



Do Savant Syndrome and Autism Spectrum Disorders Share Sex Differences? A Comprehensive Review

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Savant syndrome was described before autism. However, they soon became closely associated, as many of their symptoms (intellectual disability, repetitive behaviors, alterations in social communication, and islets of abilities) overlap. Only a few women with autism have been diagnosed with savant syndrome. The theories or hypotheses that attempt to explain savant syndrome, which are common in autism, present differential treatment according to sex. We postulate that savant syndrome associated with autism as well as autism in general is underdiagnosed in women.

Keywords: Savant syndrome; Autism spectrum disorder; Sex differences.

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INTRODUCTION

Savant syndrome (SS) has been described in scientific literature since the late 19th century [1], long before autism was described [2]. Although SS has a very low prevalence (0.06% in the United States [3] and 0.14% in Finland [4]), it has gained great interest as individuals with SS have above-average abilities in various domains such as memorization, calculation, map interpretation, musical composition, and artistic faculties, which are related to synesthetic sensory alterations [5]. These skills are also referred to as splinter abilities, as they are not linked to general ability and/or not displayed in an operational or functional manner. Thus, Miller's definition [6] of SS, "people with developmental disability displaying skills at a level inconsistent with their general intellectual functioning," seems appropriate.

There is a disharmonic and seemingly paradoxical development of special abilities and skills in SS, in which people with evident neurological problems show islands of genius [7] or special isolated skills (SIS). SS has been inextricably linked to autism [8], to the point that in the Autism Diagnostic Interview-Revised (ADI-R), the presence of SIS has been referenced as a clinically significant symptom of autism

spectrum disorder (ASD) [9]. SIS are defined as discrepancies between levels of general adaptive functioning and performance of particular skills. The discrepancies may be below, equivalent to, or above the average performance levels of the general population [9].

ASD is a neurodevelopmental disorder characterized by core deficits in the social-communicative domain, restricted interests, and repetitive behaviors [10-12]. As for all neurodevelopmental disorders, the first symptoms should be clinically significant in the first years of life (before 3 years of age). However, in the absence of biological markers, diagnosis of ASD becomes particularly complex [13] and may be delayed, or even not made until adulthood in some cases. In addition, owing both to the high heterogeneity of symptoms associated with ASD and to comorbidity with other disorders, the core symptoms of autism may be masked. Moreover, individuals without intellectual disability (ID) [14,15], women [16,17], and racial and ethnic minority youth [18-20] are more likely to be diagnosed later in life. Comorbidity with other congenital and acquired neurological disorders besides ASD includes epilepsy, brain injury, and diseases involving the left frontotemporal area [21].

It has been controversial whether to consider SS as a subtype of ASD or as an independent syndrome. Heaton and Wallace [22] considered that autism, as a continuum, is inseparably associated with SS; and that consequently, those

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with SS suffer from many of the difficulties presented in ASD and vice versa. In contrast, Treffert and Rebedew [23] suggested that it is a mistake to consider SS as a symptom associated solely with autism. There is no consensus on this issue, given that although 1 of 10 people with autism have SS, this only represents 50% of the cases of SS [24-26].

SS is also associated with symptoms of ID, independent of or associated with ASD, other disorders, or alterations in the central nervous system (CNS), and very few people with SS do not present significant concurrent symptoms. Treffert and Rebedew [23] registered 319 individuals with SS, 75% of whom had autism and/or other CNS disorders. Forty-five percent of them had more than one special ability, most frequently in art, memory, mathematics, calendar calculation, language, mechanics and spatial vision, athletics, and computer science; thus, people with autism sometimes present some spectacular abilities that often contradict their general profile, as they tend to fail simple tests of theory of mind [27]. Howlin et al. [28] noted that the prevalence of savants with autism may be high, as almost 30% of clinical cohorts in their study showed outstanding abilities. Treffert and Rebedew [23] noted that only 90% of those with SS had a congenital etiology, and 95% of them had ASD or some type of pervasive developmental disorder as described in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [29,30]. According to these data, we can maintain the hypothesis that SS is an extreme form of ASD.

Our study of SS aims precisely to find an explanation for the large difference in the proportion of sexes, which is even more pronounced in SS than in ASD. To achieve this, we conduct a scoping review of the scientific literature on the relationship of SS with sex.

ASD AS A CONTINUUM

The fifth, and current, edition of the DSM (DSM-5) [10,11] formally recognizes autism as a spectrum, providing a framework for conceptualizing autism as a continuum that spans several subclinical levels. Consequently, ASD is now understood as having a higher level of heterogeneity in phenotypic manifestations associated with a great variability in intellectual [31] and linguistic [32] developmental levels, intra-individual discrepancies in cognitive profiles [33], and a large co-occurrence of symptoms or comorbidity with other neurodevelopmental or psychiatric disorders [34,35]. Therefore, classifications were set owing to this great heterogeneity; for example, the World Health Organization [12] classifies people with autism with ID or without it, and according to the linguistic level. This classification can help in determining support needs, but does not help in determining the nature

of the disorder or its future evolution. Moreover, according to the nature of the etiology, ASD is classified into two large groups: disorders of idiopathic etiology and those of syndromic etiology [36,37]. However, syndromic etiology accounts for only 25% of ASD cases [38]. Another issue that can shed light on subsequent discussions is differentiating autism as a disorder/condition from autistic symptoms/traits. Autism is a neurodevelopmental disorder that occurs at birth, although symptoms show during the first years of life. The main symptoms described are low interest in events occurring in one's environment, poor or nonexistent social interaction, low response or no communicative interest, rigidity, and desire for environmental invariance [39]. The clinical significance of this disorder lies in that these initial symptoms affect the normal development of the child, thus generating a cascading disorder that limits a person's life at the educational, occupational, and social levels.

In contrast, autistic traits may also be present in other disorders and in the general population. Autistic traits can have different origins, including motor limitations [40], early social deprivation [41], and sensory [42] or new social habits as excessive exposure to digital devices [43]. Thus, a non-autistic deficit following a disharmonious developmental pattern may cause autistic traits to emerge or may exacerbate symptoms in people with autism. This combination may be explained by the bidirectional influence of the external environment and neurodevelopment [44,45], and it may underpin the emergence of broad autistic phenotypes or help in describing individuals as having autistic traits or sub-threshold symptoms of autism.

AUTISM AND SIS

Currently it is estimated that 67%–70% of individuals with autism do not have IDs [46,47]. Approximately 50% are estimated to possess intellectual potential for higher education [48]. Moreover, some of them are missed in the clinical diagnosis phase or camouflage their symptoms [49,50]. Although there is no diagnostic label for this group, they are referred to as having high-functioning autism [51]. This can be referred to as Asperger's syndrome or ASD with level 1 severity. Sometimes, individuals with autism show SIS that usually conflicts with their social deficits or problems in adaptive behavior and activities of daily living. Many of them possess exceptional skills in mathematics, science, or art [52-54]. These special skills, such as hyperlexia, are often related to areas of restricted interests; therefore, overlearning, repetition of certain behaviors, or dedication to the same task may lead them to develop a skill at a level above that of the average population.

Consequently, increased social-communicative impair-

ments, repetitive behaviors, seasonality, and sensory abnormalities do not necessarily indicate the existence of special skills. However, skilled individuals demonstrate a domain-general capacity for highly focused attention and outstanding general memory skills (mainly working memory assessed with digit span) [55]. Happé and Vital [56] suggested that the lack of interest in the social world and its interactions frees up cognitive resources and time to nurture and grow skills related to the restricted interests observed in individuals with autism. Studies on the presence of SIS in individuals with autism show that they are relatively frequent in the autistic population (62.5% of people with autism present some special abilities) and increase with increasing intelligence and age [57]. This suggests that these capabilities develop on the basis of a trajectory strongly influenced by biology, experience and social, economic, and academic contexts. This has led to the perception of an association between autism and SS at both popular and media levels.

Although autism does not account for 100% of SS cases, the relationship of SS symptomatology with autism is evident. This may be because SIS development is reinforced by ASD because of its characteristics including mental rigidity and processing style. This distinguishes it from other neurodegenerative disorders [6,22]. Treffert [58,59] characterized SS in terms of its relation to both ID and autism and estimated that only 1 of 1400 people with ID show SS. All individuals with SS show alterations in the CNS [23], while people with autism frequently show alterations in the prefrontal cortex. This results in deficits in the regulation of behavior and thoughts [60], planning (setting goals and developing coordinated actions to achieve them) [61-63], and executive functions.

The prevalence of SS is low, which makes it difficult to conduct differential studies. Differential psychological profile studies have been conducted with people with autism with or without SS but showed no differences between them [28,55,64]. Although differential studies are scarce and have very small sample sizes, it is conceivable that there may be numerous clinical and subclinical forms of autism.

Studies conducted by Treffert and colleague [23,58,59] comprised cases diagnosed before the introduction of the DSM-5 criteria. Consequently, it is possible that some individuals with SS that were not diagnosed with ASD at that time would now fall under the autism spectrum. The reported non-autistic people with SS had lesions in the frontal and prefrontal areas. These lesions are common in people with autism.

A common factor between SS and ASD is the low rate of cases reported in women. The current prevalence of ASD is estimated to be 1%–2% [65], with higher proportion of cases

among men, with various estimated ratios between sexes of 3:1 [66], 4:1 [67,68], and 5:1 [69,70]. However, if we analyze the prevalence data according to symptom severity, the difference decreases [71]. For example, if we consider only the prevalence of ASD accompanied by ID, the sex difference significantly decreases (2:1) [72]. In contrast, when the study refers to a population with high-functioning ASD (ASD/AF) or Asperger syndrome (AS), the prevalence figures according to sex vary markedly, reaching ratios of 9:1 or 10:1 [73,74]. However, recent mathematical modeling studies [75] have proposed a ratio of 3:4 as more appropriate in describing the sex distribution of the adult population with autism. Moreover, the same study has suggested that 80% of women with ASD remain undiagnosed at the age of 18 years. Is it possible that women with ASD and SIS have gone unnoticed? Two hypotheses make this possible.

1) The existence of some type of sexual dimorphism in ASD, for which a multifactorial theory has been postulated, involving genetic variants and environmental factors. These factors interact with characteristics specific to the female sex, including hormones and immune functions, and generate protective factors against the development of common features of ASD in women [76-79].

2) Low detection or diagnosis of ASD in women due to a sex bias in the diagnostic tools [17].

Sex differences may also be related to the definition of SS or ASD according to SIS. Explanatory theories of autistic traits must be reviewed from the perspective of sex to understand this phenomenon. In particular, we consider the theories of hyper-systemization, selective attention, executive function, and central coherence.

HYPER-SYSTEMIZATION THEORY

One explanation of sex differentiation is the Hyper-systemization Theory [80]. According to this theory, the human brain is primed to respond to environmental changes that can be intentional or unintentional. In the case of unintentional changes, the brain may deploy empathic mechanisms to predict consequences or look for systematic structures to explain the changes. The autistic mind presents very high systematization mechanisms, thus explaining the resistance to change and preference for predictable, routine tasks or mechanisms such as mathematics, repetition, rotating objects, music, and collections over less predictable tasks such as social interaction, conversation, and emotional responses. Based on the relationship between empathy and systemization, Baron-Cohen [80] established an explanatory theory of autistic behavior closely related to sex differentiation [81]. It is based on the etiological hypothesis that the

presence of elevated levels of testosterone in the amniotic fluid of mothers would promote the development of the fetal brain towards a greater capacity for systemization, thus increasing masculine traits.

SELECTIVE ATTENTION AND EXECUTIVE FUNCTION

Selective attention is a central component of cognitive functioning [82]; the ability to focus on certain aspects of the environment is crucial, —taking into account the limitations of our brains and sensory systems— to avoid continuous stimulus bombardment [83]. Extended selective attention is a common dysfunction in autism due to the cognitive rigidity [84]. This form of attention is caused by an abnormal development of the parietal and temporal areas of the brain, which generates an alteration in complex representations and an increase in reaction time to complex stimuli. According to Waterhouse et al. [84], the disorganization of the parietal and temporal multisensory regions could explain extraordinary visual and auditory memory. Extraordinary amnesic capacity is a common ability in SS. This loop of sustained selective attention to predictable stimuli leads to the emergence of certain islets of exceptional skills. Sex differences between selective attention and other cognitive skills have been documented [85]; however, replication studies in autistic populations are scarce [86]. Aspects of social cognition (social attention) are the most productive, suggesting that women with ASD may have a social advantage over men with ASD, as they demonstrate more normative social patterns [87].

The neuropsychological profiles of people with ASD may differ according to sex. In particular, a deficit in response inhibition implies impulsivity, risk-taking, and general executive dysfunction. A study by Lemon et al. [88] showed that other sex differences may also exist, demonstrating that women with autism show poorer behavioral inhibition in the stop task than men with autism.

CENTRAL COHERENCE

Weak central coherence is a common cognitive feature of individuals with autism. According to Frith [89], people generally tend to perceive environmental stimuli in a gestalt and global manner, whereas people with autism pay more attention to isolated details than to the global composition of the incoming stimulus. This altered processing of incoming information explains some special abilities, such as sequential memory [24] and deficits in categorization or conceptualization [90]. The ability to form coherent sets of information involves considering the context and how objects are related

to each other. It is a process of synthesizing information that facilitates communication and makes it coherent. Perceiving each object separately or as unrelated parts requires more cognitive resources. According to this theory, individuals with autism can develop exceptional skills in tasks that involve paying attention to local information (i.e., fragmented processing). This ability explains the interest of some individuals with autism in computer code-controlled tasks.

This special form of information processing directed at certain parts rather than the whole can result in exceptional skills such as drawing exact replicas of models or detecting errors in listings of computer software codes.

SEX AND SS

Regarding the relationship of SS with sex, the lack of published studies is striking [7], sex differences are rarely even mentioned. Although some cases of women with SS have been reported with a symptomatology similar to that of men [91], the proportion of women with SS is much lower than that of men. Studies show male-female ratios/proportions of 7:1 [92] (78% [4], 82.05% [28], or 85% of men [3]), higher than that in ASD (4:1); however, several studies [56,28] suggest that when reported by parents, this difference is smaller in childhood.

The extreme male brain hypothesis [81] attempts to explain the preponderance of men in autism and the overrepresentation of men in the high and low extremes of cognitive performance because of their better ability to systematize as opposed to the better ability of women (both normatively developing and those with AS) to empathize [93]. However, no relationship between musical or mnemonic skills and systematization performance has been demonstrated [94].

Geschwind and Galaburda's [95,96] theory of cerebral lateralization is an alternative explanation, also from a physiological perspective. It postulates that the difference in prevalence according to sex could be because of the later maturation of the left hemisphere in males, that would expose it to intra-uterine circulating testosterone at very high levels. This could slow down its development and promote a compensatory growth of the right hemisphere. The "left brain injury/right brain compensation" hypothesis, supported by Treffert [26], suggests that most individuals with SS exhibit this phenomenon due to a damage or impairment to the left hemisphere of the brain, resulting in right brain compensation. This theory is further supported by imaging findings, as well as the skewed ratio of male to female savants [7].

This hypothesis is also supported by the difference in male/female prevalence in other neurological and psychiatric disorders, as well as by the left hemisphere dysfunction fre-

quently present in individuals with autism, dyslexia, language problems, stuttering [26,58], learning disorders, giftedness, and immune deficits [97]. However, empirical evidence has not fully corroborated this hypothesis [98,99].

Finally, more recent work [100-102] has proposed “camouflage hypothesis” to explain the lower apparent prevalence of ASD in women, suggesting that women successfully mask some of the autistic symptoms in their daily lives or jobs, possibly because of a process of differential enculturation by sex. Along these lines, McCrossin has recently [103] developed an inductive prediction model for ASD prevalence in adults (>18 years old) based on a study of 1711 cases and has concluded that the true male-to-female ratio should be close to 3:4, where 80% of women with ASD would have remained undiagnosed.

CONCLUSION

Islets of exceptional abilities are common in SS and ASD to the extent that they are considered a feature of ASD in diagnostic tools, such as ADI-R. Various theories have explained this phenomenon. Similarly, interest restriction and social reinforcement of special abilities may also explain the development of these islands in a more behavioral way.

Therefore, SS and ASD are intrinsically related and have similar diagnostic problems. Typical diagnostic tools are based on the observation of externalizing symptoms, which are more frequent in men. In contrast, these instruments may have a low sensitivity in the early detection of autism in women. Moreover, this could explain the failure of detection of autism in the supposedly SS “non-autistic” women. The comorbidity of ASD with other neurodevelopmental disorders is one of the reasons for the delay in the diagnosis of ASD. Therefore, until reliable biomarkers are found, it is necessary to conceptualize autism as a condition to be treated independently from the future diagnostic label, as guided by DSM-5 with the use of the provisional category of global developmental disorder.

The concept of the spectrum introduced by DSM-5 accommodates the syndromes that exhibit difficulties in the domain of communication or social interaction, restricted interests, or repetitive behaviors as common denominators. ASD is defined as a cluster of neurodevelopmental disorders, and it is accepted that SS is part of this spectrum, except for the rare cases of supervening brain damage. This assertion is supported by the fact that most of the cases described as SS in the literature are adults, and it is possible that the diagnostic tools for ASD are not sufficiently sensitive or that the symptoms are obscured by other more externalizing and obvious symptoms. However, it is obvious that the autism spec-

trum cannot be expanded indefinitely.

It is our contention that ASD is under-diagnosed in women, due to the relationship between SS and ASD. Mathematical prediction models show much higher proportions of children than do epidemiological studies. If the number of women with high-functioning autism (without ID) diagnosed after the age of 18 years increases, it is expected that the number of women with SIS will also increase. However, it must first be clarified whether SS is a syndrome independent from ASD or a subtype (ASD-Savant). Therefore, more research is needed to determine the differences and similarities between SS and ASD or, if appropriate, the development of ASD typologies according to ability profiles and the under-representation of women in both syndromes.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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