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REVIEW

From synaptic dysfunction to atypical emotional processing in autism

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Autism spectrum disorder (ASD) is a complex neurodevelopmental condition mainly characterized by social impairments and repetitive behaviors. Among these core symptoms, a notable aspect of ASD is the presence of emotional complexities, including high rates of anxiety disorders. The inherent heterogeneity of ASD poses a unique challenge in understanding its etiological origins, yet the utilization of diverse animal models replicating ASD traits has enabled researchers to dissect the intricate relationship between autism and atypical emotional processing. In this review, we delve into the general findings about the neural circuits underpinning one of the most extensively researched and evolutionarily conserved emotional states: fear and anxiety. Additionally, we explore how distinct ASD animal models exhibit various anxiety phenotypes, making them a crucial tool for dissecting ASD's multifaceted nature. Overall, to a proper display of fear response, it is crucial to properly process and integrate sensorial and visceral cues to the fear-induced stimuli. ASD individuals exhibit altered sensory processing, possibly contributing to the emergence of atypical phobias, a prevailing anxiety disorder manifested in this population. Moreover, these individuals display distinctive alterations in a pivotal fear and anxiety processing hub, the amygdala. By examining the neurobiological mechanisms underlying fear and anxiety regulation, we can gain insights into the factors contributing to the distinctive emotional profile observed in individuals with ASD. Such insights hold the potential to pave the way for more targeted interventions and therapies that address the emotional challenges faced by individuals within the autism spectrum.

Keywords: anxiety; autism spectrum disorder; fear; interoception; threat processing

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with worldwide prevalence. The etiology of ASD remains intricate, involving complex interactions between genetic and environmental factors. Inheritability studies have provided compelling evidence supporting a strong heritability

Abbreviations
ADHD, attention deficit hyperactivity disorder; ADNP, activity-dependent neuroprotective protein; ASD, autism spectrum disorder; BNST, bed nucleus of the stria terminalis; CASPR2, contactin-associated protein-like-2; CNTNAP2, contactin-associated protein-like 2 gene; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; E, excitatory; FMR1, fragile X messenger ribonucleoprotein 1; fMRI, functional magnetic resonance imaging; FMRP, fragile X mental retardation protein; FXS, fragile X syndrome; I, inhibitory; KO, knock-out; MAP1b, microtubule-associated protein 1b; mPFC, medial prefrontal cortex; NLGN, neuroligins; NTS, nucleus of the solitary tract; PSD-95, postsynaptic density-95; PTEN, phosphatase and tensin homolog; SHANK3, SH3 and multiple ankyrin repeat domains protein 3; vHPC, ventral hippocampus.

component and genetic contribution in ASD [1,2]. Recently, using whole-exome sequencing, more than 100 candidate genes were associated with ASD, with changes ranging from single point mutations to copy number variations [3]. Notably, most of the candidate genes are involved in synaptic function and neuronal development supporting the hypothesis of altered neuronal communication and connectivity in ASD individuals and mouse models.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), ASD individuals present social communication impairments and restricted, repetitive patterns of behavior, including unusual interests and altered sensorial sensitivities [4]. Furthermore, together with these core symptoms, individuals often present psychiatric disorders such as anxiety, depression, and high levels of aggression. Recent studies demonstrate that 40–50% of the children in the autism spectrum are diagnosed with at least one anxiety disorder, a percentage considerably higher compared to the general pediatric population [5,6], and around 60% demonstrate signs of aggression toward their caregivers [7,8]. Furthermore, poor emotional regulation during school age persists until adulthood [9,10], emphasizing the importance of early interventions. Some monogenic ASD animal models also display exacerbated aggressive behaviors, increased anxiety, and decreased ability to regulate anxiety levels after stressful events [11–14], supporting the idea that ASD genetic mutations and their impact on synaptic function and neuronal connectivity might contribute to emotional dysregulation.

In this review, to establish comparisons between human and animal model data, we will consider emotions as evolutionarily conserved states instead of the conscious perception of feelings. We will start by defining the general features of emotional states, with the main focus on fear and anxiety, and the neuronal circuits linked to them. Simultaneously, we will analyze how the distinct mutations observed in ASD might influence emotional fearful states.

Defining emotional states

The definition of emotions remains a subject of active debate, mainly characterized by two viewpoints: the psychological perspective, which characterizes emotions as consciously perceived feelings [15,16], and the evolutionary perspective, which conceives them as adaptive internal states [17,18]. Within the framework of the evolutionary perspective, emotions are integrated states that encompass neurological, behavioral, autonomic, and endocrinal responses. Darwin initially postulated that emotions evolved in animals to promptly respond and adapt to environmental changes and to communicate critical social information [19,20]. Notably, both seem to be altered in individuals with ASD, who commonly exhibit difficulties in adapting to novelty and have preference for repetitive tasks, displaying also communication and social deficits [4]. Emotional states have different dimensions such as valence (positive vs negative), intensity (mild to strong), persistence (acute vs prolonged), and generalization. Individuals with ASD often exhibit distinct regulatory patterns in terms of perceiving and navigating emotional states across these various dimensions, especially in terms of generalization and intensity. Atypical processing mechanisms within the brain–body axis may explain atypical emotional profiles in ASD, contributing to the emotional regulation challenges inherent in ASD. Thus, understanding the intricate interplay between emotional processing and its underlying neural circuits may be crucial to unravel the complexities of emotional experiences in the context of ASD. Building upon this foundation, we now delve into the neural substrates of an emotional state prevalently altered in ASD: fear and anxiety. By examining the circuits governing such emotions, we aim to explore how their dysregulation may contribute to the emergence of anxiety disorders frequently observed among individuals with ASD, such as phobias.

Neurobiology of fear and anxiety

Fear and anxiety are crucial for survival and one of the most studied emotions. These highly evolutionary conserved states can be differentiated by threat (un) certainty: fear responses are elicited upon immediate, discernible threats, while anxiety emerges in anticipation of potential dangers [21,22].

Using field observation and behavioral paradigms such as Pavlovian fear conditioning where a neutral stimulus gets associated with an aversive unconditional stimulus [23], it was possible to understand that fear stimuli are generally triggered by external or internal sensorial cues, generating brain states that elicit a wide range of responses from behavioral, to autonomic to endocrinal. Simultaneously, the body constantly communicates its physiological state to the brain through a process known as interoception, providing ongoing updates about bodily conditions. Considering this framework, a successful fear response relies on individual ability to process and integrate sensorial cues with internal physiological state.

Regarding the sensorial integration of cues that trigger fear, each cue is initially processed through

different neural circuits according to its sensory modality, flowing through the thalamus to sensory-specific primary and associative cortices [24,25]. Subsequently, this sensory information converges within the lateral amygdala, a focal hub in the orchestration of fear responses, where emotional valence of the sensory stimuli gets evaluated to initiate appropriate behavioral and physiological responses. Connection between the thalamus and the amygdala allows the brain to rapidly process incoming sensory information, providing an immediate route for evaluation of potential threats [25–29]. As such, impairments in amygdalar circuits can lead to inadequate processing of sensory information, with inaccurate assignment of emotional valence to a particular stimulus. Of note, pharmacological inhibition or lesion of the amygdala leads to increased social interaction and decreased fear responses, demonstrating well this interplay between fear and sociability [30,31].

Regarding the integration of interoceptive signals, information flows to the brain mainly through the brainstem region of the nucleus of the solitary tract (NTS). From the NTS, the visceral inputs reach multiple brain regions, including the periaqueductal gray [32], parabrachial nucleus [33], the hypothalamus, and the amygdala [34]. These centers will subsequently transmit internal sensory information to the insular cortex via thalamus [35]. The insula is a region situated deep within the brain that is intricately connected to the limbic system [36]. This connectivity allows the insula to integrate external sensory information with internal physiological signals, forming a comprehensive representation of our emotional and bodily states [37,38]. Insula's role as the main interoceptive hub is well portrayed by its involvement in various processes, including perception of pain, temperature, and heartbeat, as well as other visceral sensations. Functional neuroimaging studies have consistently shown heightened insular activation during tasks involving interoceptive awareness [39,40]. Besides, alterations in insular activity have been associated with emotional disorders, such as anxiety and alexithymia, underscoring its relevance in emotional regulation [41–45].

In terms of localizing the specific input structures that trigger anxiety, this has been more challenging. Nevertheless, it is hypothesized that synchronized neural activity within the amygdala, bed nucleus of the stria terminalis (BNST), ventral hippocampus (vHPC), and medial prefrontal cortex (mPFC) is critical to assess the presence or absence of potential threats [25,46].

Despite fear and anxiety being innate emotional states crucial for survival, environmental maladaptations, genetic predisposition, and medical conditions can occur, leading to the emergence of pathological fear and anxiety conditions.

Autism spectrum disorder

Autism spectrum disorder is a heterogeneous neurodevelopmental disorder characterized by a range of symptoms that typically manifest in early childhood. The primary symptoms are impaired social interaction and restricted repetitive behaviors, including unusual interests and altered sensorial sensitivities [4]. These core symptoms are often accompanied by other psychiatric and medical conditions such as intellectual disability, epilepsy, anxiety disorders, depression, attention deficit hyperactivity disorder (ADHD), sleep disorders, and gastrointestinal problems [47]. It is estimated that ASD is present in 0.4% of Asian, 1%, of African, 1% of American, 0.5% of European, and 1.7% of the Australian population [48] with an average male-to-female ratio of 4 : 1 [49]. This complex multifactorial disorder has a strong genetic contribution mainly characterized by rare inherited and *de novo* variants. These variants range from submicroscopic duplications and deletions (copy-number variants) to small insertions or deletions (indels) and single nucleotide alterations. In a recent study, utilizing whole-exome sequencing, over 11 000 individuals diagnosed with ASD were examined leading to the identification of 102 risk genes that had *de novo* or rare variants. A significant proportion of these risk-associated genes exert roles in regulating neuronal communication and gene expression. Additionally, the authors observed an enrichment of risk gene expression at excitatory and inhibitory neuronal lineages of the human cortex, which aligns with previous observations of an excitatory–inhibitory imbalance in ASD [3]. Despite its highly heterogeneous background, with both environmental etiological factors and genetic mutations that can vary from chromosomal location to levels of penetrance, multiple efforts have been made to understand the biological basis of ASD. By generating animal models of risk-associated genes and exposure to environmental risk factors, scientists have been able to unravel some of the complex mechanisms underlying ASD's behavioral and neurological alterations.

ASD mouse models carrying common mutations related with neuronal and synaptic dysfunction

A variety of genetic animal models have been developed to study ASD, each designed to mimic specific genetic mutations or alterations associated with the disorder. Some of the most commonly used genetic

models include *Fmr1*-KO, *Pten*-KO, *Cntnap2*-KO, *Shank3*, and *Nlgn3* mutated and KO mice [50,51].

FMR1

Mutations in the Fragile X Messenger Ribonucleoprotein 1 (*FMR1*) gene are implicated in the fragile X syndrome (FXS), being one of the most common and studied monogenic causes of ASD. FXS is characterized by a silencing of the *FMR1* gene caused by a CGG repeat mutation on chromosome Xq27.3 with subsequent methylation [52]. This genetic alteration leads to a lack of the Fragile X Mental Retardation 1 protein (FMRP), a protein involved in mRNA trafficking from the nucleus to the dendrites. FMRP binds to a range of essential synaptic proteins involved in neurotransmission and structural integrity, such as postsynaptic density-95 (PSD-95), subunits GluR1 and GluR2 of the AMPA receptor, and microtubule-associated protein 1b (MAP1b) [53]. Phenotypically, *Fmr1*-KO rodents exhibit behaviors that resemble human FXS/ASD, such as social and communication deficits, repetitive behaviors, and cognitive impairments [54,55]. Interestingly, while individuals with fragile X syndrome exhibit high levels of anxiety, naive rodent models do not seem to display altered anxiety [56]. However, upon exposure to fear conditioning paradigms, *Fmr1*-KO rats become more anxious than controls, suggesting impaired adaptation to stressful situations [11]. *Fmr1*-KO rodents may hence help to reveal the neural circuits underlying the challenges faced by ASD individuals when adapting to stress.

SHANK3

The SH3 and multiple ankyrin repeat domains protein 3 (*SHANK3*) gene is located in the human chromosome 22q13.3 and encodes a scaffold protein known as SHANK3. This protein is primarily found in the postsynaptic density of excitatory synapses, where it interacts with various proteins involved in synaptic transmission, structural integrity, and signaling pathways [57]. SHANK3 mutations are linked to Phelan–McDermid syndrome, a rare genetic disorder often characterized by intellectual disabilities and ASD symptoms. *Shank3* mutant mice display some of the core features of ASD, such as deficits in social interactions, repetitive behaviors, and impaired communication, being commonly used to study ASD [12,58]. Multiple *Shank3* mutant mice have been generated, including a specialized model carrying a human genetic mutation, the *InsG3680-Shank3* mouse [59]. These animals exhibit high anxiety levels even under naive conditions. Similarly, *Shank3*-KO rats generated through CRISPR-Cas9 technology, also demonstrate increased anxiety [60]. Further studies should be performed to explore the underlying mechanisms contributing to their increased anxiety.

PTEN

Phosphatase and tensin homolog (*PTEN*) acts as a tumor suppressor gene by regulating cellular proliferation and differentiation through the inhibition of the PI3K-AKT signaling pathway. While mutations in this gene are mostly linked with cancer, they have also been identified in individuals with ASD and macrocephaly [61,62]. Similar to other models, *Pten-KO* rodents also display deficits in sociability and increased repetitive behavior. Additionally, these mice present brain overgrowth [63], a characteristic observed in a subset of individuals with ASD [42]. Regarding anxiety, certain studies have found no alterations in these rodents, particularly in females, whereas others have revealed decreased anxiety levels, specifically in males [11,64–66]. Thus, while this model may not replicate the anxiety levels observed in certain individuals with ASD, it emphasizes the heterogeneity of the disorder. Given its interesting trait of reduced anxiety, *Pten-KO* rodents could also be a useful tool to uncover new molecular pathways to alleviate anxiety and sex-related differences in anxiety-related behaviors.

ADNP

Activity-dependent neuroprotective protein (ADNP) has been frequently found to be mutated in ASD individuals [67,68]. The ADNP syndrome, also known as Helsmoortel–Ven Der Aa syndrome, is featured by intellectual disability and developmental delays, as well as motor and gastrointestinal problems. Despite being only discovered in 2014, it is one of the most commonly identified single-gene causes of ASD [69]. *hADNP* gene is located in chromosome 20q12-13.2, a region associated with tumor growth, and is implicated in cell survival as well as in mammalian brain formation [70]. In contrast to the *Pten* mutant rats, *Adnp*-haploinsufficient female mice exhibited altered anxiety-related behaviors, while male mutants had no alterations, highlighting the complex interplay of genetics and sex-specific factors in ASD [71].

CNTNAP2

Contactin-associated protein-like 2 (*CNTNAP2*) is located in the human chromosome 7q35 and encodes

an adhesion molecule named contactin-associated protein-like-2 (CASPR2), a neuronal transmembrane protein. CASPR2 is part of the neurexin superfamily and is involved in neuron–glia interactions and in the clustering of potassium channels in myelinated axons, such as Kv1 [72,73]. Several rare and common variations of this gene have been described in patients with ASD. Additionally, mutations in this gene have also been linked to language impairments and intellectual disabilities [74]. *Cntnap2* mutant mice show impairments in ASD core domains: deficits in social interactions with reduced vocal communication and repetitive and restrictive behaviors [75]. No studies have been conducted to assess anxiety levels in this mouse model.

NLGN

Neuroligins (*NLGN*) are genes that encode synaptic cell adhesion molecules involved in the formation and consolidation of synaptic connections. These proteins are located postsynaptically and, depending on their subtype, they can be more expressed in either excitatory or inhibitory synapses. For instance, NLGN1 is mainly located in excitatory synapses [76], NLGN2 in inhibitory synapses [77], NLGN3 in both excitatory and inhibitory synapses [78], and little is known about NLGN4 due to its poor evolutionary conservation, although in humans it has been shown to be present in excitatory synapses [79]. Among these subtypes, the ones associated with non-syndromic ASD are the X-linked *Nlgn3* and *Nlgn4* genes [80]. Animal models with loss of function or missense mutation in the *Nlgn3* gene display stereotypical ASD core behaviors such as deficits in social communication and repetitive behaviors. No changes in anxiety have been observed in the *Nlgn3*-KO [81] and *Nlgn3*^{R451c} mutant mice [82]. However, due to the heterogeneous localization and function of NLGN3, it is possible that different mutations may cause distinct phenotypes, as observed in humans. Together these aspects make *Nlgn* animal models a valuable tool for exploring both convergent and divergent patterns of ASD [83].

Despite the diversity, ASD models share similar synaptic dysfunction phenotypes such as disruption of excitatory (E) and inhibitory (I) neurotransmission balance (E/I imbalance). This disruption has been described in both human and multiple animal models and is associated with a decrease in the activity of parvalbumin neurons [84–86]. Such imbalance, if present in the neural circuits associated with fear and anxiety, may contribute to the high prevalence of anxiety disorders among individuals with ASD. Across different mouse models, distinct anxiogenic phenotypes are evident as well as shared changes in synaptic transmission, plasticity, and connectivity [50,87]. Identifying both commonalities and discrepancies among these mutations could offer insights into novel therapeutic avenues to treat anxiety symptoms in ASD.

Autism spectrum disorder: neuronal and synaptic dysfunction in fear- and anxiety-related circuits

One of the commonly observed comorbidities in individuals with ASD is anxiety. Around 40–50% of children with ASD experience at least one anxiety disorder [5,6], a notably higher prevalence compared to the general pediatric population's range of 5–6.5% [88,89]. Of all types of anxiety disorders, development of unusual phobias is one of the most common. These phobias can encompass intense fear of everyday objects, sounds, textures, or even specific patterns, which can lead to significant distress and challenges in daily life [90]. Why are ASD children so prone to anxiety/phobias? What neurobiological alterations are changing fear perception? Altered sensorial perception? The limbic processing of threats?

Sensorial triggering

Proper sensorial perception is essential for accurately assessing threats. Inadequate perception might lead to misinterpretation of harmless stimuli, leading to unnecessary fear responses or heightened anxiety. One of the main core symptoms of ASD is atypical sensorial perception. In fact, even though ASD individuals present sharp vision with good contrast discrimination, in terms of visual perception these individuals exhibit a strong bias over detail in static stimuli [91] but struggle with global-motion perception [92]. Neuroimaging studies using functional magnetic resonance imaging (fMRI) demonstrate that ASD individuals present atypical, enhanced responses in the primary visual cortex and primary motion area when exposed to high motion pictures [93,94]. Interestingly, this altered activity seems to depend on how long the participants are allowed to see the motion picture: longer exposure times lead to more activity in the visual and motion cortex, but shorter exposure times result in reduced activity [92]. Further investigation regarding this modified activity pattern in the visual and motion cortex during motion signal processing could potentially elucidate the increased sensitivity/aversion that individuals with ASD commonly demonstrate toward moving objects, including mechanical toys and running water [95]. Of note, *Fmr1*-KO and *Shank3* mutant rodents

show changes in how the visual cortex processes sensory information [96–98]. A recent study demonstrates that, after pre-exposure to a visual perceptual experience, *Fmr1*-KO mice have a reduced magnitude and duration of multiple oscillations of the visual cortex compared to WT. The authors further demonstrate that functional connectivity between layers differs between WT and *Fmr1*-KO post-perceptual experience [98]. Likewise, another study demonstrates that *Fmr1*-KO exhibits delayed learning on a visual discrimination task due to reduced activity of parvalbumin neurons in the visual cortex, and restoration of their activity potentiates learning to the visual task [97].

Similar to the visual system, individuals with ASD also seem to display disruptions in auditory processing, without having hearing deficits [99]. Sound is a fundamental sensory cue to provide critical information regarding potential threats. For instance, a sudden loud noise, like a gunshot, can trigger an immediate emotional fear state characterized by a heightened alertness and rapid physiological changes to prepare the body to freeze, flight, or fight, depending on the threat imminence. Auditory cues also contribute to the perception of social cues, such as tone of voice and speech patterns, which are essential for inferring emotional states and intentions of others. Overall, auditory information pairs with visual and tactile cues to create a comprehensive perception of the environment, facilitating adaptive responses to potential threats.

Around 90% of individuals with ASD are diagnosed with hypersensitivity to auditory stimuli and, in some cases, hyposensitivity. In individuals with hypersensitivity, sounds are perceived as overwhelmingly intense, causing distress or discomfort [100,101]. But some ASD individuals seem to appreciate certain sounds and enjoy making noise, being characterized as hyposensitive [102,103]. However, it is important to recognize that the dichotomy of hypersensitivity and hyposensitivity may not fully encapsulate the complexity of sensory processing variations seen in ASD. Sensory processing differences can often exhibit a dynamic interplay, where an individual might be hypersensitive to certain stimuli while being hyposensitive to others.

All the ASD animal models described in the previous section seem to present auditory alterations. Such alterations have been attributed to E/I imbalance, alterations in synaptic transmission, and changes in neuronal morphology in multiple auditory-processing brain regions such as the inferior colliculus, thalamus, and auditory cortex ([104] and detailed review in [51]). Interestingly, *Fmr1*-KO mice display a decreased fear response in tone-recall but not context-recall, which suggests a dysregulation in associating the tone to the threat [105]. In contrast, *Nlgn3*-KO demonstrates deficits in both contextual and tone recall [106], while *Shank3*-KO mice show increased fear response to the tone recall [107]. Studying the mechanisms that underlie these divergences in auditory processing during fear responses could elucidate the distinct circuits that encode pure auditory versus auditory-contextual versus pure-contextual perception and offer insights into the heterogeneity of sensorial responses observed in individuals with ASD. Of note, all these studies used fear paradigms that elicit passive defensive behavior responses. Considering that individuals with ASD often exhibit distress responses marked by aggression in the presence of auditory anxiety-inducing stimuli, it would be interesting to study how these diverse animal models elicit defensive attacks toward an anxiety/fear stimulus. Accordingly, it would be interesting to test whether the observed fear response to a tone recall would change toward more aggressive behaviors in the presence of another mouse.

Processing of threat

One of the first brain regions to be associated with threat processing was the amygdala. Even though it is currently known that threat processing encompasses a multitude of brain regions, the amygdala is still considered one of the main hubs for fear and anxiety processing. This region is part of the limbic system and has a fundamental role in deciphering emotional valence of sensory stimuli, quickly assessing whether a stimulus poses a danger threat [108]. Amygdala dysfunction can lead to improper threat assessment, contributing to anxiety and fear-related disorders. Growing evidence demonstrates that individuals with ASD have structural and functional differences in the amygdala. Structural studies have reported faster growth [109] and enlargement of the amygdala in ASD children [110,111], whereas adolescents and adults present either similar or reduced volume compared to neurotypical controls [112,113]. In accordance, infants with ASD seem to present a larger number of neurons in the amygdala, while adults present a decreased number [114,115]. Functionally, neuroimaging studies using fMRI have revealed differences in amygdala activation in response to emotional stimuli, where individuals with ASD demonstrated atypical increased activation when processing faces [116,117] or fearful expressions [118]. Together with the structural findings, it is hypothesized that ASD alterations in the amygdala could contribute to difficulties in recognizing and responding to emotional cues in social interactions. Such difficulties, together with sensory alterations,

could potentially serve as a significant precursor to the emergence of social anxiety, namely, the development of phobia toward large crowds.

Consistent with observations in human data, ASD animal models also exhibit age-dependent differences in amygdala activity. Young *Fmr1*-KO rodents exhibit hyperexcitability in the principal neurons of the lateral [119] and basolateral amygdala [120], attributed to a reduction in inhibitory transmission [121]. Conversely, adult *Fmr1*-KO rodents display changes in lateral amygdala excitatory activity, characterized by reduced excitatory synaptic transmission and impaired long-term potentiation, mechanisms responsible for memory formation. These alterations may contribute to the observed deficits in tone recall, as reflected by decreased freezing responses. Furthermore, the activation of the presynaptic metabotropic glutamatergic receptor 5 (mGluR5) can reverse synaptic transmission and plasticity deficits and normalized fear response in a rat model of FXS [122]. These amygdalar findings seem to contrast with conventional E/I imbalance described in other brain regions, where enhancing inhibitory interneuron activity typically leads to beneficial effects.

Visceral information

A fundamental aspect of fear and anxiety responses lies in the integration of internal physiological signals, a process named interoception that collectively contributes to our ability to assess the level of threat and adapt our reactions accordingly. Visceral signals originating from internal organs, such as heart rate, breathing rate, and gastrointestinal sensations, provide essential information about our physiological state. In the context of fear and anxiety, interoception enables us to detect physiological changes, such as increase or decrease of heart rate. Impaired interoception can lead to misinterpretation of bodily signals, resulting in exaggerated or inappropriate fear and anxiety responses. From the early days, individuals with ASD have been described as having interoception difficulties, often linked to gastrointestinal sensations like hunger [95]. However, it was only recently that cardiac interoception in ASD patients has generated significant attention, primarily due to its relevance in fear and anxiety-related disorders. Individuals with panic and generalized anxiety disorder consistently show greater heartbeat perception compared to controls in a heartbeat detection task. This increased accuracy in detecting heartbeats has been recognized as enhanced interoceptive accuracy. Accordingly, anxious individuals also present enhanced interoceptive sensibility, developing an increased cardiac interoceptive awareness [123,124]. These findings suggest that individuals with anxiety disorders possess the ability to detect subthreshold interoceptive signals, that are then amplified and associated with potential threats, giving rise to anxious thoughts [40,125,126]. Regarding individuals with ASD, divergent findings have been reported. While certain studies indicate that cardiac interoception remains intact [127], others propose decreased cardiac interoceptive accuracy in heartbeat detection tests, with higher interoceptive sensibility based on self-report questionnaires [128–130]. These discrepancies might be attributed to the considerable diversity within the spectrum [131], as well as age-related factors, namely, impaired interoceptive perception in children [132]. Nonetheless, these observations suggest a plausible link between low interoceptive accuracy and attention deficit, alongside alexithymia, while enhanced interoceptive sensibility could be related to anxiety symptoms.

In recent years, the insular cortex has emerged as a central player in the interoceptive aspects of fear and anxiety. In individuals with ASD, abnormal structural and functional organization has been described in the insular cortex, especially in the anterior part which is the sub-area related with emotional processing [133,134]. Neuroimaging studies demonstrated insular hypoactivity during tasks requiring the interpretation of emotional facial expressions [135,136]. This decrease in activity has been linked to the difficulties experienced by individuals with ASD in terms of social processing and their capacity to engage effectively in interpersonal interactions. It would be pertinent to conduct a more in-depth assessment of insular activity during interoceptive accuracy tasks versus interoceptive sensibility questionnaires. Such analysis could potentially elucidate whether distinct patterns of activation are present and whether these patterns contribute to the different functional organization within sub-areas of the insular cortex.

Only a limited number of studies have explored potential alterations in the insular cortex in ASD animal models. Changes in synaptic transmission linked to kainate receptors within the insula have been described in *Fmr1*-KO mice [137]. Additionally, findings from *Shank3* mutant mice indicate disruptions in the excitation–inhibition balance of the insula, which appear to be linked with impaired sensory integration of auditory and tactile stimuli [138]. Further investigations focused on assessing disruptions within the insular cortex associated with cardiac interoception and their potential implications for anxiety disorders could shed light on the mechanisms contributing to heightened anxiety among individuals with ASD.

Conclusions and future perspectives

Autism spectrum disorder has a complex landscape characterized by impairments in communication, social interaction, and sensory perception, together with heightened susceptibility to anxiety disorders. The prevalence of anxiety disorders in ASD individuals is notably higher than in the general pediatric population, with unusual phobias being a prevalent manifestation. Disturbances in sensory processing, particularly in the visual and auditory domains, coupled with alterations in the amygdala, may underlie difficulties in interpreting emotional cues. Additionally, emerging research highlights the crucial role of interoception in modulating fear and anxiety responses, adding another layer of complexity. Notably, children with ASD exhibit differences in cardiac interoception perception and insular activity, which could intersect with anxiety symptoms (Fig. 1).

Animal models provide valuable tools for dissecting biological mechanisms, bridging the gap between human observations and underlying neural circuits. Yet, many questions still persist in ASD research. How does E/I imbalance affect sensory perception and threat assessment in ASD? How does the amygdala integrate such altered sensory signals? The intricate relationship between amygdala structural changes and their repercussions on fear and anxiety in ASD requires further exploration. Moreover, to the best of our knowledge, little animal research has been performed addressing the implication of cardiac interoception in ASD. Targeting these pathways could potentially ameliorate some of the behavioral and cognitive deficits associated with the disorder. Recognizing and addressing the unique requirements of children on the autism spectrum is crucial to promote favorable development of these individuals. As such, research advances that can provide insights into the intricate physiological mechanisms contributing to ASD may pave the way for more effective interventions and improved outcomes for individuals living with ASD.

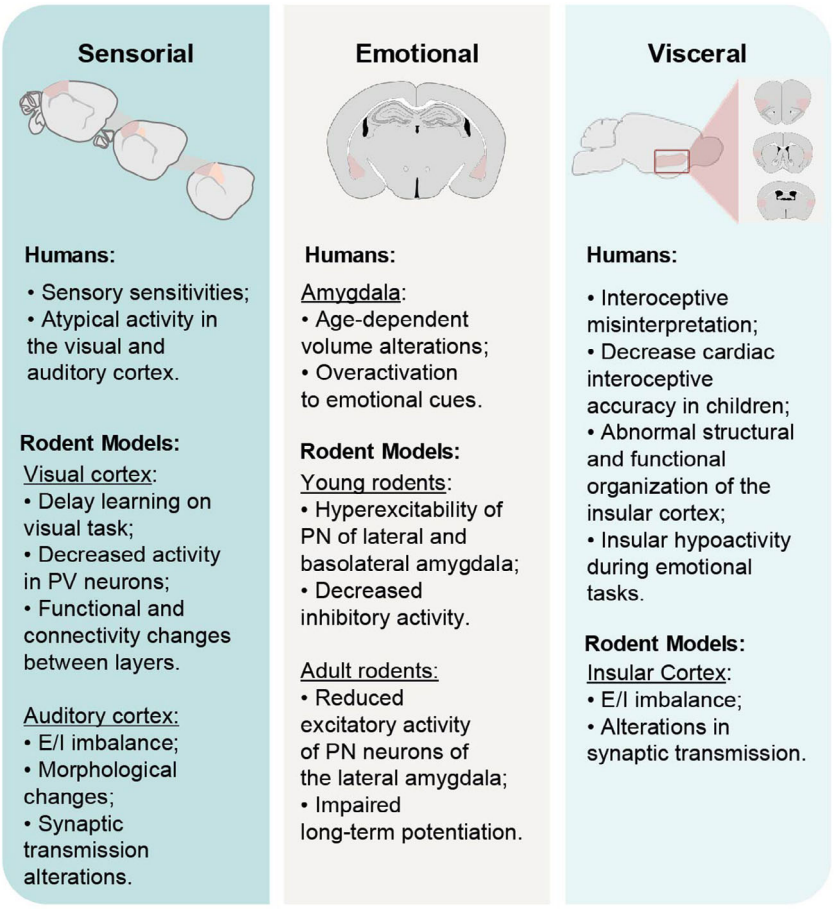

Fig. 1. Schematic depicting the main sensorial, emotional, and visceral findings from ASD patients and genetic rodent models of ASD.

Author contributions

S.R. conceptualized and wrote the paper. P.M. revised it critically for important intellectual content.

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