



# ASD+COMORBIDITY

**Dr.P. Hashemian**

**ADHD**

**Seizures**

**Schizophrenia**

*CACNA1A*

*GRIN2A*

*KCNQ2*

*GRIA3*

*SCN1A*

*SYNGAP1*

*PCDH19*

**Autism spectrum disorder**

*CACNA1C*

*MECP2*

*SHANK3*

*TRIO*

*SETD1A*

*CHD8*

*FMR1*

*CACNA1G*

*GNAL*

*FOXP1*

*KMT2B*

**Motor disorder**

*TOR1A*

*GCH1*

*SGCE*

**Depression**

**Anxiety**

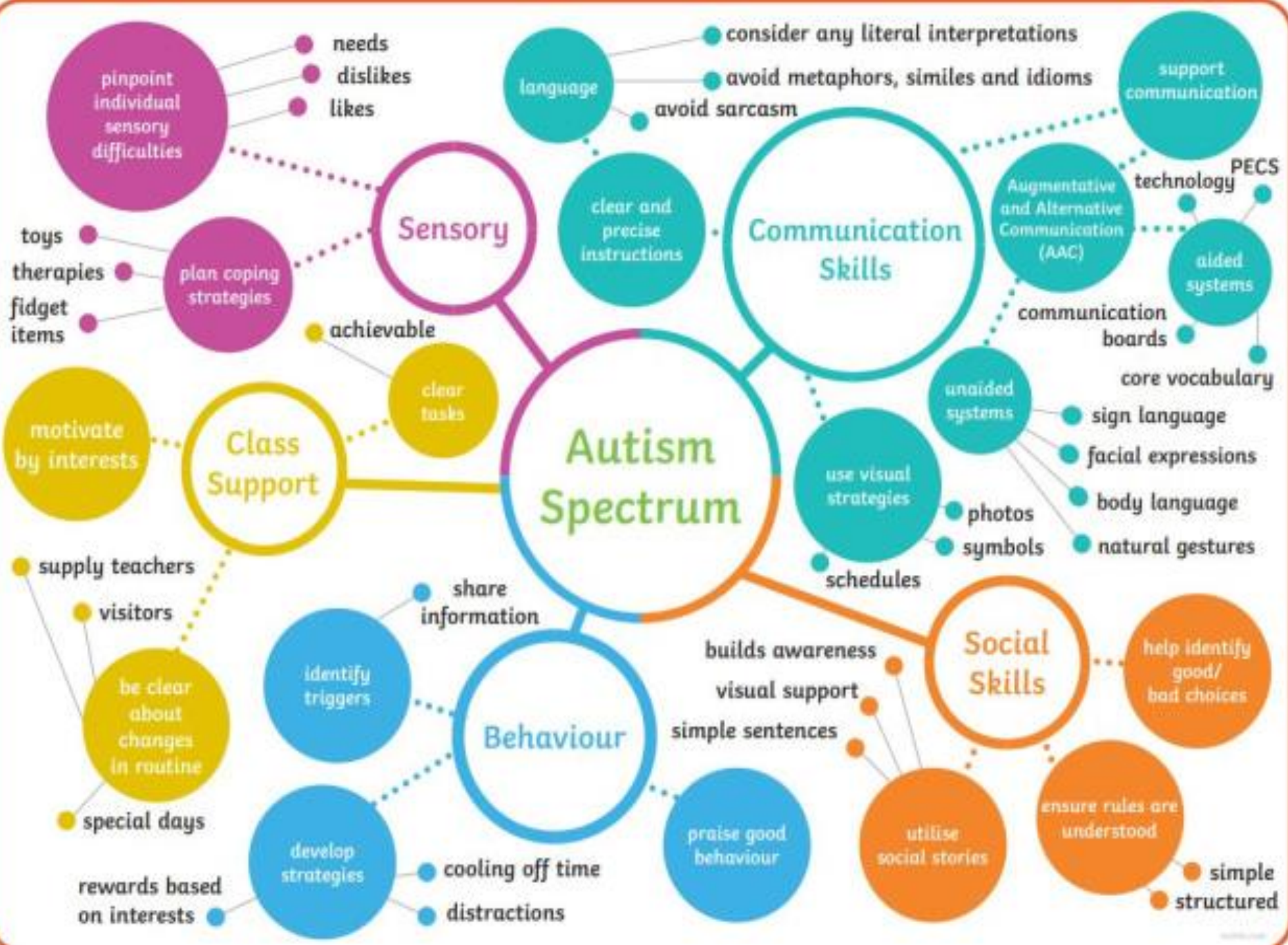
**OCD**

# Autism and comorbid conditions

The characteristics of autism, according to **DSM 5**, are as follows –

1. Persistent challenges in social communication and social interaction across multiple contexts
2. Restricted, repetitive behaviours, interests or activities
3. Hyper- or hyporeactivity to sensory input

Autism is most often, but not exclusively, linked with intellectual disabilities, ADHD, OCD, epilepsy and childhood-onset schizophrenia.



# AUTISM SPECTRUM DISORDER



**HIGH-FUNCTIONING AUTISM**

**AUTISM**

**SEVERE AUTISM**

**Level 1**

**Needs support**

Patient's social and communication skills and repetitive behaviors are only noticeable without support.

**Level 2**

**Needs substantial support**

Patient's social and communication skills and repetitive behaviors are still obvious to the casual observer, even with support in place.

**Level 3**

**Needs very substantial support**

Patient's social and communication skills and repetitive behaviors severely impair daily life.

ASPERGER ←

→ KANNER

Eye tracking dataset

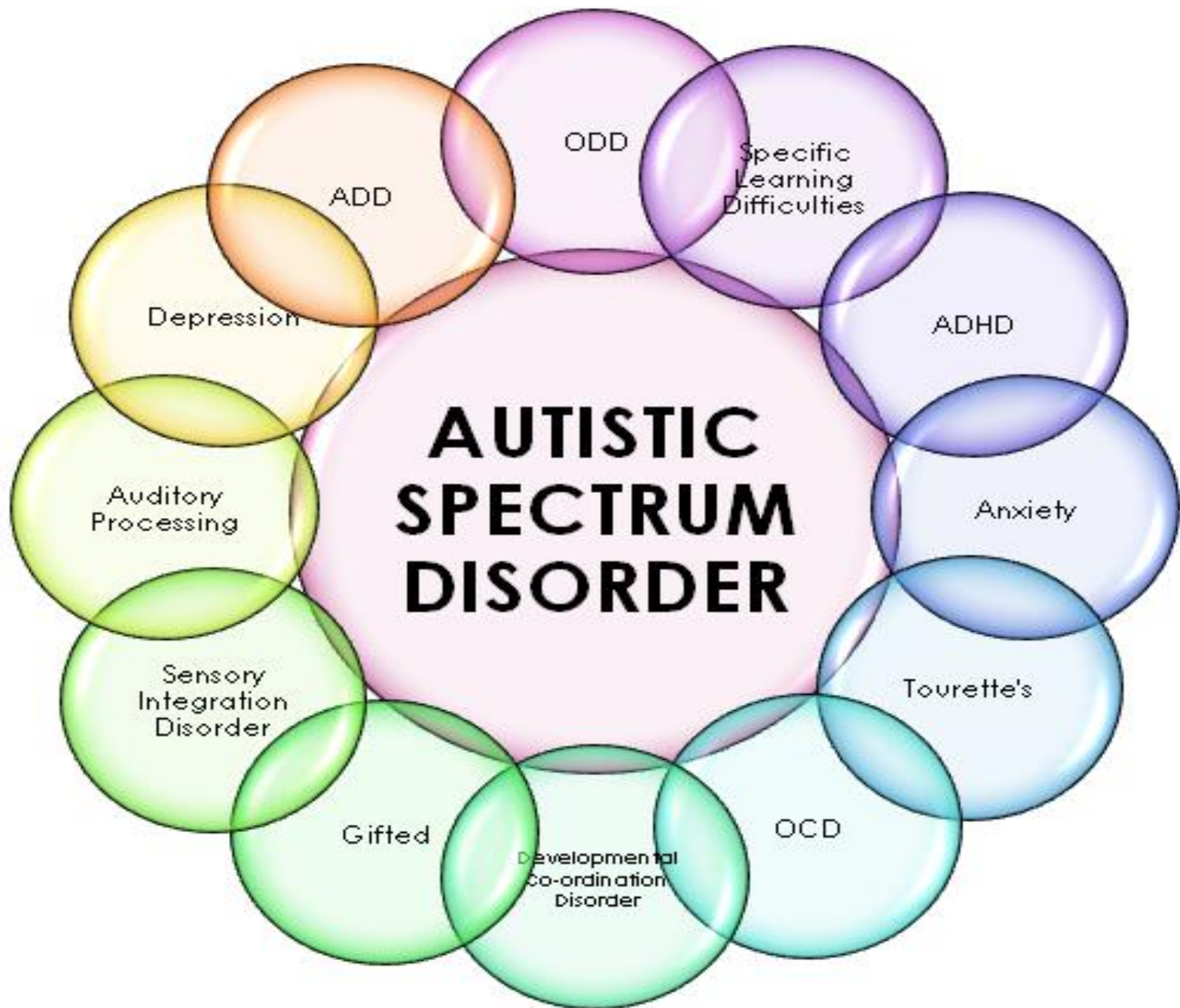
ICME dataset

MIE Fo

MIE Fo

# Psychiatric comorbidities

- As many as **85%** of children with autism also have some form of **comorbid psychiatric diagnosis**, and **35%** are taking at least 1 psychotropic medication as treatment.
- ADHD, anxiety, and depression are the most commonly diagnosed comorbidities.





**Related disorders**

**Anxiety disorder**

**Obsessive-compulsive disorders**

**Attention deficit hyperactivity disorders**

**Mood disorders**

**Sleep disorders:** Difficulty falling asleep, inability to sleep in a flat position, nighttime reawakenings, sleepwalking

**Epilepsy**

**Systemic medical disorders**

**Accidents**

**Injuries, drowning, suffocation, *etc.***

**Genetic disorders**

**Fragile X syndrome, Down syndrome, Duchenne muscular dystrophy, neurofibromatosis type I, and tuberous sclerosis complex**

## **Metabolic disorders** ◦

Mitochondrial disorders, disorders of creatine metabolism, selected amino acid disorders, disorders of folate or vitamin B12 metabolism, and selected lysosomal storage disorders

## **Endocrine disorders** ◦

*e.g.*, hypothyroidism ◦

## **Neurological disorders** ◦

Congenital abnormalities of the nervous system, epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, paralytic muscular disorders like Duchenne muscular dystrophy, increase in sympathetic and a decrease in parasympathetic activity, and dysautonomia

## **Immune dysfunction** ◦

Neuroinflammation, immune deficiency and dysfunction ◦

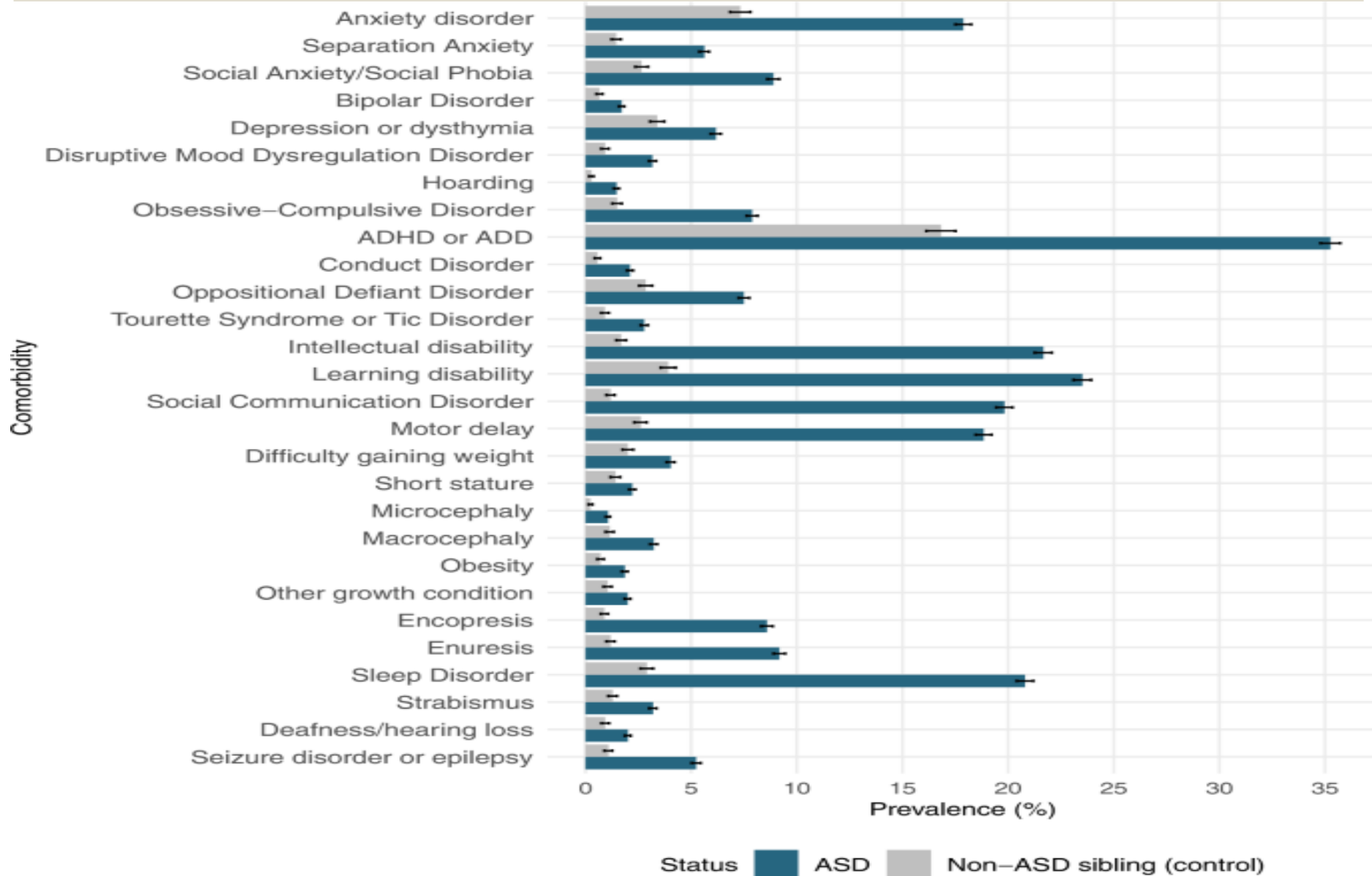
## **GI disorders** ◦

Chronic constipation, chronic diarrhea, eosinophilic esophagitis, gastroesophageal reflux and/or disease, nausea and/or vomiting, chronic flatulence, abdominal discomfort, ulcers, colitis, inflammatory bowel disease, food intolerance, and/or failure to thrive

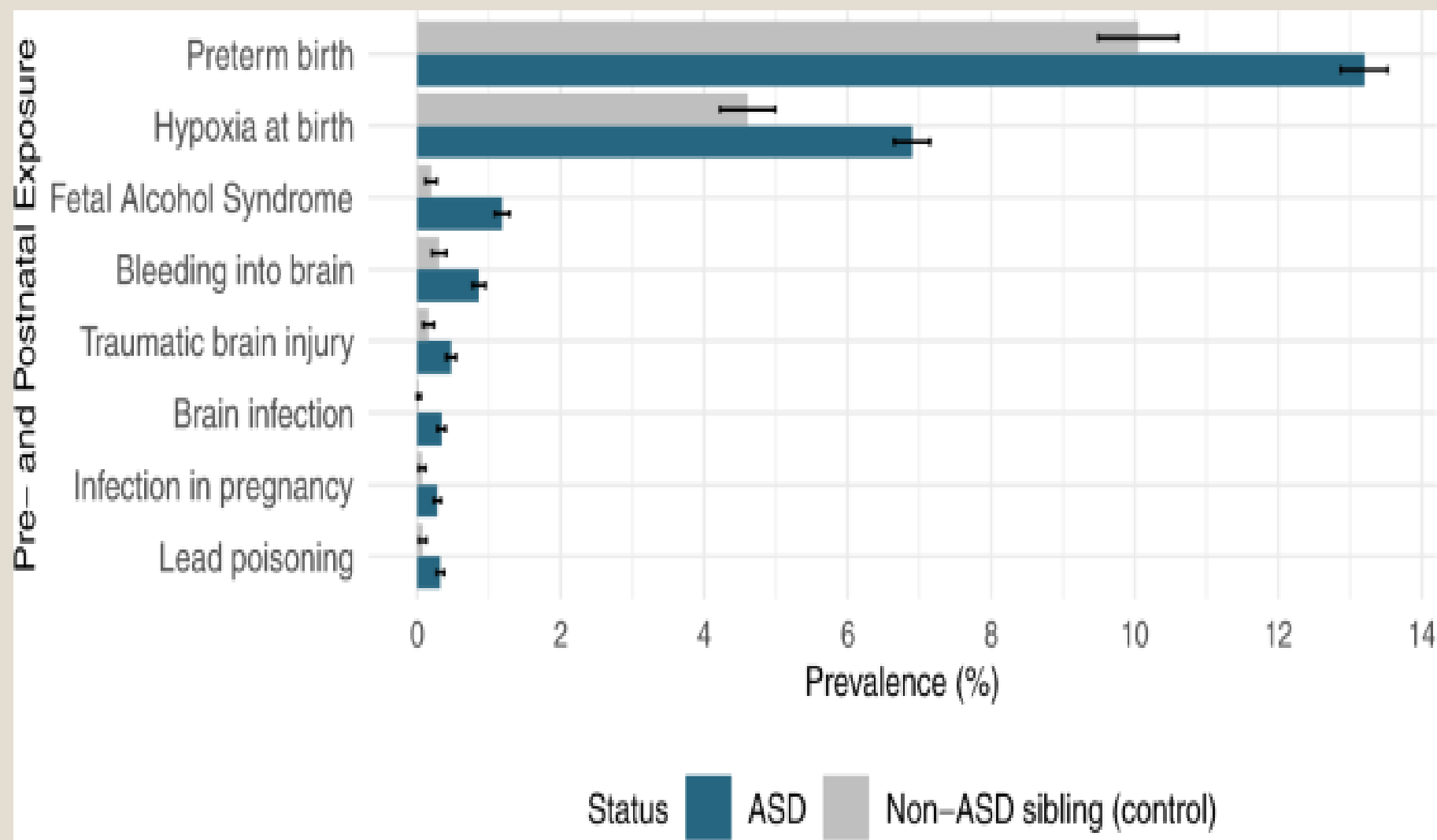
## **Feeding disorders** ◦

Selective eating, difficulty swallowing, abnormal behaviors during meals such as ritualistic behaviour, throwing tantrums or gagging and vomiting

**Fig. 2: Barplots illustrating the prevalence of comorbid conditions by ASD status**

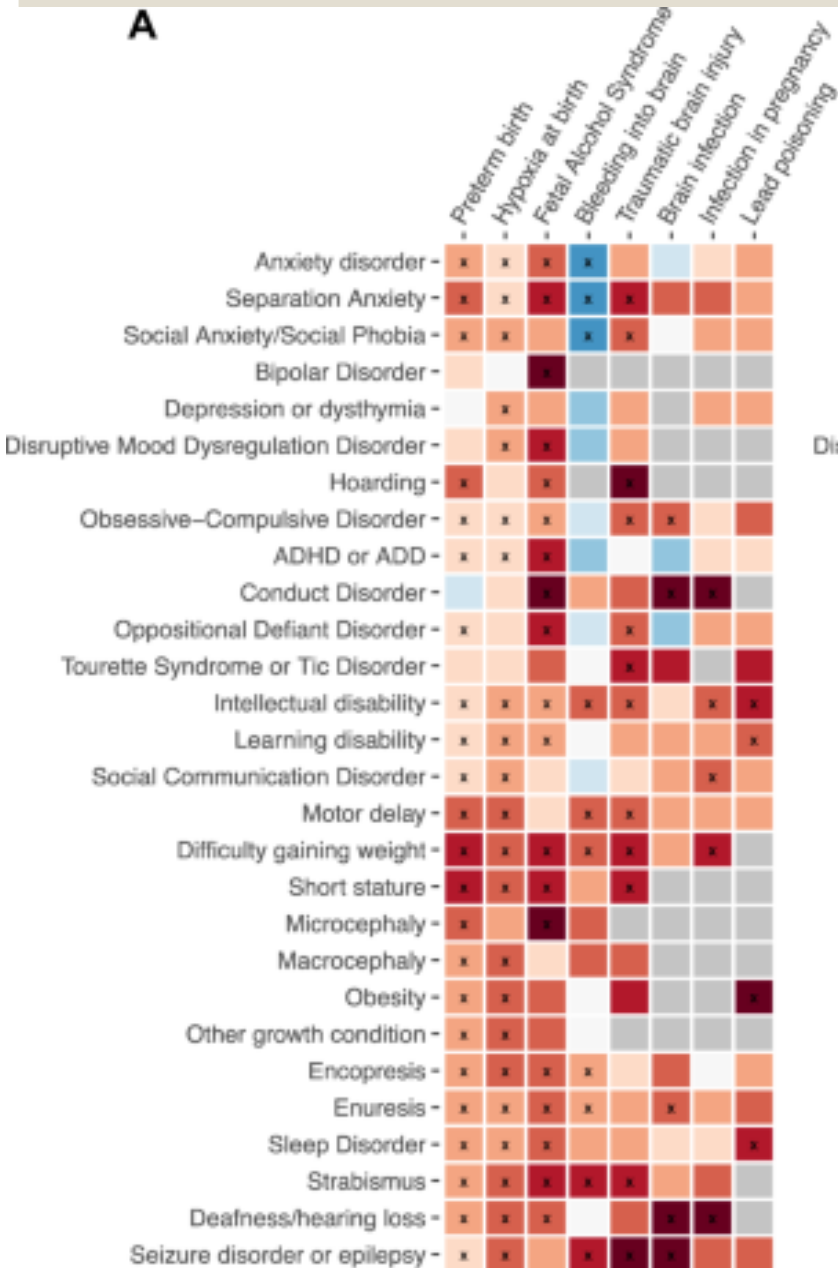


**Fig. 1: Barplots illustrating the prevalence (%) of pre- and postnatal exposures by ASD status.**

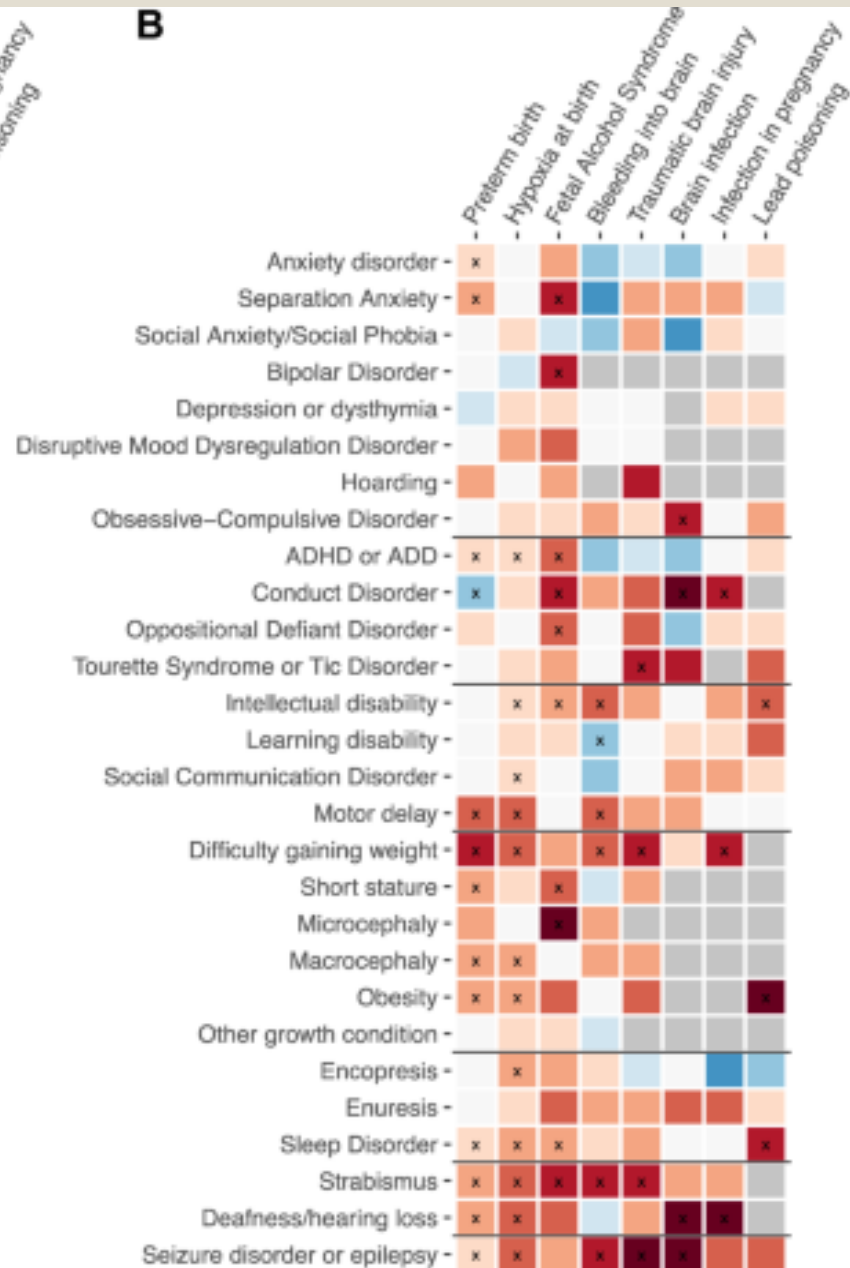


**Fig. 4: Associations between pre- and postnatal exposures and comorbidity in individuals with ASD.**

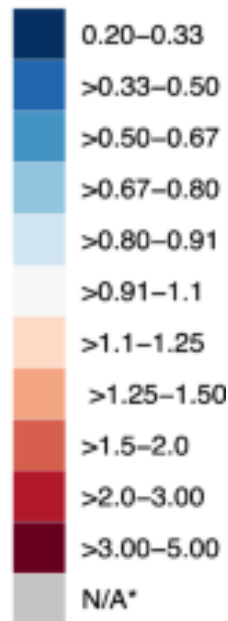
**A**



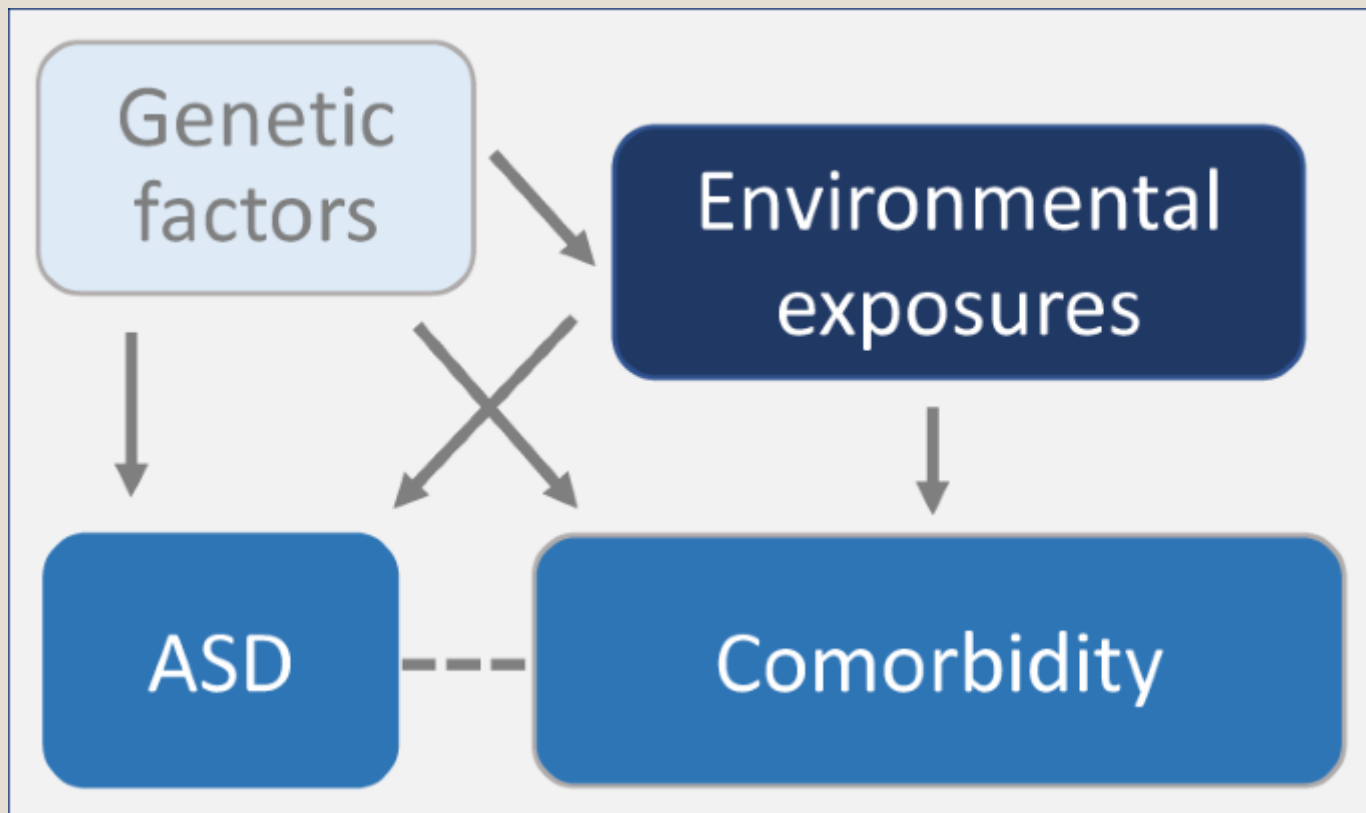
**B**



**Odds Ratio**



Schematic illustrating potential relationships between genetic vectors, environmental exposures, ASD and its comorbid conditions.



# Mental Health Conditions

- **85%** comorbid psychiatric diagnosis, and **35%** are taking at least 1 psychotropic medication (Bennett, 2022).
- **Individuals with ASD have a high prevalence of multiple mental health disorders such as:**
  - **ADHD – 50-70%** of the ASD population is affected.
  - **Depression – 26%** of the ASD population is affected vs **10%** of the general population.
  - **Anxiety – 30%** of the ASD population is affected vs **10%** of the general population.
  - **Bipolar Disorder – 11%** of the ASD population is affected vs **2%** of the general population.
  - **Schizophrenia – 7%** of the ASD population is affected vs **0.5%** of the general population.
- **ADHD, anxiety, and depression are the most diagnosed comorbidities**

## COGNITIVE COMORBIDITIES

Language impairment

Intellectual disability

Simple genetic disorders: fragile X, TS, Rett, etc.

## GENETICS

Copy number variants: 16p11-p12, 15q11-q13, 22q13, etc.

Rare variants: NRXN1, NLGN4, Shank3, Sert, etc.

## BEHAVIORAL COMORBIDITIES

Hyperactivity/impulsivity

Agitation/aggression

Anxiety

Severe constipation

## MEDICAL COMORBIDITIES

Seizure disorder

Abnormal EEG

Developmental macrocephaly

Neuroimaging: altered brain region size

Hyper-serotonemia

Altered immune/mitochondrial indices

## Core autism spectrum disorder symptoms

Impaired social communication/interaction (3/3):

- Social reciprocity
- Nonverbal communication
- Relationships

Restricted/repetitive behavior (2/4):

- Repetitive speech/behavior
- Insistence on sameness
- Restricted interests
- Sensory abnormalities



# Genetic Disorders

- . Fragile X Syndrome (FXS), Down Syndrome, and Duchenne Muscular Dystrophy.
- FXS occurs at a rate of 2%-3% for all ASD cases have FXS, and about 25%-33% of FXS patients have ASD.
- But the rate for those with Down Syndrome also having comorbid ASD is very high at 40% .
- Other disorders that have a genetic basis occur at a higher rate as well such as various mitochondrial and metabolic disorders.

# Intellectual Disability

Intellectual disability has been reported as anywhere from 25% to 70%. ◦

30% with intelligence in the normal range (IQ above 70), ◦

50% with a mild to moderate ◦

20% with a severe to profound intellectual disability (IQ below 35). ◦

Females more likely to be in severe range of an intellectual disability. ◦

- **Gender dysphoria**

- Gender dysphoria is a diagnosis given to transgender people who experience discomfort related to their gender identity.

- Autistic people are more likely to experience gender dysphoria

— Around **20%** of gender identity clinic-assessed individuals reported characteristics of ASD.

- **Hypermobility spectrum disorder and Ehlers–Danlos syndromes**

- Ehlers-Danlos syndromes (EDS) and hypermobility spectrum disorder (HSD) with autism, as a comorbidity and a co-occurrence within the same families

# Mitochondrial diseases

- Neurological manifestations include encephalopathy, stroke, cognitive regression, seizures, cardiopathies (cardiac conduction defects, hypertensive heart disease, cardiomyopathy, etc...), diabetes, visual and hearing loss, organ failure, neuropathic pain and peripheral neuropathy.
- The prevalence estimates of mitochondrial disease and dysfunction across studies ranging from about **5 to 80%**.

- Some drugs are toxic to mitochondria. These can trigger or aggravate dysfunctions or mitochondrial diseases.

- **Antiepileptics :**

- Valproic acid (also used in various other indications) and phenytoin are the most toxic. Phenobarbital, carbamazepine, oxcarbazepine, ethosuximide, zonisamide, topiramate, gabapentin and vigabatrin are also

Other types of drugs :

- **Corticosteroids** (such as cortisone), isotretinoin (Accutane) and other vitamin A derivatives, barbiturates, certain antibiotics, propofol, volatile anesthetics, non-depolarizing muscle relaxants, some local anesthetics, statins, fibrates, glitazones, **beta blockers**, biguanides, amiodarone, some chemotherapies, some neuroleptics, nucleoside reverse transcriptase inhibitors and various other drugs

## Neurofibromatosis type I ◦

Caused by the mutation of a gene on **chromosome 17** that is responsible for ◦  
production of a protein, called **neurofibromin 1**.

NF-1 is an **autosomal dominant disorder**, Neuroinflammation and immune ◦  
disorders

The prevalence of **peripheral neuropathies** would be significantly increased in ◦  
ASD.

Peripheral neuropathies may be **asymptomatic**. ◦

Peripheral neuropathy is a common manifestation of mitochondrial diseases and ◦  
**polyneuropathies** would be relatively common.

Neuropathies could also be caused by other features of ASD. ◦

- **Tuberous sclerosis**

- **25% and 61%.**

- **Turner syndrome**

- One study found that **23%** of girls with Turner syndrome who were included met criteria for a diagnosis of an autism spectrum disorder and the majority had "significant social communication difficulties"

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# Neurological Disorders, Epilepsy, and Sensory Dysfunction

Macrocephaly, hydrocephalus, cerebral palsy, migraine/headaches, ADHD, autonomic nervous system dysfunction, congenital abnormalities of the nervous system. ◦

Epilepsy occurs at a much higher rate with **30%** of the ASD population having a comorbid seizure disorder, compared to **6-7%** of the general population, and **60%** having an abnormal electroencephalogram (EEG). ◦

Sensory dysfunction also occurs at a high prevalence in individuals with autism. ◦

# Epilepsy or seizure disorders

Intellectual disability, **an underlying neurologic disorder**, family history of epilepsy, and **severe cognitive delay** increase the risk of epilepsy in patients with ASD. ◦

Symptoms to probe with parents **include repeated**, unexplained abrupt changes in behavior ◦ such as staring **spells, stiffening** of muscles, involuntary **jerking** of limbs, **or sudden sleepiness or sleep disturbance**.

Sudden, unexplained, and marked **irritability or aggression**, or regression in normal ◦ development.

# ○ Sensory problems

- Unusual responses to sensory stimuli are more common and prominent in individuals with autism, with comorbidity rates of **42–88%**.
- The prevalence of reported "**unusual sensory behaviors**" **45 to 95%** depending on factors such as age, IQ and the control group used.
- poor muscle tone, poor motor planning, and toe walking;
- **ASD is not associated with severe motor disturbances.**
- Uncomfortable to sit or stand, and may stand in an awkward position, such as with both feet together, supinating, sitting cross-legged or with one foot on top of the other or simply having an awkward gait.
-

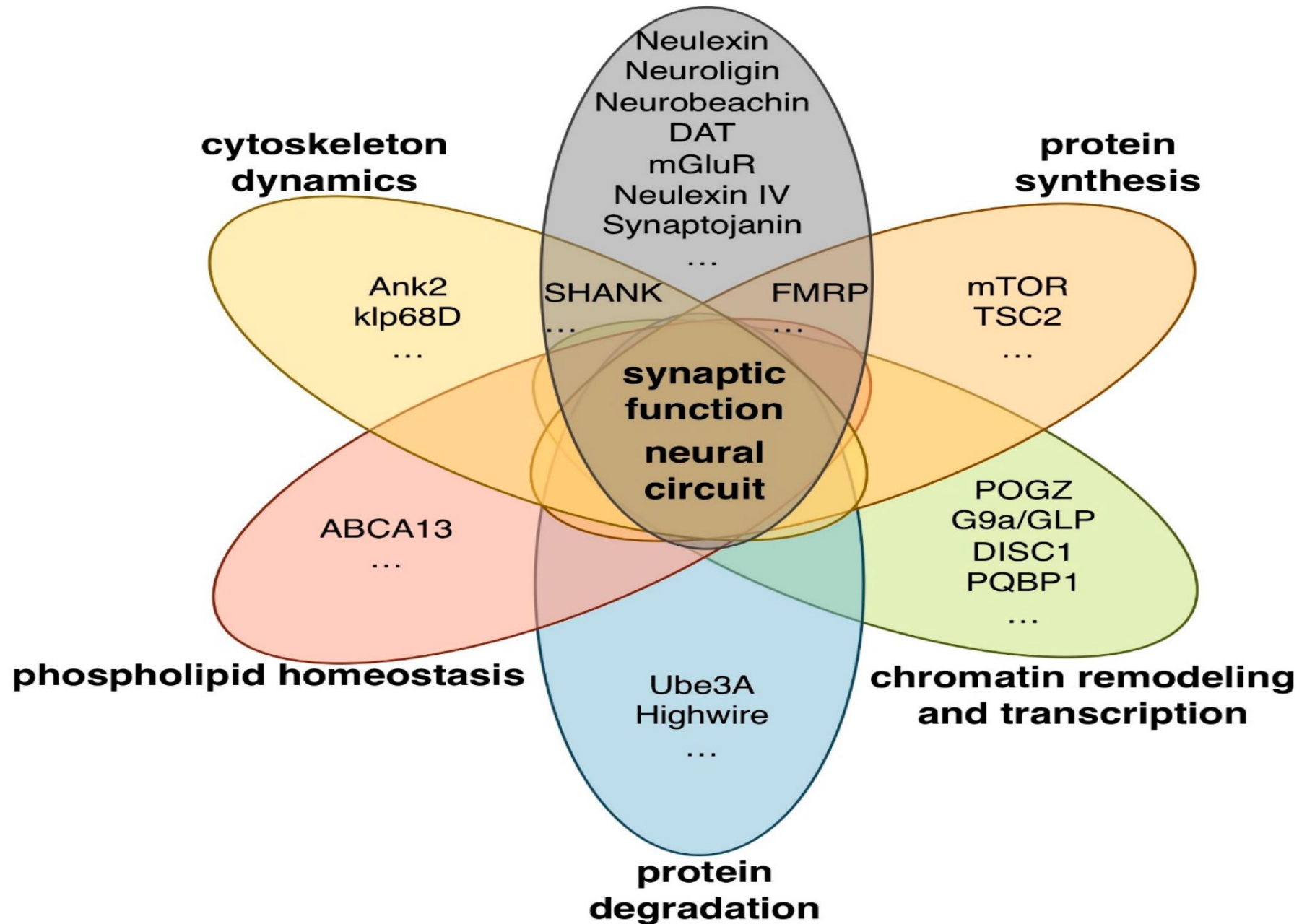
- Learning disabilities

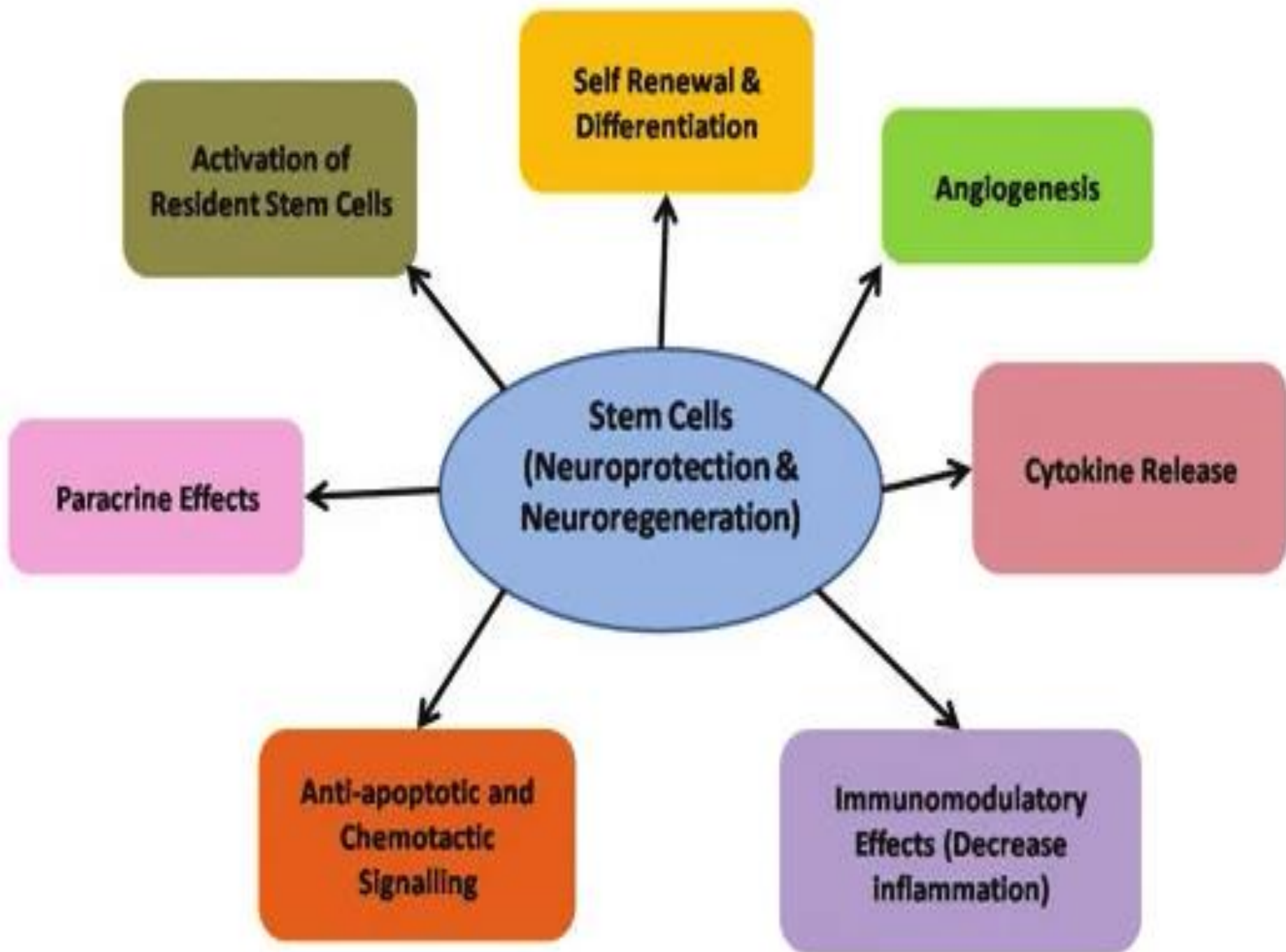
- (25–75% )

- **Developmental coordination disorder (dyspraxia)**

- Delayed in acquiring motor skills that require motor dexterity, such as bicycle riding or opening a jar, and may appear awkward or "uncomfortable in their own skin".

# synaptogenesis and synaptic plasticity





## Strabismus ◦

with rates **3–10** times that of the general population ◦

## Tinnitus ◦

**35%** of people who are autistic would be affected by tinnitus, which is much higher than in the general population. ◦

## Tourette syndrome ◦

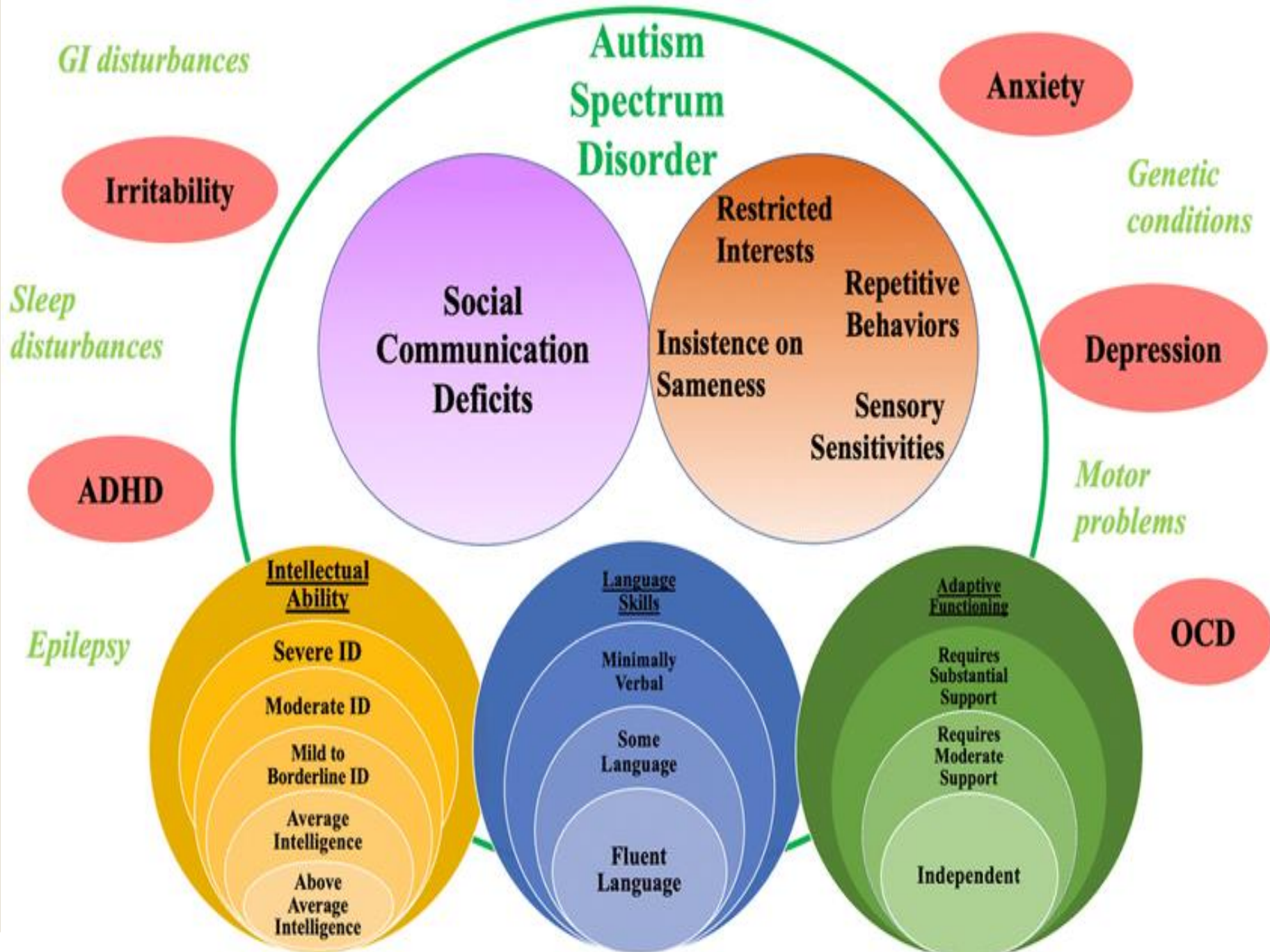
The prevalence of Tourette syndrome among individuals who are autistic is estimated to be **6.5%, higher** than the **2% to 3%** prevalence for the general population. ◦

◦

# Sleep Disorders

- Between **50% to 80%** of children with autism have a sleep disorder. ◦
- Problems include difficulty falling asleep, frequent, and prolonged ◦  
wakening, or extremely early rising
- can affect behavior, **aggression**, learning, **anxiety**, attention, **mental** ◦  
**health**, communication, and the ability to engage in their everyday  
activities and lives.





# EMERGENCY ROOM AND OUTPATIENT GUIDELINES

- Children with ASDs have a **30% higher risk of medical emergencies** than their unaffected peers.
- This risk increases to **70% in teens between the ages of 15 and 18 years.**

# Anxiety

- 11% and 84%.
- Anxiety disorders are common among children and adults with ASD.
- . Many anxiety disorders, such as social anxiety disorder and generalized anxiety disorder, are not commonly diagnosed in people with ASD because such symptoms are better explained by ASD itself, and it is often difficult to tell whether symptoms such as **compulsive checking** are part of ASD or a co-occurring anxiety problem.

# Attention-deficit hyperactivity disorder

- However, following years of clinical research, the most recent edition of the DSM ([DSM-5](#)) in 2013 removed this prohibition of co-morbidity.
- Thus, individuals with autism spectrum disorder may also have a diagnosis of ADHD, with the modifiers of inattentive, hyperactive, combined-type, or not otherwise specified.
- The term '**AuDHD**' is sometimes used for those with both autism and ADHD

# Brain fog

Brain fog is a constellation of symptoms that include reduced cognition, inability to concentrate and multitask, as well as loss of short and long-term memory. ◦

Brain fog can be present in patients with autism spectrum disorder (ASD). ◦

Its prevalence, however, remains unknown ◦

# Bipolar disorder

Bipolar disorder, or manic-depression, is itself often claimed to be comorbid with a number of conditions, including autism. Autism includes some symptoms commonly found in mood and anxiety disorders.

# Depression

Major depressive disorder has been shown by several studies to be one of the most common comorbid conditions in those with ASD, and is thought to develop and occur more in high-functioning individuals during adolescence, when the individual develops greater insight into their differences from others.

# Obsessive–compulsive disorder ◦

About **30%** of individuals with autism spectrum disorders also have OCD. ◦

# Obsessive–compulsive personality disorder ◦

excessive concern with orderliness, perfectionism, attention to details, mental and interpersonal control and ◦  
a need for control over one's environment which interferes with personal flexibility, openness to  
experience and efficiency as well as interfering with relationships.

**40%** of those diagnosed with Autism met the diagnostic requirements for a co-morbid **OCPD** diagnosis ◦

# Psychosis and schizophrenia ◦

Childhood-onset schizophrenia is preceded by childhood autistic spectrum disorders in almost half of cases, and an increasing number of similarities are being discovered between the two disorders. ◦

Studies have also found that the presence of psychosis in adulthood is significantly higher in those with autism spectrum disorders, ◦

◦

## Reduced NMDA-receptor function ◦

Reduced NMDA receptor function has been linked to reduced social interactions, locomotor hyperactivity, self-injury, prepulse inhibition (PPI) deficits, and sensory hypersensitivity, among others. ◦

**Results suggest that NMDA dysregulation could contribute to core ASD symptoms.** ◦



# Schizoid personality disorder ◦

Schizoid personality disorder (SPD) is a personality disorder characterized by a lack of interest in ◦  
social relationships, a tendency towards a solitary or sheltered lifestyle, secretiveness, emotional coldness, detachment and apathy.

Symptoms typically start in late childhood or adolescence. ◦

# ○ Feeding or eating challenges

- Selective eating and obesity are the two most common feeding or eating disorders for pediatricians to be aware of in their patients with ASD.
- **Thirty percent** of children with autism are obese, compared with 13% of the general population.
- Sensory issues, anxiety, medication side effects, social isolation, and activity level can all be underlying factors and should be discussed with patients and families.

# Vitamin deficiencies

Vitamin deficiencies are more common in autism spectrum disorders than in the general population.

- **Vitamin D** : Vitamin D deficiency was concerned in a German study **78% of hospitalized autistic population. 52% of the entire ASD group**
- **Vitamin B12** : in the brain tissue of autistic children were three times lower than those of the brain tissue of children not affected by ASD.
- **Vitamin B9 (folic acid)** : Studies have been conducted regarding folic acid supplementation in autism in children. "The results showed that folic acid supplementation significantly improved certain symptoms of autism such as sociability, verbal / preverbal cognitive language, receptive language, and emotional expression and communication. In addition, this treatment improved the concentrations of folic acid, homocysteine and redox metabolism of standardized glutathione."

**Vitamin A** : Vitamin A can induce mitochondrial dysfunction. Vitamin A and its derivatives, retinoids , disrupt mitochondrial function by a mechanism that is not fully understood."

- **Zinc** : Zinc deficiency incidence rates in children aged 0 to 3, 4 to 9 and 10 to 15 years were estimated at 43.5%, 28.1% and 3.3% for boys and at 52.5%, 28.7% and 3.5% among girls.

- **Magnesium** : Incidence rates of magnesium deficiency in children aged 0 to 3, 4 to 9 and 10 to 15 years were estimated at 27%, 17.1% and 4.2% for boys and at 22.9%, 12.7% and 4.3% among girls.

- **Calcium** : Incidence rates of calcium deficiency in children aged 0 to 3, 4 to 9 years and 10 to 15 years were estimated at 10.4%, 6.1% and 0.4% for boys and at 3.4%, 1.7% and 0.9% among girls.

It has been found that special diets that are inappropriate for children with ASD usually result in excessive amounts of certain nutrients and persistent vitamin deficiencies.[88]

- **Abnormal folate metabolism**[

- decrease in 5-methyltetrahydrofolate production, **autoantibodies to the alpha folate receptor (FR $\alpha$ )**.

- These autoantibodies have been associated with cerebral folate deficiency.

# Abnormal redox metabolism

- An imbalance in **glutathione-dependent redox metabolism** has been shown to be associated with autism spectrum disorders (ASD).
  
- Interestingly, recent DBPC studies have shown that **N-acetyl-1-cysteine**, a glutathione precursor supplement, is effective in improving the symptoms and behaviors associated with ASD.

# Gastrointestinal disorders

GI disorders affect as many as **85%** of patients with ASD. ◦

Behavioral clues that a patient may be experiencing pain related to GI problems ◦  
(**diarrhea, constipation, gaseousness, or painful bowel movements**) include **arching the back, pressing the belly, or gritting teeth.**

Many have restricted diets due to sensory sensitivities or parental choice (gluten- ◦  
and casein-free).

In some cases, medication may be causing GI side effects. While some parents ◦  
report a gluten-free diet helps improve behaviors, research doesn't back that up.

# Toileting problems

Difficulties in learning how to use the toilet during the day and at night, knowing when they need to use the toilet, communicating the need to use the toilet, being able to get to the toilet independently or in time, learning to use different toilets with which they are unfamiliar, wiping themselves, sensory differences (dislike of the noise made by toilets, the sensation of passing urine/faeces, a cold toilet seat, or a preoccupation with water in the toilet), smearing faeces, a range of continence-specific difficulties, including bowel or bladder difficulties such as bedwetting and constipation



# Immune and Auto Immune Conditions,, Allergic Disorders, Diabetes

- **25%** of children with ASD have immune deficiency and dysfunction.
- Allergic disorders are significantly more common including asthma and atopic conditions and there is a **correlation between the severity of allergies and the severity of autism.**
- Food allergies are also increased affecting **20%-25%** of ASD children, compared to **5%-8%** in the general population.
- **30% of children with autism are obese**, compared with **13%** of the general population. This may correlate with the increase in diabetes found in **8%** of the ASD population vs **4%** of the general population.

# ◦ **درمان دارویی ADHD+ASD**

- **Stimulants**
- **Atomoxetine**
- **Alpha-Agonists**
- **SGA**

# درمانهاي روانشناختي ASD

- **Applied Behavior Analysis**
- **Structured Teaching**
- **The Treatment and Education of Autistic and related Communication-handicapped Children (TEACCH; Mesibov, Shea, & Schopler, 2005)**
- **Developmental Models**
- **Greenspan and Wieder's (1997) developmental individual-difference, relationship-based (DIR) model**
- **and Gutstein and Sheely's (2002) relationship-development intervention (RDI)**

**Thanks**