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

L. Dell'Osso[1], D. Muti[1], B. Carpita[1],
I.M. Cremone[1], E. Bui[2], C. Gesi[1],
C. Carmassi[1]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy;
[2] Massachusetts General Hospital & Harvard Medical School, Boston, USA

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 [1].

While etiopathogenesis of ASD is still unknown [2], 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 [4]. These data confirm the seminal findings by Kanner and Asperger [5], 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 [6] 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-

Correspondence

Liliana Dell'Osso
Department of Clinical and Experimental Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy
• E-mail: liliana.dellosso@med.unipi.it

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 expres-

sivity. 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 careful 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 daydreaming. 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 psychopahtology. 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 [45]. Due to this peculiar clinical presentation, these subjects might be misdiagnosed as BPD patients [19 46].

In this framework, it is noteworthy that the prevalence rate of BPD in patients with ASD is 10.6% [47] while the prevalence rate of ASD in patients with BPD is about 15% [48]. Moreover, a recent study showed a positive correlation between autistic spectrum symptoms and suicidality among BPD patients [44]. 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 experrriences are also very frequently reported by BPD patients [49-51]. 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 [52]. 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 [44].

It has been reported that patients with ASD may be often exposed to traumatic experiences and they may be likely to develop PTSD [53]. Moreover, a growing body of data shows that individuals moderate forms of ASD, often come to clinical attention when other mental disorders arise [30]. Takara et al. [24] 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 [30]. It has been showed 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 [53]. 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 [19].

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 [54]. 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-SR compared to fathers in the reaction to loss or traumatic events domain. A significant correlation between the TALS-SR and the AdAS Spectrum domains was found in the subgroup of fathers [54]. Similar findings have been found by Cernvall et al. [55] 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 [7 24].

Eating Disorders: the issue of phenotypes

Several studies have been focused on the overlap between the clinical characteristics of ASD and Eating Disorders (ED) [1].

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 [56], 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 [57]. 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 [58]. 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 [59].

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 [58]. 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 [1 58].

Recently, it has been conducted a study with 138 ED patients and 160 healthy control participants (HCs) [60], 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 [56]. Moreovoer, 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 [60]. 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 [38], such as originality, creativity, divergent thinking [61]. 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 [8].

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 [62 63] 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 [6]. 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 [64-67]. The AdAS Spectrum approach could allow to test a wider range of endophenotypes in order to better investigate the genetic basis of ASD [61].

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 [2 8]. 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 [68 69], on the basis of a pathological neurodevelopmental trajectory with different outcomes [8 70].

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 [71 72]. 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.

References

1. American Psychiatric Association. *Diagnostic and statistic manual of mental disorders, 5th Edition.* Arlington: APA Publishing 2013.

2. Billeci L, Calderoni S, Conti E, et al. *The broad autism (endo)phenotype: neurostructural and neurofunctional correlates in parents of individuals with autism spectrum disorders.* Front Neurosci 2016;10:1-15.

3. Jeste SS, Geschwind DH. *Disentangling the heterogeneity of autism spectrum disorder through genetic findings.* Nat Rev Neurol 2014;10:74-81.

4. Tick B, Bolton P, Happé F, et al. *Heritability of autism spectrum disorders: a meta-analysis of twin studies.* J Child Psychol Psychiatry 2010;57:585-95.

5. Kanner L. *Autistic disturbances of affective contacts.* Nervous Child 1943;2:217-50.

6. Asperger H. *Die autistischen psychopathen im kindersalter.* Arch Prychiatr Nervenkr 1944;117:76-136.

7. Dell'Osso L, Dalle Luche R, Gesi C, et al. *From Asperger's autistischen psychopathen to DSM-5 autism spectrum disorder and beyond: a subthreshold autism spectrum model.* Clin Prat & Mental Health 2016;12:120-31.

8. Dell'Osso L, Dalle Luche R, Maj M. *Adult autism spectrum as a transnosographic dimension.* CNS Spectrums 2016;21:131-3.

9. Frank E, Cassano GB, Shear MK, et al. *The spectrum model: a more coherent approach to the complexity of psychiatric symptomatology.* CNS Spectrums 1998;3:23-34.

10. Cassano GB, Dell'Osso L, Frank E, et al. *The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology.* Jour Aff Dis 1999;3:319-28.

11. Leboyer M, Belliver F, Nosten-Bertrand M, et al. *Psychiatric genetics: search for phenotypes,* Trends Neurosci 1998;21:102-5.

12. Losh M, Sullivan PF, Trembath D, et al. *Current developments in the genetics of autism: from phenome to genome.* J Neuropath Exp Neurol 2008;67:829-37.

13. Picardi A, Fagnani C, Medda E, et al. *Genetic and environmental influences underlying the relationship between autistic traits and temperament and character dimensions in adulthood.* Compr Psych 2015;58:178-88.

14. Baron-Cohen S, Wheelwright S, Skinner R, et al. *The Autism Spectrum Quotient (AQ): evidence from Asperger syndrome/high functioning autism, males, females, scientists and matematicians.* J Autism Dev Disord 2001;31:5-17.

15. Costantino JN. *The Social Responsiveness scale.* Los Angeles: Western Psychological Services 2002.

16. Dawson G, Estes A, Munson J, et al. *Quantitative assessment of autism symptom-related traits in probands and parents.* J Autism Dev Disord 2006;37:523-36.

17. Brugha TS, Mc Manus S, Bankart J, et al. *The proportion of true cases of autism is not changing.* Br Med J 2014;348:3774.

18. Christensen DL, Baio J, Braun KV, et al. *Prevalence and characteristics of autism spectrum disorder a mong children aged 8 years.* MMWR Surveill Summ 2016;65:1-23.

19. Dell'Osso L, Dalle Luche R, Carmassi C. *A new perspective in posttraumatic stress disorder: which role for unrecognized autism spectrum?* Emerg Ment Health 2015;17:436-8.

20. Dell'Osso L, Dalle Luche R, Cerliani C, et al. *Unexpected subthreshold autism spectrum in a 25-year old male stalker hospitalized for delusional disorder: a case report.* Compr Psychiatry 2015;61:10-4.

21. Simoncini M, Miniati M, Vanelli F, et al. *Lifetime autism spectrum features in a patient with a psychotic mixed episode who attempted suicide.* Case Rep Psychiatry 2014;2014:1-4.

22. Lugnegard T, Hallerback MU, Gillberg C. *Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome.* Res Dev Disabil 2011;32:1910-7.

23. Hofvander B, Delorme R, Chaste P, et al. *Psychiatric and psychosocial problems in adults with normal intelligence autism spectrum disorders.* BMC Psychiatry 2009;9:35.

24. Takara K, Kondo T. *Autism spectrum disorder among first-visit depressed adult patients: diagnostic clues from backgrounds and past history.* Gen Hosp Psychiatry 2014;36:737-42.

25. Mito H, Matsuura N, Mukai K, et al. *The impacts of elevated autism spectrum disorder traits on clinical and psychosocial features and long-term treatment outcome in adult patients with obsessive-compulsive disorder.* Compr Psychiatry 2014;55:1526-33.

26. Sierro G, Rossier J, Mohr C. *Validation of the French Autism Spectrum Quotient scale and its relationships with schizotypy and Eysenckian personality traits.* Compr Psychiatry 2016;68:147-55.

27. Yirmiya N, Shaked M. *Psychiatric disorders in parents of children with autism: a meta-analysis.* J Child Psychol Psychiatry 2005;46:69-83.

28. Jacobi C, Agras WS, Bryson S, et al. *Behavioral validation, precursors, and concomitants of picky eating in childhood.* J Am Acad Child Adolesc Psychiatry 2003;42:76-84.

29. Karjalainen L, Gillberg C, Rastam M, et al. *Eating disorders and eating pathology in young adult and adult patients with ESSENCE.* Compr Psychiatry 2016;66:79-86.

30. Kato K, Mikami K, Akama F, et al. *Clinical features of suicide attempts in adults with autism spectrum disorders.* Gen Hosp Psychiatry 2013;35:50-3.

31. Auyeung B, Taylor K, Hackett G, et al. *Foetal testosterone and autistic traits in 18 to 24-month-old children.* Mol Autism 2010;1:11.

32. Baron-Cohen S, Cassidy S, Auyeung B, et al. *Attenuation of typical sex differences in 800 adults with autism vs 3,900 controls*, PLoS One 2014;9:e102251.

33. Lai M-C, Baron-Cohen S, Buxbaum JD. *Understanding autism in the light of sex/gender*, Mol Autism 2015;6:24.

34. Lai M-C, Lombardo MV, Auyeung B, et al. *Sex/gender differences and autism: setting the scene for future research.* J Am Acad Child Adolesc Psychiatry 2015;54:11-24.

35. Lombardo MV, Ashwin E, Auyeung B, et al. *Fetal programming effects of testosterone on the reward system and behavioral approach tendencies in humans*. Biol Psychiatry 2012;72:839-47.

36. Attwood T. *The pattern of abilities and development for girls with Asperger's syndrome.* In: Attwood T, Grandin T, Eds. *Asperger's and girls*, Arlington, TX: Future Horizons Inc 2006.

37. Clark J. *Asperger's in pink: pearls of wisdom from inside the bubble of raising a child with Asperger's*. In: Attwood T, Grandin T, Eds. *Asperger's and girls*, Arlington, TX: Future Horizons Inc 2006.

38. Dell'Osso L, Gesi C, Massimetti E, et al. *Adult Autism Subthreshold Spectrum (AdAS Spectrum): validation of a questionnaire investigating subthreshold autism spectrum*, Compr Psychiatry 2017;73:61-83.

39. Rynkiewicz A, Schuller B, Marchi E, et al. *An investigation of the 'female camouflage effect' in autism using a computerized ADOS-2 and a test of sex/gender differences*. Mol Autism 2016;7:10.

40. Fitzgerald M. *Borderline personality disorder and Asperger syndrome*. Autism 2005;9:452.

41. Niedtfeld I, Defiebre N, Regenbogen C, et

al. *Facing the problem: impaired emotion recognition during multimodal social information processing in borderline personality disorder*. J Pers Disord 2017;31:273-88.

42 Minzenberg MJ, Poole JH, Vinogradov S. *Social-emotion recognition in borderline personality disorder*. Compr Psychiatry 2006;47:468-74.

43 Mitchell AE, Dickens GL, Picchioni MM. *Facial emotion processing in borderline personality disorder: a systematic review and meta-analysis*. Neuropsychol Rev 2014;24:166-84.

44 Dell'Osso L, Cremone IM, Carpita B, et al. *Correlates of autistic traits among patients with borderline personality disorder.* Compr Psych 2018;83:7-11.

45 Dell'Osso L, Carmassi C, Stratta P, et al. *Gender differences in the relationship between maladaptive behaviors and posttraumatic stress disorder. A study on 900 L'Aquila 2009 earthquake survivors*. Front Psychiatry 2013;3:1-7.

46 King R. *Complex Post-traumatic stress disorder: implications for individuals with autism spectrum disorders-part I*. J Dev Disabil 2010;16:91-100.

47 Rydén E, Bejerot S. *Autism spectrum disorders in an adult psychiatric population. A naturalistic cross-sectional controlled study*. Clin Neuropsychiatry 2008;5:13-21.

48 Losh M, Childress D, Lam K, et al. *Defining key features of the broad autism phenotype: a comparison across parents of multiple- and single-incidence autism families*. Am J Med Genet B Neuropsychiatr Genet 2008;147:424-33.

49 Ogata SN, Silk KR, Goodrich S, et al. *Childhood sexual and physical abuse in adult patients with borderline personality disorder.* Am J Psychiatry 1990;147:1008-13.

50 Herman JL, Perry JC, Van der Kolk BA. *Childhood trauma in borderline personality disorder*. Am J Psychiatry 1989;146:490-5.

51 Paris J, Zweig-Frank H, Guzder J. *Psychological risk factors for borderline personality disorder in female patients*. Compr Psychiatry 1994;35:301-5.

52 Carmassi C, Corsi M, Gesi C, et al. *Posttraumatic stress spectrum and adult autism subthreshold spectrum in parents of children with epilepsy: correlations and gender differences*. Eur Psychiatry 2017;41:S721-2.

53 Storch EA, Sulkowski ML, Nadeau J, et al. *The phenomenology and clinical correlates of suicidal thoughts and behaviors in youth with autism spectrum disorders*. J Aut Dev Dis 2013;43:2450-9.

54 Dell'Osso L, Corsi M, Gesi C, et al. *Adult autism subthreshold spectrum (AdAS Spectrum) in parents of pediatric patients with epilepsy: correlations with posttraumatic stress symptoms.* Compr Psych 2018;83:25-30.

55 Cernvall M, Skogseid E, Carlbring P, et al. *Experimental avoidance and rumination in parents of children on cancer treatment: relationships with posttraumatic stress symptoms and symptoms of depression*. J Clin Psychol Settings 2016;23:67-76.

56 Gillberg IC, Gillberg C, Rastam M, et al. *The cognitive profile of anorexia nervosa: a comparative study including a community-based sample*. Compr Psychiatry 1996;37:23-30.

57 Tchanturia K, Smith E, Weineck F, et al. *Exploring autistic traits in anorexia: a clinical study,* Mol Aut 2013;4:1-8.

58 Dell'Osso L, Abelli M, Carpita B, et al. *Historical evolution of the concept of anorexia nervosa and relationship with ortorexia nervosa, autism and obsessive compulsive spectrum.* Neur Dis Treat 2016;12:1651-60.

59 Zucker NL, Losh M, Bulik CM, et al. *Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes*. Psychol Bull 2007;133:976-1006.

60 Dell'Osso L, Carpita B, Gesi C, et al. *Subthreshold autism spectrum disorder in patients with eating disorders.* Compr Psych 2017;81:66-72.

61 Baron-Cohen S, Richer J, Bisarya D, et al. *The systemizing quotient: an investigation of adults with Asperger syndrome or high-funcioning autism, and normal sex differ-ences. Philos Trans R Soc Lond B Biol Sci 2003;358:361-74.

62 Happé F, *Criteria, categories, and continua: autism and related disorders in DSM-5,* J Am Acad Child Adolesc Psuchiatry 2011;50:540-2.

63 Nemeroff CB, Weinberger D, Rutter M. *DSM-5: a collection of psychiatrist view on the changes, controversies and future directions.* BMC Med 2003;11:202.

64 Le Couteur A, Bailey A, Goode S, et al. *A broader phenotype of autism: the clinical spectrum in twins*. J Child Psychol Psychiatry1996;37:785-801.

65 Smith CJ, Lang CM, Kryzak L, et al. *Familial associations of intense preoccupations, an empirical factor of the restricted, repetitive behaviors and interests domain of autism*. J Child Psychol Psychiatry 2009;50:982-90.

66 Constantino JN, Zhang Y, Frazier T, et al. *Sibling recurrence and the genetic epidemiology of autism*. Am J Psychiatry 2010;167:1349-56.

67 Ronald A, Hoekstra RA. *Autism spectrum disorders and autistic traits: a decade of new twin studies.* Am J Med Genet B Neuropsychiatr Genet 2011;156B:255-74.

68 Peled A, Geva AB. *Clinical Brain profiling: a neuroscientific approach for mental disorders.* Med Hypotheses 2014;83:450-64.

69 Peled A. *Brain "globalopathies" cause mental disorders.* Med Hypotheses 2013;6:1046-55.

70 White PD, Rickards H, Zeman AZ. *Time to end the distinction between mental and neurological illness.* BMJ 2012;344:e3454.

71 Dell'Osso L, Conversano C, Corsi M, et al. *Polysubstance and behavioral addictions in a patient with bipolar disorder: role of lifetime subthreshold autism spectrum.* Case Reports in Psychiatry. 2018;2018:1547975.

72 Dell'Osso L, Carmassi C, Musetti L, et al. *Lifetime mood symptoms and adult separation anxiety in patients with complicated grief and/or post-traumatic stress disorder: a preliminary study*. PSych Res 2012;198:436-40.