patients. In this framework, it is noteworthy that the prevalence rate of BPD in patients with ASD is 10.6%, while the prevalence rate of ASD in patients with BPD is about 15%. Moreover, a recent study showed a positive correlation between autistic spectrum symptoms and suicidality among BPD patients. Furthermore, not only full-blown ASD, but also subthreshold autistic traits might enhance the overall suicidality, including both suicidal thoughts and attempts, in BPD subjects. Higher levels of autistic traits have been found in BPD subjects who report a history of abuse (physical or sexual) than in those without a history of trauma. Subjects with full-blown ASD are often bullied or suffer from violence and sexual abuse, and these experiences are also very frequently reported by BPD patients. Subjects with subthreshold ASD may both face a higher risk of exposure to trauma and have an increased vulnerability to the effects of the trauma, resulting in higher rates of PTSD and BPD-like symptoms. On the other hand, PTSD symptoms may include a feeling of detachment from others and a decreased interest in significant activities, which can be similar to autistic symptoms. The high level of autistic traits found among subjects with a history of physical/sexual abuse might be interpreted both as a risk factor for being target of certain behaviors and as a consequence of stress-related abuse.

It has been reported that patients with ASD may be often exposed to traumatic experiences and they may be likely to develop PTSD. Moreover, a growing body of data shows that individuals moderate forms of ASD, often come to clinical attention when other mental disorders arise. Takara et al. recently found a prevalence rate of ASD of 16% among first-visit depressed adult patients, while Kato et al. reported a 7.3% rate of previously unrecognized ASD among suicide attempters hospitalized. It has been shown that suicidal thoughts and behaviors seem to be common in young patients with ASD, and these are associated with the presence of depression and PTSD. It should be noted how individuals with ASD may represent a low-resilience group that could be prone to develop Trauma and Stress Related Disorders. Moreover, it has been reported that following the exposure to a natural disaster, the ability to cope with stressors decline faster over time in ASD than in healthy control subjects. To explore the relationship between PTSD and ASD in the framework of the AdAS Spectrum model, the Trauma and Loss Spectrum Questionnaire (TALS-RS) and AdAS Spectrum have been administered to a sample of 134 parents of children diagnosed with epileptic syndrome. Higher PTSD rates were found in women compared to men, with a 10.4% of parents (mothers: 13.3%; fathers: 4.5%) presenting PTSD. Mothers reported higher scores of the TALS-RS compared to fathers in the reaction to loss or traumatic events domain. A significant correlation between the TALS-RS and the AdAS Spectrum domains was found in the subgroup of fathers. Similar findings have been found by Cernvall et al. in parents of children on cancer treatment, showing how avoidance behaviors and ruminations were positively correlated with PTSD and symptoms of depression. Ruminations represent a nuclear feature of PTSD, but they are a transversal symptom, present also in major depression, PTSD and ASD.

Eating Disorders: the issue of phenotypes

Several studies have been focused on the overlap between the clinical characteristics of ASD and Eating Disorders (ED). Since the early conceptualization proposed in the ‘80s by Gillberg, suggesting that Anorexia Nervosa (AN) should be conceptualized as an empathy disorder on the same spectrum of autism, research on the link between ASD and eating disorders has evolved. More recently, many studies confirmed the overlap in behavioral and cognitive features between AN and ASD. It has been noted that rigid attitudes and behaviors are typical features of AN, which can be seen as resembling the unusually narrow interests and repetitive behaviors in ASD. The main difference is that “insistence on sameness” in AN patients becomes mainly focused on food or weight. The overlap in cognitive features is quite extensive, as both ASD and AN show difficulties on advanced “Theory of Mind” tests, deficits in emotional intelligence, social anhedonia, poor performance on tests of set-shifting, and excellent skills on tests on attention to details. The behavioral and cognitive similarities are confirmed on a neurobiological level, as both ASD and AN are correlated with atypical structure and functioning of the fusiform face area, superior temporal sulcus, amygdala, and in the orbitofrontal cortex, which are involved in social processing. ED could share some traits of both ASD and Obsessive-Compulsive Disorder (OCD) in terms of obsession for proper nutrition, focus on weight loss, concern and rituals about food and food consumptions, rumination about eating. These patients are at risk for social isolation due to their sense of moral superiority and their intolerance to others’ food beliefs. These intrusive features and behaviors share some similarities with deficits in social-emotional reciprocity, restricted and repetitive patterns of behavior and interests, and inflexible adherence to routines, that are typical of patients with low levels of autistic spectrum disorder. On the other hand, in
subjects with ASD an higher rate of eating problems has been reported since childhood, and the most frequent pattern appear related to food selection. The tendency to be over-selective or have an aversion to specific textures, colors, smells, and temperatures and to show rigidity to specific foods is associated with an increased risk toward underweight condition. Recently, it has been conducted a study with 138 ED patients and 160 healthy control participants (HCs) assessed by the SCID-5, the Eating Disorders Inventory version 2 (EDI-2) and the AdAS Spectrum. ED patients showed significantly higher AdAS Spectrum total scores than HCs, confirming previous studies. Moreover, ED patients showed higher scores on all AdAS Spectrum domains with the exception of “non verbal communication” and “hyper/hypo-reactivity to sensory input” with binge eating/purging subtype of AN (AN-BP) participants, and of “childhood/adolescence” domain for AN-BP and with binge eating disorder participants. Subjects with restrictive AN scored significantly higher than subjects with binge-eating behaviors on the AdAS Spectrum total score, and on the “Inflexibility and adherence to routine and Restricted interest/rumination” AdAS Spectrum domain scores. Significant correlations emerged between the Interpersonal distrust EDI-2 sub-scale and the “non verbal communication” and the “restricted interest and rumination” AdAS Spectrum domains; as well as between the Social insecurity EDI-2 sub-scale and the “Inflexibility and adherence to routine” and “restricted interest and rumination” domains. These results suggest the presence of a continuum across ED diagnostic groups, featuring also different degrees of severity. This discrete continuum confirms the strong psychopathological overlap between ED and ASD, corroborating the possible conceptualization of ED, and in particular of restrictive ED, as a part of the “female ASD phenotype”.

The Subthreshold Autism Spectrum Model

Based on these data, the Adult Autism Subthreshold Spectrum Model has been developed. This is a comprehensive psychopathological theory including the full-blown symptoms, mild and atypical manifestations, behavioral traits, and personality features associated with the ASD diagnostic category. These traits can be risk factors for other mental disorders, being distributed across a continuum from normality to pathology and including also positive aspects of neuroatypicality, such as originality, creativity, divergent thinking. ASD manifestations often overlap with other mental disorders leading the investigations on a possible link between the AdAS spectrum and the full-blown clinical manifestations of mental disorders. This model might have a huge impact in clinical practice, as AdAS instruments might help both to early detection of high-risk subjects and to identify ASD in different clinical presentations.

However, the AdAS Spectrum questionnaire – and its Model – allows investigations about the relationships between autism spectrum and other mental disorders, leading to a better understanding of psychopathology. The Subthreshold Autism Spectrum Model and AdAS questionnaire could be also employed for investigate the genetic basis of autism. In fact, the DSM-5 still separate what should be considered autism, and what should not and the DSM-5 criteria for ASD disregards atypical manifestations and more subtle phenomena such as the broad autism phenotype or the subthreshold autism spectrum. Although general population obviously do not generally meet ASD criteria, it should not be forgotten that it does share genetic underpinnings with the clinical population. The AdAS Spectrum approach could allow to test a wider range of endophenotypes in order to better investigate the genetic basis of ASD. The Subthreshold Autism Spectrum Model has the potential to overcome the descriptive artifice of comorbidity. Considering the shared genetic risk and overlapping clinical features of different mental disorders with ASD, it should be noted that a neurodevelopmental deviation may represent a common vulnerability factor for the majority of mental disorders. The severity and the specific morphological features of the neurodevelopmental damage would lead to different grades of neuroatypicality, resulting in different psychiatric disorders. Such an hypothesis is consistent with the definition of psychiatric disorders as “globalopathies”, involving not only some specific brain networks, but the whole-brain organization, on the basis of a pathological neurodevelopmental trajectory with different outcomes. According to this model, the AdAS Spectrum questionnaire might allow to assess some broad dimensions, which could predispose subjects to develop different kinds of clinical presentations. In this framework, some features associated with autistic psychopathology (such as ruminative thinking, social withdrawal, rigidity, perfectionism, social phobia, anhedonia, lack of empathy) might be reconsidered as an autistic core shared by different kind of disorders, reflecting the high rates of comorbidity between ASD and other mental disorders. The AdAS Spectrum Model can be considered a transnosographic dimension involved in different conditions. This should allow clinicians, by using the AdAS Spectrum assessment, to shed light on the physiopathology and clinical course, as well as on possible treatment response, of most mental disorders.

Conflict of Interest

The authors have no conflict of interests.
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