The Meltdown Pathway: A Multidisciplinary Account of Autistic Meltdowns

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Abstract

Autistic meltdowns are involuntary fits of intense frustration, rage, and often physical violence elicited by sensory and cognitive stressors easily tolerated by neurotypicals. While nearly 70% of autistic individuals display the "crisis behaviors" associated with meltdowns, the neural mechanisms that underlie this maladaptive response are not yet well understood. This has thus far hampered progress towards a dedicated therapeutic intervention–beyond traditional medications—that limits their frequency and severity. Here, we aim to initiate an interdisciplinary dialogue on the etiology of meltdowns. In doing so, we frame meltdowns as a consequence of underlying chronic hypervigilance and acute hyperreactivity to objectively benign stressors driven by differences in the insular cortex—a multimodal integration hub that adapts autonomic state and behavior to meet environmental demands. We first discuss meltdowns through the lens of neurophysiology and argue that intra-insular hypoconnectivity engenders vagal withdrawal and sympathetic hyperarousal in autism, driving chronic hypervigilance and reducing the threshold of stressors those with autism can tolerate before experiencing a meltdown. Next, we turn to neuropsychology and present evidence that meltdowns reflect an inability to properly integrate contextual evidence, particularly social cues, when acutely assessing ambiguous signs of danger in the environment—a process termed neuroception. Finally, we build on contemporary predictive coding accounts of autism to argue that meltdowns are ultimately driven by chronic failures of sensory attenuation and coherent deep inference within the interoceptive hierarchy, possibly linked to oxytocin deficiency during infancy. Throughout, we synthesize each perspective to construct a multidisciplinary, insula-based model of meltdowns.

Key Words: Autism spectrum disorder, anterior insula, neuroception, predictive coding, polyvagal theory

1. **Introduction:**

"Imagine not being able to shut out noises all around you every minute of your life. Wouldn't there come a breaking point for you?" (Lipsky & Richards, 2009)

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by core deficits in social communication, cognitive flexibility, and sensory processing. The sociocognitive aspects of the autistic phenotype are often most recognizable, given that they impair fundamental aspects of social functioning—from emotional reciprocity and relationship formation to communication through verbal and non-verbal cues (American Psychiatric Association, 2013). However, abnormalities in sensory processing are also *central* to the autistic phenotype. Specifically, those with ASD are known to experience "hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment" (American Psychiatric Association, 2013). Rather than using prior experiences to construct a well-integrated, coherent portrait of their sensory reality, those with autism tend to fixate on subtle details in their environment (Lawson et al., 2014; Palmer et al., 2017; Van de Cruys et al., 2014)—such as the hum of a switched-off television set and the hints of perfume that remain in the air after a guest has already left the room (Belek, 2019; Bertone et al., 2005; Happe & Frith, 2006; Iarocci & McDonald, 2006; Lane et al., 2019; Smith et al., 2015; Smith Roley et al., 2007).

Chronic hypersensitivity to auditory (Rotschafer, 2021; Yamasaki et al., 2014), visual (Ashwin et al., 2009), tactile (Fukuyama et al., 2017), and olfactory (Ashwin et al., 2014) stimuli can give rise to "sensory overload"—a frustrating sensory experience wrought with excessive and overwhelming detail. Although there is wide variation in the specific sets of environmental stimuli or situations that can overwhelm different autistic patients (Cesaroni & Garber, 1991;

Grandin, 1992; Kern et al., 2006; Kientz & Dunn, 1997; Marco et al., 2011; Tecchio et al., 2003; Watling et al., 2001), those with ASD universally report intense physical and emotional distress when experiencing sensory overload (Belek, 2019; Jones et al., 2003; Leekam et al., 2007; Marco et al., 2011; Pellicano, 2013). The behavioral manifestation of hypersensitivity-induced distress can take several forms and is the primary focus of this article.

1.1. Clinical Description of Autistic Meltdowns:

People with autism, especially those with a high-functioning diagnosis, often cope with sensory overload by "shutting-down," or withdrawing from their environment altogether (Belek, 2019; Lipsky, 2011b). However, shutdowns can rapidly progress to, or be bypassed by, aggressive behaviors indicative of intense arousal of the sympathetic nervous system—a clinical profile termed "behavioral crisis" (or colloquially, "meltdown") (Beversdorf et al., 2008; Guinchat et al., 2015; Lipsky, 2011b; McGonigle et al., 2014; Vasa et al., 2020). Patients in crisis will generally hit, kick, bite, or run away from caregivers, creating a distressing situation for everyone involved (Alhaddad et al., 2019; Debbaudt, 2009; Mazefsky & Handen, 2011). It is estimated that 68% of children and adolescents with ASD have displayed such aggressive behaviors at some point in their lives (Kanne & Mazurek, 2011), although there is no epidemiological data currently available to describe the prevalence of meltdowns themselves among this patient demographic.

As has been emphasized in recent literature, it is critical to distinguish between the behavioral phenotypes of a "tantrum" and an autistic meltdown. While tantrums are intentional displays of rebellion or anger to achieve some goal, meltdowns are *involuntary* states of intense arousal that manifest as violent and uncontrollable outbursts (Lipsky, 2011b; Mazefsky &

Handen, 2011, p. 259; Montaque et al., 2018). During a meltdown, an autistic individual will have limited situational awareness and experience impaired verbal reasoning, making it difficult to extinguish the crisis through rational discussion and reassurance alone (Lipsky & Richards, 2009, pp. 17-18). These behavioral observations, in tandem with evidence of broadly enhanced sympathetic arousal in autistic patients experiencing crisis (Goodwin et al., 2006; Picard, 2009), portray the meltdown state as a pronounced fight-or-flight response (Lipsky, 2011b; Lipsky & Richards, 2009, p. 20).

1.2. Causes of Autistic Meltdowns:

While meltdowns have traditionally been framed as hypersensitivity stress responses to sensory overload, the actual causes of behavioral crisis can vary widely between patients, situations, and contexts. In her first-hand, ethnographic account of autistic crisis behaviors, *From Anxiety to Meltdown*, Debroah Lipsky distinguishes between meltdowns caused by sensory overload and those related to cognitive tasks. Sensory meltdowns are caused by exposure to one or more hypersensitivity trigger—such as a crowded public venue (which contains many overwhelming visual, auditory, and tactile stimuli). In comparison, cognitive meltdowns result when an autistic person feels they have an incomplete or ambiguous understanding of why something has happened. This often occurs when they are provided unsatisfactory or seemingly illogical answers to questions, or when their expectations for the future are violated by the unpredictable realities of daily life. Meltdowns can be precipitated by the frustration involved in integrating multiple pieces of information, abrupt transitions, time limits, miscommunications, and overwhelming social situations (Lipsky, 2011a; Lipsky & Richards, 2009). The meltdown response can also represent the “tip of an iceberg”—representing the unfortunate climax of

several overwhelming experiences that gradually diminish an autistic individual's ability to self-regulate (Mesibov et al., 2005; Stark et al., 2015).

Behaviors reminiscent of autistic meltdowns can be observed in neurotypical populations. However, these responses are generally limited in frequency, far less severe, and occur in response to more obviously stressful events—such as the sudden passing of a loved one (Ishida et al., 2015), intense fatigue (Scheydt et al., 2017; Süllwold, 1991), or exposure to an acute physical threat (Bracha, 2004). This begs the question: why do those with autism exhibit pronounced sympathetic arousal in response to cognitive and sensory stressors that are easily tolerated by others? We can organize our thinking about this question and model the meltdown response in three different ways. Those with autism either (1) have a baseline hypervigilance ("autistic hypervigilance") that reduces the threshold of additional stressors they can tolerate before experiencing a fight-or-flight response (**Figure 1a**); (2) interpret the cognitive or sensory stressors that trigger meltdowns as being much more dangerous or threatening than they appear to neurotypicals (in other words, they experience "hyperreactivity") (**Figure 1b**), or (3) a combination of both (**Figure 1c**).

1.3. Objectives:

In this paper, we explore current evidence that autistic crisis behaviors are a consequence of both autistic hypervigilance and hyperreactivity. In doing so, our objective is to initiate an *interdisciplinary* dialogue about the neural substrates underlying autistic meltdowns. Specifically, we seek to understand meltdowns through the lens of three distinct autism literatures. First, we mobilize the neurophysiology literature to frame autistic hypervigilance—and by extension meltdowns—as a behavioral correlate of hypoconnectivity within the insular

cortex. The insula is a multimodal integration center that both processes (bottom-up) and coordinates (top-down) activity in the autonomic nervous system in parallel with behavior—processes termed interoception and interoceptive inference, respectively (Benarroch, 2019; Craig, 2009). We then turn to neuropsychology and argue that autistic hyperreactivity and the meltdown response reflect a fundamental failure of insular neuroception—a subpersonal threat appraisal that integrates contextual evidence and adapts autonomic and behavioral states to meet environmental challenges. Finally, we apply a predictive coding framework and argue that chronic hypervigilance, acute hyperreactivity, and meltdowns reflect a failure of coherent deep inference within the interoceptive hierarchy. In each section, we synthesize these three perspectives to show that autistic meltdowns are a manifestation of both acute (hyperreactivity) and chronic (hypervigilance) failures of context-dependent threat appraisal, likely resulting from dysfunction of the anterior insula.

2. Neurophysiological Perspective: Intra-Insular Hypoconnectivity in Autism Drives Chronic Hypervigilance:

2.1. Polyvagal Theory:

In his polyvagal theory, Stephen Porges (1995, 2001, 2007) argued that the mammalian autonomic and behavioral response to threats could be classified into three distinct "phylogenetic stages." He characterized stage I responses as avoidance behaviors and "shutdowns" associated with activity of the unmyelinated vagus—a parasympathetic efferent that descends from the Dorsal Motor Nucleus of the Vagus (DMNV). Sympathetic fight or flight responses to threats are classified as stage II behaviors and are associated with activity in sympathetic efferents originating from the rostral ventromedial medulla (RVMM). Conversely, a soothed, "stage III"

autonomic state is furnished by activity of the myelinated vagus—a parasympathetic efferent which originates in the Nucleus ambiguus (NAmb) of the medulla. Stage III autonomic states are typically accompanied by adaptive coping behaviors, including self-soothing and social communication (Patriquin et al., 2019; Porges, 1995; Silvani et al., 2016).

Porges (2007) argued that activity in the myelinated branch of the vagus is functionally integrated with that of the cranial nerves controlling facial expressions into a "Social Engagement System." This network coordinates stage III autonomic reflexes with positive affect and facilitates appropriate verbal/non-verbal social engagement with non-threatening stimuli (Patriquin et al., 2019). In fact, higher parasympathetic outflow, measured via high-frequency spectral indices of heart rate variability (HF-HRV) and respiratory sinus arrhythmia (RSA), has been correlated with greater emotional expressivity (Cole et al., 1996), lower trait anxiety (Watkins et al., 1998), increased positive affect (Goodlin, 2015; Lü et al., 2013; Oveis et al., 2009; Wang et al., 2013), enhanced perceived strength of social networks (Kok & Fredrickson, 2010), and improved executive function (Hansen et al., 2003; Johnsen et al., 2003). The reliable coincidence of vagal outflow with these sophisticated patterns of socio-emotional behavior suggests an intimate relationship between the *cortical* networks that regulate autonomic, affective, and social cognition. According to the Neurovisceral Integration Model, the insula, anterior cingulate cortex, amygdala and other regions of the cortex serve broad roles in coordinating these three dimensions of behavior (Song et al., 2016; Thayer et al., 2009). These cortical regions combine with the subcortical, midbrain, and brainstem structures outlined in **Figure 2** to make up the central autonomic network, which is responsible for selecting and implementing appropriate autonomic and behavioral responses to novel (and therefore potentially threatening) environmental stimuli (Benarroch, 1993).

2.2. Role of the Insula in Autonomic Regulation, Sensory Processing, and Behavior:

Overlaid on the reflexive brainstem circuits in the central autonomic network is a robust cortical architecture that supports nuanced, context-sensitive autonomic responses to threat in animals. In other words, processing at the cortical level helps an organism select a polyvagal response most suitable for their context. Key players in the cortical autonomic network include the medial prefrontal cortex (McKlveen et al., 2015), the anterior cingulate cortex (Gianaros et al., 2005; Luu & Posner, 2003), and the insular cortex (Cechetto, 2014; Silvani et al., 2016). We focus much of our discussion going forward on the insular cortex, a cortical hub that coordinates bottom-up interoception (perception of internal body states), sensorimotor processing and socio-emotional functioning with top-down autonomic control (Uddin et al., 2017). For our purposes, we will review current evidence of the insula's role as a bottom-up sensory integration cortex (Gogolla, 2017) and a top-down modulator of the autonomic nervous system (ANS).

The insula is thought to be the first cortical relay station that receives and processes bottom-up interoceptive data from the visceral organs (ie. cardiac activity, blood pressure, digestive processes, etc.). However, beyond serving as the primary interoceptive cortex, the insula also serves as a multimodal integration center that uses exteroceptive sensory data to contextualize peripheral body states (Benarroch, 2019; H. C. Evrard, 2019). It is well-documented that thalamo-insular and cortico-insular efferents carrying auditory, visual, vestibular, proprioceptive, gustatory, olfactory and pain-related sensory data terminate in the insula of humans (Baier et al., 2013; Benarroch, 2019; Chikazoe et al., 2019; Deen et al., 2011; Frank et al., 2014; Lopez et al., 2012; Mazzola et al., 2017).

In his seminal homeostatic model of insular function, neuroanatomist Bud Craig proposed that the multimodal contextualization of interoceptive data proceeds systematically along a posterior-anterior gradient (or rostral-caudal gradient in humans). According to his model, interoceptive signals received in the posterior insula are integrated with exteroceptive signals in the mid and anterior insula. These data are further integrated with information from limbic (anterior cingulate) and frontal (dorsolateral and ventromedial prefrontal cortex) efferents in the anterior insula (AI), contextualizing internal body states within the external environment and giving rise to an embodied "sense of self" (Craig, 2009, 2010, 2015; H. C. Evrard, 2019; Namkung et al., 2017). The anatomical details of Craig's model have been largely supported in humans using tractography, fMRI, and stroke studies (Benarroch, 2019; H. C. Evrard, 2019; Rodgers et al., 2008; Shura et al., 2014).

Beyond its role in bottom-up interoceptive processing, the insula serves a complementary role in top-down autonomic and behavior regulation (Craig, 2009; Goswami et al., 2011; Taylor et al., 2010). Situated at the highest levels of the central autonomic network, the insula integrates incoming streams of interoceptive and exteroceptive sensory data and selects a polyvagal response that best meets the moment. In this way, the insula serves as a crucial crossroads between the body and outside world. It is important to emphasize that insular activity initiates more than just autonomic reflexes. Rather, it prepares an organism to meet environmental challenges by evoking parallel shifts in autonomic and behavioral state (Gehrlach et al., 2019; Rogers-Carter et al., 2018). For instance, Gehrlach et al. (2019) demonstrated that optogenetic activation of the posterior insular cortex in mice induced parallel increases in respiratory rate and defensive behaviors. Reciprocal connections between the insula and motor command centers (including primary motor cortex, supplementary motor area and pre-supplementary motor area)

allows the insula to influence motor plans and shape behavior (Benarroch, 2019; Ghaziri et al., 2017). The cytoarchitecture and functional connectivity of the primate insular cortex are summarized in **Figure 3**.

While the role of insular processing in autonomic regulation is well-established, mapping the *specific* insular loci that trigger different phylogenetic stages of the threat response has proven more difficult. **Supplementary Table 1** reviews progress towards identifying insular loci responsible for top-down sympathetic and parasympathetic control—termed pressor and depressor loci, respectively. As outlined in the table; lesioning, micro-stimulation, and neuroimaging studies in rodent and human subjects over the past thirty years have yielded very mixed results. This is likely due to interspecies variation, methodological differences, low sample sizes, and the limitations of using human participants in brain mapping studies. Additionally, postulates that once dominated the field—such as the putative lateralization of sympathetic and parasympathetic control to the right and left insula, respectively (Craig, 2002, 2009, 2015; Hilz et al., 2001; Lane et al., 2001; Oppenheimer & Cechetto, 2016; Oppenheimer et al., 1992; Williamson et al., 1997; Zamrini et al., 1990)—are now being called into question by contradictory new evidence (Beissner et al., 2013; Chouchou et al., 2019; Kimmerly et al., 2005; Valenza et al., 2019).

It is therefore important to recognize that the precise localization of pressor and depressor insular loci along right-left and anterior-posterior axes is still an ongoing area of investigation. However, for our purposes, we consider the regions defined in Beissner et al. (2013) and Chouchou et al. (2019) to be the most reliable candidates. Through a comprehensive meta-analysis of 43 neuroimaging studies, Beissner et al. (2013) identified parasympathetic-associated loci within bilateral anterior insulae and sympathetic-associated loci within the left

posterior insula and the right ventral AI. Chouchou et al. (2019) established a slightly different, more general causal dichotomy between anterior/posterior insular stimulation and parasympathetic/sympathetic cardiac outflow, respectively. Specifically, they observed cardiac pressor regions primarily in the posterior insula and depressor regions in anterior portions of the mid-insula. Given the robust sample sizes used in both studies and the *causative* relationships established by the latter, we will emphasize Beissner and Chouchou's anterior-posterior framework in our model of the central autonomic network. Specifically, we will regard cardiac depressor regions as being *primarily* localized closer to the anterior pole of the insula, bilaterally, and cardiac pressor loci as being localized *primarily* within the left posterior insula and the right AI. Pressor and depressor loci mediate their respective autonomic responses by initiating different top-down motor pathways within the central autonomic network (Silvani et al., 2016). In fact, pressor and depressor loci project to topographically distinct regions of the lateral hypothalamus, parabrachial nucleus, and NTS (Yasui et al., 1991). Pressor regions also more heavily innervate the BNST (Yasui et al., 1991) and the amygdala (Cerliani et al., 2012; Ghaziri et al., 2018), both of which are associated with stage II sympathetic outflow (Lebow & Chen, 2016).

2.3. Evidence of Chronic Polyvagal Dysfunction in Autism (Autistic Hypervigilance)

As far back as 1964, Hutt et al. described autistic individuals as being in a "chronic and inflexibl[y] high state of arousal." They based this description on observations that children with ASD exhibited a characteristic behavioral withdrawal and had markedly higher frequency EEG waves than their neurotypical counterparts. Interestingly, Hutt also linked this state of hyperarousal with the expression of crisis behaviors (Hutt et al., 1964; Patriquin et al., 2019). In

the half-century since, substantial evidence has been gathered to suggest that those with autism exhibit the autonomic (Bal et al., 2010; Bujnakova et al., 2016; Daluwatte et al., 2013; Goodwin et al., 2006; Guy et al., 2014; Hollocks et al., 2014; Kootz & Cohen, 1981; Kushki et al., 2014; Mathewson et al., 2011; Ming et al., 2010; Ming et al., 2005; Patriquin et al., 2019; Porges et al., 2013; Vaughan Van Hecke et al., 2009; Watson et al., 2012; Woodard et al., 2012) and behavioral (Buitelaar, 1995; Porges, 2001) markers of stage II polyvagal responses on a near-continuous basis. Inflexible stage II responses have been particularly well-documented in autistic patients with intellectual impairments (Patriquin et al., 2019). It is this chronic hypervigilance that we propose to be reducing an ASD patient's ability to tolerate *additional* cognitive/sensory stressors before melting down into a full-blown fight-or-flight response (**Figure 1a**). While this hypervigilant autonomic and behavioral phenotype seems to emulate a classical stage II response, it could in theory be mediated by either tonic parasympathetic withdrawal, sympathetic over-activation, or a combination of both. Here, we briefly review evidence for parasympathetic and sympathetic abnormalities in ASD, keeping in mind that autistic hypervigilance may be mediated by different patterns of autonomic anomalies in different individuals (for a comprehensive review, see Patriquin et al. (2019)).

ASD patients have been described extensively in the literature as chronically lacking a "vagal brake" on their behavior, preventing them from adopting stage III coping strategies when faced with non-threatening, but unpredictable situations like social encounters (Bal et al., 2010; Patriquin et al., 2019; Porges, 2005). The persistence of this chronic "vagal withdrawal" in ASD has been supported by comparative evaluations of RSA, a surrogate measure of parasympathetic output positively correlated with vagal modulation of cardiac activity (Tonhajzerova et al., 2016). Several studies have demonstrated significantly lower RSA scores in individuals with

autism compared to typically developing controls (Bal et al., 2010; Denver, 2004; Edmiston et al., 2016; Guy et al., 2014; Ming et al., 2005; Neuhaus et al., 2014; Patriquin et al., 2019; Porges et al., 2013; Sheinkopf et al., 2019; Toichi & Kamio, 2003; Vaughan Van Hecke et al., 2009). Additionally, during exposure to consecutive sensory challenges of different modalities (visual, olfactory, auditory, etc.), the RSA scores of autistic children do not exhibit as much modality-to-modality variation as those of neurotypicals (Schaaf et al., 2015). Those with ASD also have lower HF-HRV indicies (Bharath et al., 2019; Matsushima et al., 2016)—a related measure that directly predicts parasympathetic cardiovagal input (Beissner et al., 2013; Rajendra Acharya et al., 2006). Vagal nerve stimulation has also been shown to improve some cognitive symptoms in ASD patients with a comorbid seizure disorder (Murphy et al., 2000; Park, 2003; Porges, 2005, pp. 72-73), further substantiating the role of vagal withdrawal in autism.

There is less of a consensus about the role of sympathetic abnormalities in ASD, although accounts seem to generally point towards sympathetic overactivity as a common mediator of autistic hypervigilance. This model is supported by physiological evidence that autistic patients have enhanced baseline pupil dilation (Anderson & Colombo, 2009; Anderson et al., 2013; Blaser et al., 2014) and elevated electrodermal activity (EDA)—a non-invasive marker of sympathetic outflow (Hirstein et al., 2001; Kushki et al., 2013). The literature also indicates that ASD patients display increased baseline plasma levels of norepinephrine (NE), the primary neurotransmitter of the sympathetic nervous system (Cook, 1990; Israngkun et al., 1986; Lake et al., 1977; Launay et al., 1987; Leboyer et al., 1994; Leventhal et al., 1990). This finding is further substantiated by observations that autistic patients produce urine with higher baseline levels of vanillyl mandelic acid (VMA) (Bharath et al., 2019) and homovanillic acid (HA)

(Kałuzna-Czaplińska et al., 2010)—both catecholamine breakdown products—compared to neurotypicals.

Moreover, improvement in verbal problem-solving and increased functional connectivity in the cerebral cortex has been observed following the administration of β-adrenergic antagonists, which block the sympatho-excitatory effects of NE, to autistic individuals (Anderson et al., 2013; Beversdorf et al., 2008; Narayanan et al., 2010). These findings suggest that sympathetic over-activation plays an important role in the social and cognitive behaviors associated with ASD. Despite these findings, several recent studies have reported null or contradictory results on nearly every parameter described above, including EDA (Bujnakova et al., 2016; Fenning et al., 2019; Gu et al., 2015; Panju et al., 2015) and VMA levels (Minderaa et al., 1994). This is likely a reflection of both methodological differences between studies as well as actual variation in the baseline sympathetic tone exhibited by different individuals with autism. Therefore, while there is robust evidence for general parasympathetic withdrawal in ASD, there are likely inter-individual differences in sympathetic activity across the vast and heterogeneous ASD population.

2.4. Neural Substrates of Polyvagal Dysfunction in Autism:

In recent years, researchers have considered several neural substrates to understand the striking autonomic abnormalities associated with ASD. Brainstem nuclei such as the DMNV (Kamitakahara et al., 2017) and NAmb (Delafield-Butt & Trevarthen, 2018; Kamitakahara et al., 2017) have been considered probable loci of ASD-related dysfunction, given their proximal roles in mediating stage I and III polyvagal responses, respectively. However, there is very little empirical evidence that supports the dysfunction of these specific brainstem structures in autism

(Dadalko & Travers, 2018; Delafield-Butt & Trevarthen, 2018; Rodier et al., 1996). McGinnis et al. (2013) offer a provocative analysis of NTS dysfunction in autism. They argue that the NTS is highly susceptible to ischemia and toxin accumulation—both of which are proposed risk factors for ASD (Desoto & Hitlan, 2007; Driscoll et al., 2018; Modabbernia et al., 2017; Palmer et al., 2009; Roberts et al., 2013; Skogheim et al., 2021; Windham et al., 2006)—due to the enhanced fenestration of its blood-brain barrier. Their review also presents evidence that cerebral blood flow, a parasympathetic-mediated phenomenon (Truijen & Van Lieshout, 2010) known to be globally depressed in autism (Bjørklund et al., 2018; Burroni et al., 2008), is controlled by the NTS. They show that, while lesioning the NTS impairs cerebrovascular autoregulation (Ishitsuka et al., 1986), NTS stimulation enhances cortical blood flow (Golanov & Reis, 2001; Nakai & Ogino, 1984), indicating that dysfunction of the NTS itself or the regulatory mechanisms that control it may underlie ASD-related autonomic abnormalities.

Several studies have also proposed the amygdala as a primary mediator of autistic hypervigilance (Bal et al., 2010; Kushki et al., 2014; Ming et al., 2005; Patriquin et al., 2019; Vaughan Van Hecke et al., 2009). However, no study to date has offered a specific neural mechanism to explain how amygdala dysfunction may contribute to vagal withdrawal. Researchers in the field are now arguing that it may be more promising to instead study dysfunction of the broader neural networks in which the amygdala participates (Zalla & Sperduti, 2013), particularly focusing on the higher-cortical areas that regulate this limbic structure (Birmingham et al., 2011; Paul et al., 2010). As emphasized previously, autistic hypervigilance presents with *both* autonomic and behavioral signs. If the locus of pathophysiology were in a brainstem or subcortical member of the central autonomic network, ASD would be a peripheral dysautonomia, and we would not see such severe social and behavioral correlates. Given that

vagal withdrawal in ASD is accompanied by deficits in socio-cognitive, emotional, and behavioral regulation, this necessarily implies dysfunction at the highest cortical levels of the central autonomic network—where these three functions are coordinated—rather than at the peripheral or brainstem level. These observations particularly suggest that dysfunction of the insular cortex, which we previously described to be a nexus of autonomic, social, and emotional functioning (Craig, 2009, 2015; Shura et al., 2014), may underlie the autonomic symptoms of autism.

2.5. Insular Contributions to Hypervigilance in Autism:

Neuroanatomical observations further substantiate the insula's role in autistic meltdowns. Over the past two decades, several studies have reported hypoactivity in the anterior insula of autistic patients across a diverse range of experimental tasks and conditions (Di Martino et al., 2009; Eilam-Stock et al., 2014; Paakki et al., 2010; Pitskel et al., 2011; Silani et al., 2008; Uddin & Menon, 2009). Furthermore, Failla et al. (2017) reported evidence of decreased connectivity between the anterior and posterior insula of autistic children—an anatomical feature of ASD supported by the studies summarized in **Supplementary Table 3**. In the context of this intra-insular hypo-connectivity, decreased anterior insula activity in autism can be understood as a consequence of impaired insular processing along the posterior-anterior axis. This would theoretically limit the neural input received by the mid and anterior insula, leading to defects in the behavioral functions these brain regions carry out. In fact, hypofunction of the AI has already been mobilized to explain the socioemotional and cognitive deficits associated with ASD (Caria & de Falco, 2015; Di Martino et al., 2009; Nomi & Uddin, 2015; Odriozola et al., 2016; Uddin & Menon, 2009).

As mentioned earlier, while the behavioral and autonomic components of a stage III response are predominantly initiated by depressor loci in the anterior insula, those of stage II responses are triggered by pressor loci in the posterior insula. The chronic impairment of posterior-anterior insular processing in autism therefore *minimizes the functional input* into depressor regions in the anterior insula, which we propose leads to chronic vagal withdrawal. Moreover, we predict that insular activity generated by incoming interoceptive data—unable to reach the anterior insula—may instead activate pressor regions located more posteriorly (particularly in the left insula). This disruption of sympathovagal balance would replace stage III responses with a *persistent* stage II response, giving rise to the autonomic and behavioral correlates of autistic hypervigilance. We propose this chronic hypervigilance reduces the threshold of additional stressors a person with autism can tolerate before experiencing a behavioral meltdown (**Model 1; Figure 1a**). **Figure 4** depicts how intra-insular hypo-connectivity may contribute to chronic vagal withdrawal and sympathetic hyperarousal in autism.

3. Neuropsychological Perspective: Acute Failure of Neuroception Drives Autistic Hyperreactivity

According to the model of chronic hypervigilance described in the previous section, those with autism are primed to experience and interact with the world as if danger lurks behind every corner. Their baseline autonomic physiology and behavior are constantly tuned to prepare them to face potentially threatening situations. However, beyond this baseline hypervigilance, it is also possible that failures of the *acute* threat appraisal process contribute to the etiology of meltdowns. As described earlier, meltdowns themselves are stage II responses to *acute* sensory

or cognitive triggers that are easily tolerated by neurotypicals—including crowded public venues, uncomfortable clothing, abrupt transitions and miscommunications (Lipsky, 2011a). It has been documented that benign tactile stimuli elicit an acute EDA response in autistic adults double that observed in neurotypicals, suggesting that those with autism interpret acute changes in their sensory environment as being much more threatening than they actually are (in other words, they experience "hyperreactivity") (**Figure 1b**) (Fukuyama et al., 2017).

In this section, we mobilize neuroception—a neuropsychology-based model of threat assessment—to rationalize why those with autism are predisposed to respond indiscriminately to any *acute* environmental stressor (be it a bear or a firework) with an immediate and inflexible stage II response. In other words, we offer a neuroception-based explanation for why those with autism seem to have a reduced capacity to acutely deploy the vagal brake when encountering new and *potentially* (but not necessarily) threatening sensory data—supporting the role of *hyperreactivity* (**Figure 1b**) and sensory hypersensitivities in meltdown etiology. In doing so, we also attempt to build a more complete model of the insula-driven threat response in neurotypicals and those with autism by grappling with several questions that our neurophysiology-based model of meltdowns left us with. These questions include: how does the insula of neurotypicals decide which novel situations are safe enough to not warrant a stage II response, allowing progression to stage III response, and how does this relate to the anatomical restriction of depressor regions to the anterior insula? In other words, how does the processing of novel and potentially threatening stimuli in the posterior insula differ from that in the anterior insula—without which we see such severe impairments of the threat response. Does the temporal progression of phylogenetic threat response stages (from stage I to III) in neurotypicals correlate with the anatomical progression of interoceptive data along the insula's posterior-anterior axis?

3.1. Neuroception and Polyvagal Theory:

When faced with unexpected and *potentially* threatening exteroceptive stimuli, the brain evaluates the situation's "threat level" and decides which stage of the threat response (eg. stage I, II, or III) to initiate through a subconscious process called neuroception (Patriquin et al., 2019; Porges, 2004). Neuroception draws on exteroceptive context cues, interoceptive feedback, and prior experience to 1) determine whether an acute change in the environment is threatening and 2) tune autonomic physiology and behavior accordingly (Porges, 2022). For example, the brain integrates the facial expressions, posture and vocal prosody of newly encountered strangers to determine whether they are safe or threatening. Either prosocial (stage III) or defensive (stage II) behavioral repertoires are then deployed to meet the moment. Situations determined to be threatening will disinhibit limbic structures like the amygdala and elicit stage II fight-or-flight responses. By contrast, the threat response in safe contexts tends to proceed sequentially, with unfamiliar stimuli first eliciting an increase in sympathetic tone that gradually fades as the stimulus is recognized as unthreatening, and the vagal brake is re-engaged (Porges, 2004). This stepwise sympathetic withdrawal tends to accompany amygdalar (Hoffman et al., 2007; Liberzon et al., 2000; Plichta et al., 2014; Williams et al., 2005), somatosensory (Mobascher et al., 2010), and behavioral habituation (Wilson, 1987) to exteroceptive stimuli that become constant or familiar. For our purposes, when we discuss neuroception, we are exclusively referring to the acute (1-2 minute) evaluation of a novel, unfamiliar, unexpected and potentially dangerous change in the environment.

3.2. Role of the Insula in Neuroception:

Given its intersecting roles across cognitive and affective domains, the insula has been proposed to be one of the primary neural substrates of neuroception (Critchley, 2005; Minichino et al., 2017; Porges, 2007). The insula has access to parallel streams of interoceptive and exteroceptive data, and is therefore uniquely positioned to answer the question: do my current behavioral and autonomic states prepare me to face my current environment? However, where and how neuroception fits into Bud Craig's traditional homeostatic model of insular function has not yet been explored. We believe attempting to map the insular substrates of neuroception in safe and threatening contexts will help us develop some intuition for why the insula's top-down autonomic control centers are structured the way they are, how threat appraisal differs in the anterior and posterior insula and why intra-insular hypoconnectivity drives autistic hyperreactivity. For our purposes, we propose the basic working model summarized in **Figure 5**.

We want to emphasize two key elements of this model. First, we assert that the exteroceptive context cues used to guide neuroception in the posterior and anterior insulae are likely very different. While the anterior insula has access to well-integrated and fully contextualized multimodal data, neuroception in the posterior insula relies on information that is comparatively uncontextualized. To illustrate this proposed difference, we will use the example of an unexpected firework show. Imagine a young child—who has never seen fireworks before—having fun at an amusement park with his family. He initially perceives his context to be safe and is expressing a stage III autonomic and behavioral state. Suddenly, he begins hearing loud, repeated explosions and sees flashing lights in the corner of his eye. According to the homeostatic model of insular function, the following multimodal data—each of which we refer to as 'neuroceptive cues'—converge on the child's posterior insula as the firework show begins: the sound of repeated explosions (danger cue), flashing lights (danger cue), people around him—

including his parents—smiling and laughing (safety cue) and (at least at first) interoceptive data reflecting the child's initially calm autonomic state (safety cue). Each of these individual data points report conflicting information that has not yet been integrated into a coherent portrait of the child's environment. Despite this ambiguity, the lights and explosions are fairly unambiguous—albeit general—instinctual signs of *potential* danger, and there is a clear mismatch between the child's new, potentially dangerous environment and their internal body state. Under our model, the posterior insula will react to this mismatch by initiating a stage II autonomic and behavioral response. This corresponds to the top horizontal panel in **Figure 5** and the first leg of the threat response in safe, but novel, contexts.

To overturn this initial stage II response, the child's brain would have to conclude that the neuroceptive cues indicating safety are actually more reliable readouts of the environment's threat level than those indicating danger. He would have to place more confidence in other people's reactions to the firework show than his own innate reaction to it, as his only real safety cues are the calm and happy responses of people around him at the park (as indicated by facial expressions, vocal prosody, etc.) (Porges, 2009). This is the case for many unfamiliar, potentially threatening situations—from crowded stores during the holidays to loud graduation ceremonies. Furthermore, the child would likely place different amounts of confidence in the reactions of his parents and those of a stranger to the fireworks, which might lead to different neuroception patterns if the child is with family or alone. Accordingly, weighing the relative reliability of safety and danger cues requires each cue to be fully contextualized—both within the current environment and within a person's past experiences.

Within the insula, this kind of demanding cognitive process could only happen in the anterior insula. By the time neuroceptive cues reach this part of the insula, they have been fully

integrated and contextualized by prior knowledge, observational learning cues and other factors from the ventromedial and dorsolateral prefrontal cortex (Gonzalez & Fanselow, 2020; Horga et al., 2011; Penick & Solomon, 1991; Stark et al., 2018; Szeska et al., 2022), anterior cingulate cortex and parietal lobe (Chang et al., 2013; Deen et al., 2011; Gu et al., 2013; Nomi et al., 2016; Uddin et al., 2014). The anterior insula also plays an important role in deciphering and embodying the emotions of others, which allows people to weigh the reactions of those around in their own threat assessments (Gu et al., 2012). Neuroception in the anterior insula corresponds to the bottom horizontal panel in **Figure 5**—the second leg of the threat response in safe, but novel, contexts. In summary, while the anterior insula has the capacity to weigh the reliability of multiple pieces of ambiguous sensory evidence to distinguish safe and dangerous environments, the posterior insula is starved of the appropriate context and can only evaluate a potential threat at face value.

Our working model argues that neuroception in the neurotypical posterior insula occurs to help furnish an initial behavioral and autonomic response to a change in the environment while the anterior insula gathers information and performs a more thorough and time-consuming threat assessment. This leads us to the second key element of our model that we seek to emphasize: because the anterior insula can make highly informed threat assessments, even in ambiguous situations, it can initiate either stage II or stage III autonomic and behavioral responses. By contrast, because the posterior insula can only identify the inherent threat level of individual neuroceptive cues, it can only initiate stage II responses when faced with a novel, potentially threatening situation. We propose this may be why depressor regions are restricted to the anterior insula, while pressor regions exist along the entire insula (although they are primarily concentrated in the posterior insula).

3.3. Failure of Neuroception in Autism Drives Hyperreactivity:

Chronic hypervigilance and acute hyperreactivity in ASD have been described by many as reflecting a critical failure in the neuroception of safety vs. threat, preventing the transition from stage II sympathetic to stage III parasympathetic responses to unfamiliar stimuli (Patriquin et al., 2019; Porges, 2004; Singletary, 2015; Vaughan Van Hecke et al., 2009). This perspective is supported by evidence of attenuated neural and behavioral habituation to stimuli across sensory modalities in ASD. These findings are summarized in **Supplementary Table 2**. A particularly interesting study by Green et al., (2015 & 2019) demonstrated that only autistic youth with sensory hypersensitivity—a known cause of sensory meltdowns (Belek, 2019; Jones et al., 2003; Leekam et al., 2007; Marco et al., 2011; Pellicano, 2013)—exhibit attenuated neural habituation of the amygdala and sensory cortex in response to novel tactile and auditory stimuli. When considered alongside our discussion of neuroception above, these data indicate that sensory hypersensitivity in autism—and by extension hyperreactivity and meltdowns—could have one of three causes: (1) overreliance on threat cues in anterior insula-based neuroception; (2) under-reliance on safety cues in anterior insula-based neuroception; or (3) use of only posterior insula-based neuroception to evaluate new, potentially threatening environmental changes.

In the context of our neurophysiology-based model (**Figure 4**), any of these causes are possible. The central idea of our "meltdown pathway" model is that intra-insular hypoconnectivity prevents the progressive integration of multimodal data along the posterior-anterior axis, limiting the functional input into the anterior insula. If the hypoconnectivity is minor, this could limit the delivery and integration of subtle but important neuroceptive cues—

especially social cues, like vocal prosody and facial expressions—to the anterior insula. Returning to our fireworks example, this would prevent the child from being able to confidently rely on the only safety cue in their environment—the calm, happy people around him. Hatfield et al. (2017) employed similar logic to argue that the interoceptive, autonomic and behavioral correlates of autism reflect impaired integration and contextualization of interoceptive cues along the posterior-anterior axis of the insula—possibly due to intra-insular hypoconnectivity. On the other hand, if the hypoconnectivity is more severe, this would disrupt the delivery of safety and danger cues to the anterior insula altogether, and neuroception would take place exclusively in the posterior insula. In this case, the child would indiscriminately respond to changes in the environment that are potentially threatening—be it a bear or a firework—with an unmitigated stage II response.

This logic can be extrapolated to understand why safe situations that contain ambiguous signs of potential danger—such as crowded shopping malls, subway cars or abrupt changes in context—can evoke meltdowns from those with autism (Lipsky, 2011a; Lipsky & Richards, 2009). We want to emphasize that the stage I-III polyvagal responses mounted following insular neuroception are not analogous to the automatic, reflex-like responses elicited by so-called "low-road" processing of danger signals by the amygdala. The latter are threat responses that occur on the timescale of seconds, whereas polyvagal stages are deployed over the course of minutes to hours and correspond to "high-road" danger processing routes (Pessoa & Adolphs, 2010). We also want to emphasize that, in our model, neurotypicals likely only rely on posterior insula-based neuroception for very short periods (tens of seconds to minutes) after being presented with ambiguous danger signals. This explains why, in safe contexts, the behavioral and autonomic markers of a stage II response are barely expressed before being quickly replaced by an adaptive

stage III response. It is only when the social, experiential, and contextual insights gained from neuroception in the anterior insula are attenuated (or removed)—as in autism—that the acute behavioral and autonomic consequences of posterior insula-based neuroception can be observed. We propose these consequences manifest as meltdowns.

4. Cognitive Science Perspective: Predictive Coding Account of Meltdowns:

In the previous two sections, we built an integrated model of autistic meltdowns in which chronic hypoactivity of the anterior insula prevents those with autism from effectively using context cues—especially social cues—to resolve ambiguous sensory data that indicate *potential* danger in their environment. This, we argue, manifests as chronic hypervigilance and acute hyperreactivity (or "hypersensitivity") to sensory stimuli deemed trivial by neurotypicals. In this final section, we discuss how our model fits within contemporary predictive coding accounts of autism. Over the past decade, predictive coding-based sensory processing models have furnished new ways of thinking about the neural mechanisms that underlie the sensory and social symptoms of autism (Palmer et al., 2017; Quattrocki & Friston, 2014; Van de Cruys et al., 2014; Van de Cruys et al., 2019). We seek to build on these accounts and advance the perspective that chronic hypervigilance, acute hyperreactivity and ultimately meltdowns in autism reflect a failure of coherent deep inference within the interoceptive predictive coding hierarchy.

4.1. Overview of Predictive Coding Theory:

Predictive coding is a neurocognitive framework that seeks to unpack sensory perception and action in the context of hierarchical information processing. According to this theory, higher regions of the central nervous system (CNS) generate recursive, top-down predictions about the

hidden causes of sensory phenomena that are continuously compared with data reported by sensory epithelia (Friston, 2009). Should these data match the brain's hypotheses—termed 'priors'—they are said to be accurately predicted and no longer 'newsworthy' for the individual's ongoing perception of their lived world. Therefore, the sensory information (i.e., prediction errors) will not be sent on to higher CNS regions for further processing. However, if there is a discrepancy between the brain's prior and the sensory reality, a prediction error (PE) is generated and sent up the cortical hierarchy (Ainley et al., 2016). This process, called 'prediction error minimization,' proceeds iteratively within and between reproducible units that span the CNS hierarchy—from peripheral reflex arcs to the cortex. Each level of the hierarchy contains error units—in which incoming data is compared with top-down predictions from the level above—and expectation units—where priors are both updated based on incoming PEs and fed back to further influence error processing at lower levels (Shipp, 2016; Shipp et al., 2013). Error minimization ensures that only *novel and therefore relevant sensory information* is sent to higher cortical regions for perceptual inference.

At lower levels of the CNS, generative models issue relatively concrete, modality-specific predictions. In other words, basic features of exteroceptive, proprioceptive, and interoceptive data are processed in distinct, low-level hierarchies. Once PEs reach higher levels of the hierarchy, they encounter deep generative models issuing multimodal predictions (Seth & Friston, 2016). These priors predict the forest for the trees, constraining the integration of multimodal sensory data within a coherent set of contexts (ie. the overall state of the environment and the organism). This allows more intricate, abstract, and context-sensitive features of unpredicted sensory data to be extracted at each level of the hierarchy, creating an

increasingly rich and well-defined portrait of the environment (Shipp, 2016; Van de Cruys et al., 2014; Wacongne et al., 2011) (**Figure 6**).

Predictive coding theory is rooted in the statistical principles of the Bayesian brain hypothesis, which—on a predictive coding account—conceives of bottom-up prediction errors and top-down predictions as the message passing necessary for Bayesian belief updating. In other words, error minimization updates prior beliefs about the causes of sensory input into posterior beliefs (i.e., expectations or representations)—that generate top-down predictions. When considered from this computational perspective, error minimization is analogous to a two-sample t-test between the data reported by sensory organs and those predicted by the brain (Friston, 2010; Van de Cruys et al., 2014). As with any data analysis, both the center *and* spread of sensory data play critical roles in the assessment of statistical significance. Within predictive coding, *precision* quantifies the spread or uncertainty associated with various (sub personal) Bayesian beliefs.

Specifically, precision is mathematically defined as the inverse variance of a prior or PE's distribution, as it is represented by the brain (Feldman & Friston, 2010). In other words, it quantifies the *predictability* of what is predicted by the brain and the *reliability* of what is reported by sensory organs. According to this definition, PEs at any hierarchical level that are deemed more precise—than expectations at the level above—tend to be viewed as more reliable by the brain and will therefore carry more weight during error minimization. Conversely, it will be very difficult for an imprecise PE to update a precise prior (Ainley et al., 2016). Neurologically, PE precision is thought to correspond to the post-synaptic gain of superficial pyramidal cells (Ainley et al., 2016; Friston, 2009, 2010; Quattrocki & Friston, 2014), which is

modulated in turn by the neuropsychological construct of attention (Ainley et al., 2016; Smout et al., 2019).

The true relative precisions of priors and PE's are unknown and must also be anticipated (predicted) by the brain. In other words, the brain must assign precision to different streams of sensory data during error minimization—in the same way that we choose reliable sources of information (Friston, 2010; Van de Cruys et al., 2014). A key aspect of this 'precision engineered' message passing in the brain is that it entails both the attentional selection of precise prediction errors and their context-dependent attenuation. Attenuation through decreasing precision is an important complement to attentional selection; especially, in filtering out redundant information that we generate ourselves. Perhaps the clearest example here is saccadic suppression: namely, the transient reduction of sensory precision during saccadic eye movements, which produce self-generated optic flow (that we never actually 'see'). Modulating precision across sensory hierarchies in response to environmental changes is another way the brain adapts error minimization to suit an organism within its constantly changing context (beyond updating multimodal predictions issued by deep generative models) (Seth & Friston, 2016). Under this framework, the brain is viewed as a statistical organ that constantly integrates previous experiences, multimodal context clues, and an organism's state to select dependable information streams and generate adaptive perceptual experiences (Hohwy, 2013; Hsu et al., 2020; Van de Cruys et al., 2014).

4.2. Active Inference Across Exteroceptive and Interoceptive Domains:

Beyond mediating perception through belief updating, prediction errors can also *fulfill* top-down predictions through action within a predictive coding framework (Friston, 2016; Seth

& Friston, 2016). Active inference refers to the idea that prediction errors can be resolved through either perception or action (Friston et al., 2010; Seth & Friston, 2016). When prediction errors are resolved through perception, as described above, the brain's generative models are updated in light of new sensory evidence gathered from the environment. By contrast, when prediction errors are resolved through action, outflow through top-down motor (proprioception) or autonomic (interoception) pathways is tuned until bottom-up sensory evidence matches top-down predictions. What determines whether a prediction error will drive action or perception—as well as the types of actions a prediction error can drive—varies between different levels of the hierarchy.

At low levels of the hierarchy (ie. the spinal cord and peripheral efferents), proprioceptive and interoceptive prediction errors can be resolved by driving peripheral reflex arcs. In this context, descending predictions provide the set point for homeostatic motor and autonomic control that is fulfilled by reflexes. For instance, if stretch receptors in a particular muscle report a position different from that predicted by the spinal cord or alpha motor neurons, the resulting prediction error will drive a reflex that shifts the muscle's position back to its set point (Fel'dman, 1966; Parr et al., 2021). Similarly, if the vagus nerve detects a shift in some autonomic parameter (ie. heart rate, blood pressure, rate of peristalsis, etc.) from its set point, the resulting prediction error will drive a corrective autonomic reflex that shifts the influence of parasympathetic and sympathetic efferents on visceral processes. For a prediction error to drive a reflex instead of perception, it must remain in the periphery and not reach the brain. In other words, the access of those prediction errors to higher levels of the hierarchy must be transiently attenuated or "gated." To clarify, the prediction errors *themselves* are not being attenuated—those are needed to drive the reflex. Rather, by attenuating the *access* of those prediction errors

to higher levels of processing, the brain can ignore sensory evidence suggesting deviations from motor and autonomic set points (Friston et al., 2010; Seth & Friston, 2016).

Prediction errors that reach higher levels of the hierarchy (ie. the cerebral cortex) can be used to drive a much more sophisticated form of active inference—planning. Active inference as planning is operationally defined by a generative model that predicts the consequences of action. This type of inference can adapt an organism's internal state and behavior to meet environmental challenges following a shift in context. Under this framework, the homeostatic reflexes discussed above can be transiently suspended, and unattenuated prediction errors can instead be used to develop and implement a robust, context-appropriate plan (Kaplan & Friston, 2018). In other words, while reflexes enforce homeostatic set points, plans permit allostasis (Botvinick & Toussaint, 2012; Pezzulo et al., 2015). Another key difference between reflexes and plans is their temporal scale. Whereas a reflex occurs in the moment, a plan unfolds over time. Given this, we classify neuroception and its corresponding polyvagal responses as "allostatic plans" generated by active inference in the cortex—more specifically, in the insula—under an active inference framework. What determines whether a prediction error reaching the brain will drive perception or action is the prior precision; whereas a broad prior will be updated to guide perception, a precise prior will be fulfilled through action (Friston et al., 2010).

4.3. Interoceptive Inference: Active Inference in the Interoceptive Hierarchy

The insular cortex represents a high-level predictive coding hierarchy in which interoceptive and exteroceptive data are thought to be progressively integrated to guide interoception, regulate autonomic physiology and shape behavior (Ainley et al., 2016). There are many different models of how the interoceptive hierarchy is organized, and the specific role

exteroceptive data plays in the minimization of interoceptive error signals is debatable (Ainley et al., 2016; Allen, 2020; Barrett, 2017; Barrett & Simmons, 2015; Paulus et al., 2019; Seth & Friston, 2016). For our purposes though, we employ a simplified model in which the interoceptive hierarchy behaves as described above (**Figure 6)**, with deep levels of the hierarchy (ie. the anterior insula) issuing multisensory predictions about future interactions between interoceptive and exteroceptive states (Allen, 2020; Barrett, 2017; Seth & Friston, 2016). In other words, priors issued by generative models deep in the hierarchy predict the *multisensory* consequences of action and represent multimodal snapshots of an organism's internal and external environment. (Barrett, 2017; Seth & Friston, 2016).

Consequently, as a prediction error penetrates deeper into the interoceptive hierarchy, it can be used to drive plans involving top-down motor and autonomic networks of increasing diversity in response to environmental changes detected by increasingly diverse (in terms of modality) sensory evidence. It is important to recognize that the multimodal information received by the insula has already enjoyed quite a bit of deep hierarchical processing. For instance, rather than receiving direct prediction errors from V1, the insula receives highly processed data issued by the visual brain, and likewise, from the prefrontal cortex, anterior cingulate, amygdala, and other brain regions (Baier et al., 2013; Benarroch, 2019; Chikazoe et al., 2019; Deen et al., 2011; Frank et al., 2014; Lopez et al., 2012; Mazzola et al., 2017). By progressively integrating these rich multisensory inputs with the comparatively "raw" interoceptive data entering the posterior insula, posterior-to-anterior insular processing contextualizes interoceptive data within the external environment and implements adaptive, context-appropriate allostatic plans (Craig, 2009, 2010, 2015; H. C. Evrard, 2019; Namkung et

al., 2017; Seth & Friston, 2016). This integrated model of the insular predictive coding hierarchy is illustrated conceptually in **Figure 7**.

As a practical example, under this model, the anterior insula of the child in our fireworks example would need to juggle (at least) two (counterfactual) multimodal predictions in response to the sudden fireworks show: #1 the fireworks are dangerous, and my body should be preparing to fight or flight; #2 the fireworks are a spectacle to be enjoyed alongside family and friends, and I should be expressing a stage III autonomic and behavioral state. In the first few seconds to minutes after the fireworks start, the only pieces of sensory evidence the child relies on are the loud noises and bright lights coming from the fireworks—objective, albeit ambiguous, signs of danger that immediately grab his attention. These highly precise bottom-up data generate large prediction errors that travel all the way up the predictive coding hierarchy and update the child's multimodal predictions. He now expects external danger paired with internal mobilization, and this updated model will enforce an initial stage II allostatic plan (prediction #1 above). It is only when the child recognizes their parents' highly salient (and therefore highly precise) smiling faces—that they shift their internal model to prediction #2 and deploy the vagal brake. Similar intuitive examples are provided in Paulus et al. (2019).

4.4. Contemporary Predictive Coding Models of Autism

In recent years, predictive coding theory has been mobilized by several groups to characterize the sensorimotor and social aspects of the autistic phenotype. Lawson et al. formalized this perspective in 2014, when they argued that enhanced PE precision reliably explains the sensory and social deficits in ASD. This failure to attenuate sensory precision is thought to stem from a dysfunction of top-down mechanisms that control post-synaptic gain,

which the authors claimed to be a functional consequence of known neurochemical abnormalities in ASD (Lawson et al., 2014). Van de Cruys et al. (2014) offered a similar perspective, arguing that autistic patients are unable to *flexibly modulate* their sensory precision in response to different stimuli, possibly due to abnormalities in the acetylcholine and norepinephrine neurotransmitter systems. Their account implies that *all* incoming sensory data, including sensory noise, is afforded a uniformly high precision, without regard for its reliability or relevance to the individual's ongoing sensory experience. In other words, the autistic brain is thought to send *all* incoming sensory data up the cortical hierarchy to be consciously perceived, creating a sensory experience wrought with excessive, uninformative and unnecessary detail. Palmer et al. (2017) provide an excellent overview of current evidence supporting Lawson et al. (2014) and Van de Cruys et al. (2014)'s aberrant precision accounts of autism. Quattrocki and Friston (2014) extended this discussion into the interoceptive domain, arguing that persistent oxytocin deficiency during infancy can explain the social and autonomic phenotypes found in autism. In neurotypicals, oxytocin is thought to attenuate interoceptive prediction errors in the insula during self-generated action (ie. homeostatic regulation, allostatic behaviors, social interaction). Lacking this selective filter on the bottom-up interoceptive data stream, autistic infants fail to form clear associations between body states (ie. stage I-III polyvagal stage) and exteroceptive context clues. In other words, they fail to fully acquire the deep hierarchical models (in the anterior insula) required for social cognition, autonomic regulation and emotional processing (Quattrocki & Friston, 2014).

4.5. Integrating Neurophysiological, Neuropsychological and Predictive Coding Models of Meltdowns

We can now apply these contemporary predictive coding theories of autism alongside the other perspectives advanced in this review to construct a comprehensive model of meltdowns. First, aberrant precision accounts of autism shed light on why those with autism experience hypervigilance (**Figure 1a**): their brains are constantly amplifying uninformative, irrelevant sensory details in their environment—from the feeling of clothes touching their skin to the subtle flickering of lightbulbs overhead and background noises in crowded public places. Because these prediction errors are unattenuated, the sensory details they carry are likely being reported to levels of the cortex capable of organizing an allostatic plan—like the insula—rather than a short-lived reflexive response. We speculate that these extemporaneous and confusing inputs—to which neurotypicals do not usually attend—are likely labeled as ambiguous danger signals that 1) require further context clues to resolve and 2) need to be addressed through an allostatic plan. For example, an autistic student sitting in a school cafeteria with friends (an objectively safe context) who constantly attends to each sound reverberating through the noisy cafeteria may recognize the situation as a danger from which they need to escape.

Now, if unattenuated sensory precision were the only deficit in autism, we would not see meltdowns in this population. Even if they found the sensory experience in the cafeteria unpleasant, they would be able to utilize deep generative models to integrate other cues from the environment, especially social cues (e.g., their friends laughing and having fun), along with their interoceptive state to 1) recognize that the situation is safe and 2) either enforce a stage III autonomic and behavioral state or calmly find a quieter area to finish their lunch. We argue that unattenuated precision in autism is compounded by impairments of deep processing within the interoceptive hierarchy, leading to meltdowns. Taking Quattrocki and Friston (2014)'s model a step further, we propose that oxytocin deficiency during a critical developmental window (John

& Jaeggi, 2021) prevents lower levels of the insular hierarchy (e.g., posterior insula) from impressing themselves upon higher levels (e.g., anterior insula), leading to failures of deep processing and interoceptive inference. This impairment in insular processing is reflected neuroanatomically as the intra-insular hypoconnectivity (**Supplementary Table 3**) and anterior insula hypoactivity (Di Martino et al., 2009; Eilam-Stock et al., 2014; Paakki et al., 2010; Pitskel et al., 2011; Silani et al., 2008; Uddin & Menon, 2009) discussed earlier. In neurotypicals, the anterior insula unpacks and assimilates interoceptive information in the context afforded by every other modality the brain has to offer with the aim of prescribing an adaptive allostatic plan. Lacking coherent intra-insular processing, autistic children fail to form sophisticated generative models in which autonomic state, multiple environmental cues, and social cues are co-represented.

Linking back to our discussion of neuroception, this prevents those with autism—especially young children—from utilizing social cues (e.g., their parents smiling and laughing) and other context clues to appropriately tune their threat assessments of ambiguous danger signals (e.g., fireworks, loud public venues, tight clothes, etc.). Rather, we argue that these children rely on more rudimentary generative models in their interoceptive hierarchy (e.g., those in the posterior insula), which function more like high-level coincidence detectors between an exteroceptive sign of danger (e.g., a loud public venue) and a given allostatic state (e.g., sympathetic arousal and fight-or-flight behaviors). We would expect children relying on these generative models to exhibit hyperreactivity (**Figure 1b**) and respond to stimuli easily tolerated by neurotypicals with meltdowns—immediate autonomic and behavioral responses to ambiguous environmental stressors that can never be nuanced, contextualized, or resolved by high-level

processing in the mid and anterior insula. The contributions of both unattenuated sensory precision and impaired deep processing are illustrated conceptually in **Figure 8**.

5. Future Directions and Limitations:

Our primary objective in this review is to initiate an interdisciplinary dialogue on the neural mechanisms underlying autistic meltdowns. However, before we can further dissect their etiology, the epidemiological and clinical profile of meltdowns must be more deliberately characterized. This area is so ripe for exploration, with so many fundamental questions about meltdowns still unanswered. Do all autistic patients have meltdowns? If not, what proportion of them do? Are there certain clusters of clinical features (intelligence level, social competence, etc.) that predict meltdown frequency and/or severity? In what contexts are meltdowns most likely to occur? Are children who received early intervention therapy (<2 years of age) less likely to experience meltdowns? Are there sensory cues of a specific modality (e.g., visual, auditory, tactile) that are universally more likely to trigger meltdowns within the autistic population? Or is there more inter-individual heterogeneity?

One of the main barriers to understanding ASD is the heterogeneity of the autistic phenotype. Different patients are known to vary widely in the degree to which their cognition, sensory processing, social, and autonomic functioning are impaired, making it very difficult to develop broad generalizations that apply to the entire autism population (Wozniak et al., 2017). For these reasons, the model presented in this article will apply to varying degrees to different subsets of the ASD population. To further nuance our model in the future, classification schemes that appreciate how *clusters* of behavioral symptoms intersect to create different autism subtypes

must be developed. Of relevance to this review, it would be particularly useful to further investigate how the integrity of intra-insular tracts relates to the frequency and severity of SH, autonomic dysregulation, and meltdown behaviors. The heterogeneity of intra-insular connectivity within the ASD population is evidenced by the substantial variation in interoceptive awareness and accuracy between autistic individuals (DuBois et al., 2016).

In this paper, we make the claim that there are systematic differences in the generative models created in the posterior and anterior insula. Specifically, we argue that children with autism rely on the rudimentary models found in the posterior insula, which function more like high-level coincidence detectors between exteroceptive and interoceptive cues, while neurotypicals rely on anterior insula models that integrate interoceptive and exteroceptive cues to prescribe an adaptive allostatic plan. Future theoretical and empirical studies should be conducted to further define how these generative models are rudimentary or sophisticated (e.g., they could have high temporal or counterfactual depth (of policies), they could be hierarchical, they could have many parameters, etc.).

Based upon the theoretical perspectives advanced in this review, one might predict that autistic patients who have more frequent and severe meltdowns will exhibit enhanced autonomic arousal and sensory hypersensitivity in response to a broader array of hypersensitivity triggers. These behaviors likely reflect intra-insular hypo-connectivity, which can be confirmed using fMRI. A *causal* link between these neuroanatomical abnormalities and meltdown-associated behaviors can be further drawn through murine studies. Specifically, future investigations could attempt to recapitulate the meltdown behaviors characteristic of autism by selectively lesioning the intra-insular tracts of developing mice. It will also be important going forward to further investigate why the severity and modality-specificity of sensory hypersensitivity varies between

different autism patients (O'Neill & Jones, 1997); and, moreover, how the nature of sensory hypersensitivity contributes to meltdown severity. We expect that such variation reflects individual differences in the integrity of modality-specific intra-insular tracts. For instance, it may be that those who are highly sensitive to certain sounds have a primary disconnection in the intra-insular structures that carry auditory information from the posterior insula to the AI to be integrated. Using effective connectivity analysis tools such as Dynamic Causal Modelling to link different hypersensitivities with specific intra-insular abnormalities will help substantiate the present model of meltdown neurophysiology and guide the development of personalized therapeutics for crisis behaviors and sensory hypersensitivity in the future. Doing such studies will also yield important new insights into the neural mechanisms by which modality-specific exteroceptive data is processed and integrated with interoceptive data in the insular hierarchy—another *critical* area of ongoing research (Craig, 2015).

Here, we only consider the role of sensory hypersensitivity in meltdown progression, but not sensory hyposensitivity. However, it is well-documented that autistic individuals suffer from both (Leekam et al., 2007; Marco et al., 2011). Thus, it will be important to consider the role of hypo-sensitivities in triggering crisis behaviors in future studies. Lastly, the involvement of other cortical substrates—including the amygdala, ACC, and mPFC—in meltdown neurophysiology should be further investigated, as these three structures critically mediate attention, top-down autonomic control, and emotion as part of the central autonomic network (Sklerov et al., 2019). In the future, further study of how each of these structures interacts with the insula of autistic people, and how these interactions vary across the diverse autism population, will help us further elaborate the neural model of autistic hypervigilance, sensory hypersensitivity, and crisis behaviors presented here. Finally, we built our predictive coding model of meltdowns using only

one perspective on how the interoceptive predictive coding hierarchy within the insular cortex is organized. The neural mechanisms involved in progressively integrating and processing interoceptive and exteroceptive data in the insula remain unclear, and we invite further study of meltdown etiology through the lens of additional models of insular predictive coding.

6. Therapeutic Implications

In this article, we built a multidisciplinary model of meltdown physiology that implicates impaired intra-insular processing in autistic hypervigilance, hyperreactivity and ultimately crisis behaviors. Specifically, we argued that meltdowns reflect an underlying hypo-connectivity within the insula, which (when viewed from a physiological perspective) reduces the influence of pressor regions on physiology and behavior and (when viewed from a neuroceptive or computational perspective) impairs context-dependent threat appraisal. Therefore, an intervention which reinstates intra-insular connectivity at an early enough age could theoretically 1) enhance overall pressor activity in autistic patients and 2) promote the acquisition of high-level generative models in the anterior insula. In principle, this might be accomplished using an interoceptive training program that reinforces hierarchical insular processing. As mentioned earlier, the insula serves as the primary interoceptive cortex in which bottom-up visceral cues are processed and integrated with data from other modalities along a posterior-to-anterior gradient (Craig, 2002; Henry C. Evrard, 2019). Building a training program which enhances both the progression of interoceptive data from the posterior insula as well as the predictive capacity of the anterior insula may help strengthen key intra-insular tracts along which interoceptive and exteroceptive data are progressively integrated.

For example, one could develop a technology which exogenously recapitulates the predictive coding of efferent heartbeat data using auditory feedback. The program's "passive training mode" would do so by generating attention-directing tones when a user's instantaneous heart rate begins to change. In this way, the device would only the user know when *novel* interoceptive data is being reported, which is exactly what happens during true error minimization in the insula. Moreover, the device could be engineered such that the frequency and intensity of the tone produced indicate the direction (increase or decrease) and magnitude, respectively, of the heart rate change. By supplementing a user's endogenous primary interoceptive cortex with detailed, multimodal sensory feedback delivered in accordance with the principles of predictive coding, the program would theoretically promote appropriate error minimization within the autistic insula. Additionally, autistic children using the program's "active training mode" would have the opportunity to practice predicting their heart rate deviations after engaging with the passive training mode. In theory, using both passive and active training modes will enrich the development of adaptive generative models within the insula, which will in turn strengthen intra-insular tracts. Moreover, providing such auditory feedback to premature neonates—who are 3-4 times more likely to develop autism (Agrawal et al., 2018)—in conjunction with an oxytocin replacement therapy (Sikich et al., 2021) could promote the acquisition of adaptive, context-sensitive generative models early in life. It would also be interesting to see whether autistic children administered intranasal oxytocin replacement therapy from a young age exhibit reductions in the frequency and severity of their meltdowns.

7. Conclusions:

In this paper, we initiate an interdisciplinary dialogue on the neural basis of autistic hypervigilance, hyperreactivity, and meltdowns. Drawing from the neurophysiology literature, we provide evidence that intra-insular hypoconnectivity drives chronic hypervigilance, reducing the influence of depressor circuits on autonomic physiology and behavior. We then turn to neurophysiology to argue that hyperreactivity stems from an inability to use context clues from the environment (especially social cues) during neuroception. Finally, we apply contemporary predictive coding accounts of autism to frame hypervigilance, hyperreactivity, and meltdowns as a manifestation of both unattenuated sensory precision and incoherent deep inference in the anterior insula. This pattern of neural activity engenders immediate autonomic and behavioral responses to ambiguous environmental stressors that can never be adequately contextualized.

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References

Agrawal, S., Rao, S. C., Bulsara, M. K., & Patole, S. K. (2018). Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis. *Pediatrics*, *142*(3). https://doi.org/10.1542/peds.2018-0134

Ainley, V., Apps, M. A., Fotopoulou, A., & Tsakiris, M. (2016). 'Bodily precision': a predictive coding account of individual differences in interoceptive accuracy. *Philos Trans R Soc Lond B Biol Sci*, *371*(1708). https://doi.org/10.1098/rstb.2016.0003

Al-Otaibi, F., Wong, S. W. H., Shoemaker, J. K., Parrent, A. G., & Mirsattari, S. M. (2010). The Cardioinhibitory Responses of the Right Posterior Insular Cortex in an Epileptic Patient. *Stereotactic and Functional Neurosurgery*, *88*(6), 390-397. https://doi.org/10.1159/000321182

Alhaddad, A. Y., Cabibihan, J.-J., & Bonarini, A. (2019). Head Impact Severity Measures for Small Social Robots Thrown During Meltdown in Autism. *International Journal of Social Robotics*, *11*(2), 255-270. https://doi.org/10.1007/s12369-018-0494-3

Allen, M. (2020). Unravelling the Neurobiology of Interoceptive Inference. *Trends Cogn Sci*, *24*(4), 265-266. https://doi.org/10.1016/j.tics.2020.02.002

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). American Psychiatric Association. http://proxy.library.cornell.edu/login?url=https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

Anderson, C. J., & Colombo, J. (2009). Larger tonic pupil size in young children with autism spectrum disorder. *Developmental psychobiology*, *51*(2), 207-211. https://doi.org/10.1002/dev.20352

Anderson, C. J., Colombo, J., & Unruh, K. E. (2013). Pupil and salivary indicators of autonomic dysfunction in autism spectrum disorder. *Developmental psychobiology*, *55*(5), 465-482. https://doi.org/10.1002/dev.21051

Ashwin, C., Chapman, E., Howells, J., Rhydderch, D., Walker, I., & Baron-Cohen, S. (2014). Enhanced olfactory sensitivity in autism spectrum conditions. *Molecular Autism*, *5*(1), 53. https://doi.org/10.1186/2040-2392-5-53

Ashwin, E., Ashwin, C., Rhydderch, D., Howells, J., & Baron-Cohen, S. (2009). Eagle-Eyed Visual Acuity: An Experimental Investigation of Enhanced Perception in Autism. *Biological Psychiatry*, *65*(1), 17-21. https://doi.org/https://doi.org/10.1016/j.biopsych.2008.06.012

Baier, B., Zu Eulenburg, P., Best, C., Geber, C., Müller-Forell, W., Birklein, F., & Dieterich, M. (2013). Posterior insular cortex - a site of vestibular-somatosensory interaction? *Brain and behavior*, *3*(5), 519-524. https://doi.org/10.1002/brb3.155

Bal, E., Harden, E., Lamb, D., Van Hecke, A. V., Denver, J. W., & Porges, S. W. (2010). Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. *J Autism Dev Disord*, *40*(3), 358-370. https://doi.org/10.1007/s10803-009-0884-3

Barrett, L. F. (2017). The theory of constructed emotion: an active inference account of interoception and categorization. *Soc Cogn Affect Neurosci*, *12*(1), 1-23. https://doi.org/10.1093/scan/nsw154

Barrett, L. F., & Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nat Rev Neurosci*, *16*(7), 419-429. https://doi.org/10.1038/nrn3950

Beissner, F., Meissner, K., Bär, K.-J., & Napadow, V. (2013). The Autonomic Brain: An Activation Likelihood Estimation Meta-Analysis for Central Processing of Autonomic Function. *The Journal of Neuroscience*, *33*(25), 10503. https://doi.org/10.1523/JNEUROSCI.1103-13.2013

Belek, B. (2019). Articulating Sensory Sensitivity: From Bodies with Autism to Autistic Bodies. *Med Anthropol*, *38*(1), 30-43. https://doi.org/10.1080/01459740.2018.1460750

Benarroch, E. E. (1993). The Central Autonomic Network: Functional Organization, Dysfunction, and Perspective. *Mayo Clinic Proceedings*, *68*(10), 988-1001. https://doi.org/https://doi.org/10.1016/S0025-6196(12)62272-1

Benarroch, E. E. (2019). Insular cortex: Functional complexity and clinical correlations. *Neurology*, *93*(21), 932-938. https://doi.org/10.1212/wnl.0000000000008525

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain*, *128*(Pt 10), 2430-2441. https://doi.org/10.1093/brain/awh561

Beversdorf, D. Q., Carpenter, A. L., Miller, R. F., Cios, J. S., & Hillier, A. (2008). Effect of propranolol on verbal problem solving in autism spectrum disorder. *Neurocase*, *14*(4), 378-383. https://doi.org/10.1080/13554790802368661

Bharath, R., Moodithaya, S. S., Bhat, S. U., Mirajkar, A. M., & Shetty, S. B. (2019). Comparison of Physiological and Biochemical Autonomic Indices in Children with and without Autism Spectrum Disorders. *Medicina (Kaunas, Lithuania)*, *55*(7). Retrieved 2019/07//, from http://europepmc.org/abstract/MED/31284658
https://doi.org/10.3390/medicina55070346
https://europepmc.org/articles/PMC6681286
https://europepmc.org/articles/PMC6681286?pdf=render

Birmingham, E., Cerf, M., & Adolphs, R. (2011). Comparing social attention in autism and amygdala lesions: effects of stimulus and task condition. *Social neuroscience*, *6*(5-6), 420-435. https://doi.org/10.1080/17470919.2011.561547

Bjørklund, G., Kern, J. K., Urbina, M. A., Saad, K., El-Houfey, A. A., Geier, D. A., Chirumbolo, S., Geier, M. R., Mehta, J. A., & Aaseth, J. (2018). Cerebral hypoperfusion in autism spectrum disorder. *Acta Neurobiol Exp (Wars)*, *78*(1), 21-29.

Blaser, E., Eglington, L., Carter, A. S., & Kaldy, Z. (2014). Pupillometry Reveals a Mechanism for the Autism Spectrum Disorder (ASD) Advantage in Visual Tasks. *Scientific Reports*, *4*(1), 4301. https://doi.org/10.1038/srep04301

Botvinick, M., & Toussaint, M. (2012). Planning as inference. *Trends Cogn Sci*, *16*(10), 485-488. https://doi.org/10.1016/j.tics.2012.08.006

Bracha, D. H. S. (2004). Freeze, Flight, Fight, Fright, Faint: Adaptationist Perspectives on the Acute Stress Response Spectrum. In (Vol. 9, pp. 679-685).

Buitelaar, J. K. (1995). Attachment and social withdrawal in autism: Hypotheses and findings. *Behaviour*, *132*, 319-350. https://doi.org/10.1163/156853995X00595

Bujnakova, I., Ondrejka, I., Mestanik, M., Visnovcova, Z., Mestanikova, A., Hrtanek, I., Fleskova, D., Calkovska, A., & Tonhajzerova, I. (2016). Autism spectrum disorder is associated with autonomic underarousal. *Physiol Res*, *65*(Suppl 5), S673-s682. https://doi.org/10.33549/physiolres.933528

Burroni, L., Orsi, A., Monti, L., Hayek, Y., Rocchi, R., & Vattimo, A. G. (2008). Regional cerebral blood flow in childhood autism: a SPET study with SPM evaluation. *Nuclear medicine communications*, *29*(2), 150-156. https://doi.org/10.1097/mnm.0b013e3282f1bb8e

Cardinaux, A., Nejati, H., Rogers, C., Tsourides, K., Gandhi, T., Kjelgaard, M., & Sinha, P. (2016). Reduced Habituation to Naturalistic Stimuli in Autism. *Journal of Vision*, *16*(12), 478-478. https://doi.org/10.1167/16.12.478

Caria, A., & de Falco, S. (2015). Anterior insular cortex regulation in autism spectrum disorders. *Frontiers in behavioral neuroscience*, *9*, 38-38. https://doi.org/10.3389/fnbeh.2015.00038

Cechetto, D. F. (2014). Cortical control of the autonomic nervous system. *Exp Physiol*, *99*(2), 326-331. https://doi.org/10.1113/expphysiol.2013.075192

Cerliani, L., Thomas, R. M., Jbabdi, S., Siero, J. C., Nanetti, L., Crippa, A., Gazzola, V., D'Arceuil, H., & Keysers, C. (2012). Probabilistic tractography recovers a rostrocaudal

trajectory of connectivity variability in the human insular cortex. *Hum Brain Mapp*, *33*(9), 2005-2034. https://doi.org/10.1002/hbm.21338

Cesaroni, L., & Garber, M. (1991). Exploring the experience of autism through firsthand accounts. *J Autism Dev Disord*, *21*(3), 303-313. https://doi.org/10.1007/bf02207327

Chang, L. J., Yarkoni, T., Khaw, M. W., & Sanfey, A. G. (2013). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb Cortex*, *23*(3), 739-749. https://doi.org/10.1093/cercor/bhs065

Chikazoe, J., Lee, D. H., Kriegeskorte, N., & Anderson, A. K. (2019). Distinct representations of basic taste qualities in human gustatory cortex. *Nature Communications*, *10*(1), 1048. https://doi.org/10.1038/s41467-019-08857-z

Chouchou, F., Mauguière, F., Vallayer, O., Catenoix, H., Isnard, J., Montavont, A., Jung, J., Pichot, V., Rheims, S., & Mazzola, L. (2019). How the insula speaks to the heart: Cardiac responses to insular stimulation in humans. *Human Brain Mapping*, *40*(9), 2611-2622. https://doi.org/10.1002/hbm.24548

Cole, P. M., Zahn-Waxler, C., Fox, N. A., Usher, B. A., & Welsh, J. D. (1996). Individual differences in emotion regulation and behavior problems in preschool children. *J Abnorm Psychol*, *105*(4), 518-529.

Cook, E. H. (1990). Autism: review of neurochemical investigation. *Synapse*, *6*(3), 292-308. https://doi.org/10.1002/syn.890060309

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*, *3*(8), 655-666. https://doi.org/10.1038/nrn894

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci*, *10*(1), 59-70. https://doi.org/10.1038/nrn2555

Craig, A. D. (2010). The sentient self. *Brain Struct Funct*, *214*(5-6), 563-577. https://doi.org/10.1007/s00429-010-0248-y

Craig, A. D. (2015). *How do you feel?: An interoceptive moment with your neurobiological self*. Princeton University Press.

Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol*, *493*(1), 154-166. https://doi.org/10.1002/cne.20749

Critchley, H. D., Corfield, D. R., Chandler, M. P., Mathias, C. J., & Dolan, R. J. (2000). Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *The Journal of Physiology*, *523*(1), 259-270. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00259.x

Dadalko, O. I., & Travers, B. G. (2018). Evidence for Brainstem Contributions to Autism Spectrum Disorders. *Front Integr Neurosci*, *12*, 47. https://doi.org/10.3389/fnint.2018.00047

Daluwatte, C., Miles, J. H., Christ, S. E., Beversdorf, D. Q., Takahashi, T. N., & Yao, G. (2013). Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. *Journal of autism and developmental disorders*, *43*(8), 1910-1925. https://doi.org/10.1007/s10803-012-1741-3

de Morree, H. M., Rutten, G. J., Szabó, B. M., Sitskoorn, M. M., & Kop, W. J. (2016). Effects of Insula Resection on Autonomic Nervous System Activity. *J Neurosurg Anesthesiol*, *28*(2), 153-158. https://doi.org/10.1097/ana.0000000000000207

Debbaudt, D. (2009). Patients with autism and other high risks: a growing challenge for healthcare security. *J Healthc Prot Manage*, *25*(1), 14-26.

Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cereb Cortex*, *21*(7), 1498-1506. https://doi.org/10.1093/cercor/bhq186

Delafield-Butt, J., & Trevarthen, C. (2018). On the brainstem origin of autism: Disruption to movements of the primary self. In E. B. Torres & C. Whyatt (Eds.), *Frontiers in neuroscience. Autism: The movement-sensing perspective* (pp. 119–137). Taylor & Francis CRC Press.

Denver, J. W. (2004). The Social Engagement System: Functional Differences in Individuals with Autism.

Desoto, M. C., & Hitlan, R. T. (2007). Blood levels of mercury are related to diagnosis of autism: a reanalysis of an important data set. *J Child Neurol*, *22*(11), 1308-1311. https://doi.org/10.1177/0883073807307111

Di Martino, A., Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., & Milham, M. P. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol Psychiatry*, *65*(1), 63-74. https://doi.org/10.1016/j.biopsych.2008.09.022

Di Martino, A., Yan, C. G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., Anderson, J. S., Assaf, M., Bookheimer, S. Y., Dapretto, M., Deen, B., Delmonte, S., Dinstein, I., Ertl-Wagner, B., Fair, D. A., Gallagher, L., Kennedy, D. P., Keown, C. L., Keysers, C., . . . Milham, M. P. (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry*, *19*(6), 659-667. https://doi.org/10.1038/mp.2013.78

Driscoll, D. J. O., Felice, V. D., Kenny, L. C., Boylan, G. B., & O'Keeffe, G. W. (2018). Mild prenatal hypoxia-ischemia leads to social deficits and central and peripheral inflammation in exposed offspring. *Brain Behav Immun*, *69*, 418-427. https://doi.org/10.1016/j.bbi.2018.01.001

DuBois, D., Ameis, S. H., Lai, M.-C., Casanova, M. F., & Desarkar, P. (2016). Interoception in Autism Spectrum Disorder: A review. *International Journal of Developmental Neuroscience*, *52*, 104-111. https://doi.org/https://doi.org/10.1016/j.ijdevneu.2016.05.001

Edmiston, E. K., Jones, R. M., & Corbett, B. A. (2016). Physiological Response to Social Evaluative Threat in Adolescents with Autism Spectrum Disorder. *Journal of autism and developmental disorders*, *46*(9), 2992-3005. https://doi.org/10.1007/s10803-016-2842-1

Eilam-Stock, T., Xu, P., Cao, M., Gu, X., Van Dam, N. T., Anagnostou, E., Kolevzon, A., Soorya, L., Park, Y., Siller, M., He, Y., Hof, P. R., & Fan, J. (2014). Abnormal autonomic and associated brain activities during rest in autism spectrum disorder. *Brain*, *137*(Pt 1), 153-171. https://doi.org/10.1093/brain/awt294

Evrard, H. C. (2019). The Organization of the Primate Insular Cortex. *Front Neuroanat*, *13*, 43. https://doi.org/10.3389/fnana.2019.00043

Evrard, H. C. (2019). The Organization of the Primate Insular Cortex [Review]. *Frontiers in Neuroanatomy*, *13*(43). https://doi.org/10.3389/fnana.2019.00043

Failla, M. D., Peters, B. R., Karbasforoushan, H., Foss-Feig, J. H., Schauder, K. B., Heflin, B. H., & Cascio, C. J. (2017). Intrainsular connectivity and somatosensory responsiveness in young children with ASD. *Molecular Autism*, *8*(1), 25. https://doi.org/10.1186/s13229-017-0143-y

Fel'dman, A. G. (1966). [On functional tuning of nervous system during controlled or preservation of stationary pose. 3. Mechanographic analysis of human performance of

simple movement tasks]. *Biofizika*, *11*(4), 667-675. (O funktsional'noĭ nastroĭke nervnoĭ sistemy pri upravlenii dvizhennem ili sokhranenii statsionarnoĭ pozy. 3. Mekhanograficheskiĭ analiz vypolneniia chelovekom prosteĭshikh dvigatel'nykh zadach.)

Feldman, H., & Friston, K. J. (2010). Attention, uncertainty, and free-energy. *Frontiers in human neuroscience*, *4*, 215-215. https://doi.org/10.3389/fnhum.2010.00215

Fenning, R. M., Erath, S. A., Baker, J. K., Messinger, D. S., Moffitt, J., Baucom, B. R., & Kaeppler, A. K. (2019). Sympathetic-Parasympathetic Interaction and Externalizing Problems in Children with Autism Spectrum Disorder. *Autism Research*, *12*(12), 1805-1816. https://doi.org/10.1002/aur.2187

Frank, S. M., Baumann, O., Mattingley, J. B., & Greenlee, M. W. (2014). Vestibular and visual responses in human posterior insular cortex. *J Neurophysiol*, *112*(10), 2481-2491. https://doi.org/10.1152/jn.00078.2014

Friston, K. (2009). The free-energy principle: a rough guide to the brain? *Trends Cogn Sci*, *13*(7), 293-301. https://doi.org/10.1016/j.tics.2009.04.005

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience*, *11*(2), 127-138. https://doi.org/10.1038/nrn2787

Friston, K. (2016). The Bayesian Savant. *Biol Psychiatry*, *80*(2), 87-89. https://doi.org/10.1016/j.biopsych.2016.05.006

Friston, K. J., Daunizeau, J., Kilner, J., & Kiebel, S. J. (2010). Action and behavior: a free-energy formulation. *Biological Cybernetics*, *102*(3), 227-260. https://doi.org/10.1007/s00422-010-0364-z

Fukuyama, H., Kumagaya, S.-i., Asada, K., Ayaya, S., & Kato, M. (2017). Autonomic versus perceptual accounts for tactile hypersensitivity in autism spectrum disorder. *Scientific Reports*, *7*(1), 8259. https://doi.org/10.1038/s41598-017-08730-3

Gehrlach, D. A., Dolensek, N., Klein, A. S., Roy Chowdhury, R., Matthys, A., Junghänel, M., Gaitanos, T. N., Podgornik, A., Black, T. D., Reddy Vaka, N., Conzelmann, K.-K., & Gogolla, N. (2019). Aversive state processing in the posterior insular cortex. *Nature Neuroscience*, *22*(9), 1424-1437. https://doi.org/10.1038/s41593-019-0469-1

Ghaziri, J., Tucholka, A., Girard, G., Boucher, O., Houde, J.-C., Descoteaux, M., Obaid, S., Gilbert, G., Rouleau, I., & Nguyen, D. K. (2018). Subcortical structural connectivity of insular subregions. *Scientific Reports*, *8*(1), 8596. https://doi.org/10.1038/s41598-018-26995-0

Ghaziri, J., Tucholka, A., Girard, G., Houde, J.-C., Boucher, O., Gilbert, G., Descoteaux, M., Lippé, S., Rainville, P., & Nguyen, D. K. (2017). The Corticocortical Structural Connectivity of the Human Insula. *Cerebral Cortex*, *27*(2), 1216-1228. https://doi.org/10.1093/cercor/bhv308

Gianaros, P. J., Derbtshire, S. W. G., May, J. C., Siegle, G. J., Gamalo, M. A., & Jennings, J. R. (2005). Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology*, *42*(6), 627-635. https://doi.org/10.1111/j.1469-8986.2005.00366.x

Gogolla, N. (2017). The insular cortex. *Current Biology*, *27*(12), R580-R586. https://doi.org/https://doi.org/10.1016/j.cub.2017.05.010

Golanov, E. V., & Reis, D. J. (2001). Neurons of nucleus of the solitary tract synchronize the EEG and elevate cerebral blood flow via a novel medullary area. *Brain Research*, *892*(1), 1-12. https://doi.org/https://doi.org/10.1016/S0006-8993(00)02949-8

Gomot, M., Bernard, F. A., Davis, M. H., Belmonte, M. K., Ashwin, C., Bullmore, E. T., & Baron-Cohen, S. (2006). Change detection in children with autism: An auditory event-

related fMRI study. *NeuroImage*, *29*(2), 475-484. https://doi.org/https://doi.org/10.1016/j.neuroimage.2005.07.027

Gonzalez, S. T., & Fanselow, M. S. (2020). The role of the ventromedial prefrontal cortex and context in regulating fear learning and extinction. *Psychol Neurosci*, *13*(3), 459-472. https://doi.org/10.1037/pne0000207

Goodlin, E. A. (2015). The Relationship Between Vagal Tone, A Marker of Parasympathetic Activity, and Pro-Social Behavior *Scripps Senior Theses Paper 624*. https://doi.org/p://scholarship.claremont.edu/scripps_theses/624

Goodwin, M. S., Groden, J., Velicer, W. F., Lipsitt, L. P., Baron, M. G., Hofmann, S. G., & Groden, G. (2006). Cardiovascular Arousal in Individuals With Autism. *Focus on Autism and Other Developmental Disabilities*, *21*(2), 100-123. https://doi.org/10.1177/10883576060210020101

Goswami, R., Frances, M. F., & Shoemaker, J. K. (2011). Representation of somatosensory inputs within the cortical autonomic network. *NeuroImage*, *54*(2), 1211-1220. https://doi.org/10.1016/j.neuroimage.2010.09.050

Grandin, T. (1992). An Inside View of Autism. In E. Schopler & G. B. Mesibov (Eds.), *High-Functioning Individuals with Autism*. Springer US. https://doi.org/10.1007/978-1-4899-2456-8

Green, S. A., Hernandez, L., Lawrence, K. E., Liu, J., Tsang, T., Yeargin, J., Cummings, K., Laugeson, E., Dapretto, M., & Bookheimer, S. Y. (2019). Distinct Patterns of Neural Habituation and Generalization in Children and Adolescents With Autism With Low and High Sensory Overresponsivity. *Am J Psychiatry*, *176*(12), 1010-1020. https://doi.org/10.1176/appi.ajp.2019.18121333

Green, S. A., Hernandez, L., Tottenham, N., Krasileva, K., Bookheimer, S. Y., & Dapretto, M. (2015). Neurobiology of Sensory Overresponsivity in Youth With Autism Spectrum Disorders. *JAMA Psychiatry*, *72*(8), 778-786. https://doi.org/10.1001/jamapsychiatry.2015.0737

Gu, X., Eilam-Stock, T., Zhou, T., Anagnostou, E., Kolevzon, A., Soorya, L., Hof, P. R., Friston, K. J., & Fan, J. (2015). Autonomic and brain responses associated with empathy deficits in autism spectrum disorder. *Hum Brain Mapp*, *36*(9), 3323-3338. https://doi.org/10.1002/hbm.22840

Gu, X., Gao, Z., Wang, X., Liu, X., Knight, R. T., Hof, P. R., & Fan, J. (2012). Anterior insular cortex is necessary for empathetic pain perception. *Brain*, *135*(9), 2726-2735. https://doi.org/10.1093/brain/aws199

Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. *J Comp Neurol*, *521*(15), 3371-3388. https://doi.org/10.1002/cne.23368

Guinchat, V., Cravero, C., Diaz, L., Perisse, D., Xavier, J., Amiet, C., Gourfinkel-An, I., Bodeau, N., Wachtel, L., Cohen, D., & Consoli, A. (2015). Acute behavioral crises in psychiatric inpatients with autism spectrum disorder (ASD): recognition of concomitant medical or non-ASD psychiatric conditions predicts enhanced improvement. *Res Dev Disabil*, *38*, 242-255. https://doi.org/10.1016/j.ridd.2014.12.020

Guiraud, J. A., Kushnerenko, E., Tomalski, P., Davies, K., Ribeiro, H., & Johnson, M. H. (2011). Differential habituation to repeated sounds in infants at high risk for autism. *Neuroreport*, *22*(16), 845-849. https://doi.org/10.1097/WNR.0b013e32834c0bec

Guy, L., Souders, M., Bradstreet, L., DeLussey, C., & Herrington, J. D. (2014). Brief report: emotion regulation and respiratory sinus arrhythmia in autism spectrum disorder. *J Autism Dev Disord*, *44*(10), 2614-2620. https://doi.org/10.1007/s10803-014-2124-8

Hansen, A. L., Johnsen, B. H., & Thayer, J. F. (2003). Vagal influence on working memory and attention. *Int J Psychophysiol*, *48*(3), 263-274. https://doi.org/10.1016/s0167-8760(03)00073-4

Happe, F., & Frith, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J Autism Dev Disord*, *36*(1), 5-25. https://doi.org/10.1007/s10803-005-0039-0

Hatfield, T. R., Brown, R. F., Giummarra, M. J., & Lenggenhager, B. (2017). Autism spectrum disorder and interoception: Abnormalities in global integration? *Autism*, *23*(1), 212-222. https://doi.org/10.1177/1362361317738392

Hilz, M. J., Dütsch, M., Perrine, K., Nelson, P. K., Rauhut, U., & Devinsky, O. (2001). Hemispheric influence on autonomic modulation and baroreflex sensitivity. *Ann Neurol*, *49*(5), 575-584.

Hirstein, W., Iversen, P., & Ramachandran, V. S. (2001). Autonomic responses of autistic children to people and objects. *Proceedings. Biological sciences*, *268*(1479), 1883-1888. https://doi.org/10.1098/rspb.2001.1724

Hoffman, K. L., Gothard, K. M., Schmid, M. C., & Logothetis, N. K. (2007). Facial-expression and gaze-selective responses in the monkey amygdala. *Curr Biol*, *17*(9), 766-772. https://doi.org/10.1016/j.cub.2007.03.040

Hohwy, J. (2013). 59Prediction error, context, and precision. In J. Hohwy (Ed.), *The Predictive Mind* (pp. 0). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199682737.003.0004

Hollocks, M. J., Howlin, P., Papadopoulos, A. S., Khondoker, M., & Simonoff, E. (2014). Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. *Psychoneuroendocrinology*, *46*, 32-45. https://doi.org/10.1016/j.psyneuen.2014.04.004

Horga, G., Maia, T. V., Wang, P., Wang, Z., Marsh, R., & Peterson, B. S. (2011). Adaptation to Conflict via Context-Driven Anticipatory Signals in the Dorsomedial Prefrontal Cortex. *The Journal of Neuroscience*, *31*(45), 16208. https://doi.org/10.1523/JNEUROSCI.2783-11.2011

Hsu, Y.-F., Xu, W., Parviainen, T., & Hämäläinen, J. A. (2020). Context-dependent minimisation of prediction errors involves temporal-frontal activation. *NeuroImage*, *207*, 116355. https://doi.org/https://doi.org/10.1016/j.neuroimage.2019.116355

Hudac, C. M., DesChamps, T. D., Arnett, A. B., Cairney, B. E., Ma, R., Webb, S. J., & Bernier, R. A. (2018). Early enhanced processing and delayed habituation to deviance sounds in autism spectrum disorder. *Brain Cogn*, *123*, 110-119. https://doi.org/10.1016/j.bandc.2018.03.004

Hutt, C., Hutt, S. J., Lee, D., & Ounsted, C. (1964). Arousal and Childhood Autism. *Nature*, *204*(4961), 908-909. https://doi.org/10.1038/204908a0

Iarocci, G., & McDonald, J. (2006). Sensory integration and the perceptual experience of persons with autism. *J Autism Dev Disord*, *36*(1), 77-90. https://doi.org/10.1007/s10803-005-0044-3

Ishida, M., Onishi, H., Toyama, H., Tsutsumi, C., Endo, C., Tanahashi, I., Takahashi, T., & Uchitomi, Y. (2015). Missing memories of death: Dissociative amnesia in the bereaved

the day after a cancer death. *Palliative and Supportive Care*, *13*(6), 1787-1790. https://doi.org/10.1017/S1478951515000541

Ishitsuka, T., Iadecola, C., Underwood, M. D., & Reis, D. J. (1986). Lesions of nucleus tractus solitarii globally impair cerebrovascular autoregulation. *Am J Physiol*, *251*(2 Pt 2), H269-281. https://doi.org/10.1152/ajpheart.1986.251.2.H269

Israngkun, P. P., Newman, H. A., Patel, S. T., Duruibe, V. A., & Abou-Issa, H. (1986). Potential biochemical markers for infantile autism. *Neurochem Pathol*, *5*(1), 51-70. https://doi.org/10.1007/bf03028036

John, S., & Jaeggi, A. V. (2021). Oxytocin levels tend to be lower in autistic children: A meta-analysis of 31 studies. *Autism*, *25*(8), 2152-2161. https://doi.org/10.1177/13623613211034375

Johnsen, B. H., Thayer, J. F., Laberg, J. C., Wormnes, B., Raadal, M., Skaret, E., Kvale, G., & Berg, E. (2003). Attentional and physiological characteristics of patients with dental anxiety. *J Anxiety Disord*, *17*(1), 75-87. https://doi.org/10.1016/s0887-6185(02)00178-0

Jones, R. S. P., Quigney, C., & Huws, J. C. (2003). First-hand accounts of sensory perceptual experiences in autism: a qualitative analysis. *Journal of Intellectual & Developmental Disability*, *28*(2), 112-121. https://doi.org/10.1080/1366825031000147058

Kałuzna-Czaplińska, J., Socha, E., & Rynkowski, J. (2010). Determination of homovanillic acid and vanillylmandelic acid in urine of autistic children by gas chromatography/mass spectrometry. *Med Sci Monit*, *16*(9), Cr445-450.

Kamitakahara, A., Wu, H. H., & Levitt, P. (2017). Distinct projection targets define subpopulations of mouse brainstem vagal neurons that express the autism-associated MET receptor tyrosine kinase. *J Comp Neurol*, *525*(18), 3787-3808. https://doi.org/10.1002/cne.24294

Kanne, S. M., & Mazurek, M. O. (2011). Aggression in children and adolescents with ASD: prevalence and risk factors. *J Autism Dev Disord*, *41*(7), 926-937. https://doi.org/10.1007/s10803-010-1118-4

Kaplan, R., & Friston, K. J. (2018). Planning and navigation as active inference. *Biological Cybernetics*, *112*(4), 323-343. https://doi.org/10.1007/s00422-018-0753-2

Kern, J. K., Trivedi, M. H., Garver, C. R., Grannemann, B. D., Andrews, A. A., Savla, J. S., Johnson, D. G., Mehta, J. A., & Schroeder, J. L. (2006). The pattern of sensory processing abnormalities in autism. *Autism*, *10*(5), 480-494. https://doi.org/10.1177/1362361306066564

Kientz, M. A., & Dunn, W. (1997). A comparison of the performance of children with and without autism on the Sensory Profile. *Am J Occup Ther*, *51*(7), 530-537. https://doi.org/10.5014/ajot.51.7.530

Kimmerly, D. S., O'Leary, D. D., Menon, R. S., Gati, J. S., & Shoemaker, J. K. (2005). Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. *J Physiol*, *569*(Pt 1), 331-345. https://doi.org/10.1113/jphysiol.2005.091637

Kleinhans, N. M., Johnson, L. C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., & Aylward, E. (2009). Reduced Neural Habituation in the Amygdala and Social Impairments in Autism Spectrum Disorders. *American Journal of Psychiatry*, *166*(4), 467-475. https://doi.org/10.1176/appi.ajp.2008.07101681

Kok, B. E., & Fredrickson, B. L. (2010). Upward spirals of the heart: autonomic flexibility, as indexed by vagal tone, reciprocally and prospectively predicts positive emotions and

social connectedness. *Biological psychology*, *85*(3), 432-436. https://doi.org/10.1016/j.biopsycho.2010.09.005

Kootz, J. P., & Cohen, D. J. (1981). Modulation of Sensory Intake in Autistic Children: Cardiovascular and Behavioral Indices. *Journal of the American Academy of Child Psychiatry*, *20*(4), 692-701. https://doi.org/https://doi.org/10.1097/00004583-198102000-00002

Kosaka, H., Omori, M., Munesue, T., Ishitobi, M., Matsumura, Y., Takahashi, T., Narita, K., Murata, T., Saito, D. N., Uchiyama, H., Morita, T., Kikuchi, M., Mizukami, K., Okazawa, H., Sadato, N., & Wada, Y. (2010). Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. *NeuroImage*, *50*(4), 1357-1363. https://doi.org/10.1016/j.neuroimage.2010.01.085

Kushki, A., Brian, J., Dupuis, A., & Anagnostou, E. (2014). Functional autonomic nervous system profile in children with autism spectrum disorder. *Molecular autism*, *5*(1), 39-39. https://doi.org/10.1186/2040-2392-5-39

Kushki, A., Drumm, E., Pla Mobarak, M., Tanel, N., Dupuis, A., Chau, T., & Anagnostou, E. (2013). Investigating the autonomic nervous system response to anxiety in children with autism spectrum disorders. *PLoS One*, *8*(4), e59730. https://doi.org/10.1371/journal.pone.0059730

Lacuey, N., Hampson, J. P., Theeranaew, W., Zonjy, B., Vithala, A., Hupp, N. J., Loparo, K. A., Miller, J. P., & Lhatoo, S. D. (2018). Cortical Structures Associated With Human Blood Pressure Control. *JAMA neurology*, *75*(2), 194-202. https://doi.org/10.1001/jamaneurol.2017.3344

Lake, C. R., Ziegler, M. G., & Murphy, D. L. (1977). Increased norepinephrine levels and decreased dopamine-beta-hydroxylase activity in primary autism. *Arch Gen Psychiatry*, *34*(5), 553-556. https://doi.org/10.1001/archpsyc.1977.01770170063005

Lane, R. D., Reiman, E. M., Ahern, G. L., & Thayer, J. F. (2001). 21. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion [Article]. *Brain and Cognition*, *47*(1-2), 97-100. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0002366742&partnerID=40&md5=6c145a363f624150ca616d89b62a6e33

Lane, S. J., Mailloux, Z., Schoen, S., Bundy, A., May-Benson, T. A., Parham, L. D., Smith Roley, S., & Schaaf, R. C. (2019). Neural Foundations of Ayres Sensory Integration((R)). *Brain Sci*, *9*(7). https://doi.org/10.3390/brainsci9070153

Launay, J. M., Bursztejn, C., Ferrari, P., Dreux, C., Braconnier, A., Zarifian, E., Lancrenon, S., & Fermanian, J. (1987). Catecholamines metabolism in infantile autism: a controlled study of 22 autistic children. *J Autism Dev Disord*, *17*(3), 333-347. https://doi.org/10.1007/bf01487064

Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Frontiers in human neuroscience*, *8*, 302-302. https://doi.org/10.3389/fnhum.2014.00302

Lebow, M. A., & Chen, A. (2016). Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. *Molecular Psychiatry*, *21*(4), 450-463. https://doi.org/10.1038/mp.2016.1

Leboyer, M., Bouvard, M. P., Recasens, C., Philippe, A., Guilloud-Bataille, M., Bondoux, D., Tabuteau, F., Dugas, M., Panksepp, J., Launay, J. M., & et al. (1994). Difference between plasma N- and C-terminally directed beta-endorphin immunoreactivity in infantile autism. *Am J Psychiatry*, *151*(12), 1797-1801. https://doi.org/10.1176/ajp.151.12.1797

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord*, *37*(5), 894-910. https://doi.org/10.1007/s10803-006-0218-7

Leventhal, B. L., Cook, E. H., Morford, M., Ravitz, A., & Freedman, D. X. (1990). Relationships of whole blood serotonin and plasma norepinephrine within families. *Journal of Autism and Developmental Disorders*, *20*(4), 499-511. https://doi.org/10.1007/BF02216055

Liberzon, I., Taylor, S. F., Fig, L. M., Decker, L. R., Koeppe, R. A., & Minoshima, S. (2000). Limbic activation and psychophysiologic responses to aversive visual stimuli. Interaction with cognitive task. *Neuropsychopharmacology*, *23*(5), 508-516. https://doi.org/10.1016/s0893-133x(00)00157-3

Lipsky, D. (2011a). *From anxiety to meltdown : how individuals on the autism spectrum deal with anxiety, experience meltdowns, manifest tantrums, and how you can intervene effectively*. Jessica Kingsley Publishers.

Lipsky, D. (2011b). *From anxiety to meltdown : how individuals on the autism spectrum deal with anxiety, experience meltdowns, manifest tantrums, and how you can intervene effectively*. Jessica Kingsley Publishers.

Lipsky, D., & Richards, W. (2009). *Managing Meltdowns: Using the S.C.A.R.E.D. Calming Technique with Children and Adults with Autism*. Jessica Kingsley Publishers.

Lopez, C., Blanke, O., & Mast, F. W. (2012). The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis. *Neuroscience*, *212*, 159-179. https://doi.org/10.1016/j.neuroscience.2012.03.028

Lü, W., Wang, Z., & Liu, Y. (2013). A pilot study on changes of cardiac vagal tone in individuals with low trait positive affect: the effect of positive psychotherapy. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, *88*(2), 213-217. https://doi.org/10.1016/j.ijpsycho.2013.04.012

Luu, P., & Posner, M. I. (2003). Anterior cingulate cortex regulation of sympathetic activity. *Brain*, *126*(10), 2119-2120. https://doi.org/10.1093/brain/awg257

Marco, E. J., Hinkley, L. B., Hill, S. S., & Nagarajan, S. S. (2011). Sensory processing in autism: a review of neurophysiologic findings. *Pediatr Res*, *69*(5 Pt 2), 48R-54R. https://doi.org/10.1203/PDR.0b013e3182130c54

Mathewson, K. J., Drmic, I. E., Jetha, M. K., Bryson, S. E., Goldberg, J. O., Hall, G. B., Santesso, D. L., Segalowitz, S. J., & Schmidt, L. A. (2011). Behavioral and cardiac responses to emotional stroop in adults with autism spectrum disorders: influence of medication. *Autism Res*, *4*(2), 98-108. https://doi.org/10.1002/aur.176

Matsushima, K., Matsubayashi, J., Toichi, M., Funabiki, Y., Kato, T., Awaya, T., & Kato, T. (2016). Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum disorders. *Research in Autism Spectrum Disorders*, *25*, 37-46. https://doi.org/https://doi.org/10.1016/j.rasd.2015.12.006

Mazefsky, C. A., & Handen, B. L. (2011). Addressing behavioral and emotional challenges in school-age children and adolescents with ASD. In M. J. Lubetsky, B. L. Handen, & J. J. McGonigle (Eds.), *Autism spectrum disorder* (pp. 253-270). Oxford University Press.

Mazzola, L., Royet, J. P., Catenoix, H., Montavont, A., Isnard, J., & Mauguière, F. (2017). Gustatory and olfactory responses to stimulation of the human insula. *Ann Neurol*, *82*(3), 360-370. https://doi.org/10.1002/ana.25010

McGinnis, W. R., Audhya, T., & Edelson, S. M. (2013). Proposed toxic and hypoxic impairment of a brainstem locus in autism. *Int J Environ Res Public Health*, *10*(12), 6955-7000. https://doi.org/10.3390/ijerph10126955

McGonigle, J. J., Venkat, A., Beresford, C., Campbell, T. P., & Gabriels, R. L. (2014). Management of agitation in individuals with autism spectrum disorders in the emergency department. *Child Adolesc Psychiatr Clin N Am*, *23*(1), 83-95. https://doi.org/10.1016/j.chc.2013.08.003

McKlveen, J. M., Myers, B., & Herman, J. P. (2015). The Medial Prefrontal Cortex: Coordinator of Autonomic, Neuroendocrine and Behavioural Responses to Stress. *Journal of Neuroendocrinology*, *27*(6), 446-456. https://doi.org/10.1111/jne.12272

Mesibov, G. B., Shea, V., Schopler, E., & Adams, L. W. (2005). *The TEACCH Approach to Autism Spectrum Disorders*. Springer. https://books.google.com/books?id=zo3sInxa3Q0C

Minderaa, R. B., Anderson, G. M., Volkmar, F. R., Akkerhuis, G. W., & Cohen, D. J. (1994). Noradrenergic and adrenergic functioning in autism. *Biol Psychiatry*, *36*(4), 237-241. https://doi.org/10.1016/0006-3223(94)90605-x

Ming, X., Bain, J. M., Smith, D., Brimacombe, M., Gold von-Simson, G., & Axelrod, F. B. (2010). Assessing Autonomic Dysfunction Symptoms in Children: A Pilot Study. *Journal of Child Neurology*, *26*(4), 420-427. https://doi.org/10.1177/0883073810381921

Ming, X., Julu, P. O. O., Brimacombe, M., Connor, S., & Daniels, M. L. (2005). Reduced cardiac parasympathetic activity in children with autism. *Brain and Development*, *27*(7), 509-516. https://doi.org/https://doi.org/10.1016/j.braindev.2005.01.003

Minichino, A., Ando, A., Francesconi, M., Salatino, A., Delle Chiaie, R., & Cadenhead, K. (2017). Investigating the link between drug-naive first episode psychoses (FEPs), weight gain abnormalities and brain structural damages: Relevance and implications for therapy. *Prog Neuropsychopharmacol Biol Psychiatry*, *77*, 9-22. https://doi.org/10.1016/j.pnpbp.2017.03.020

Mobascher, A., Brinkmeyer, J., Warbrick, T., Musso, F., Schlemper, V., Wittsack, H. J., Saleh, A., Schnitzler, A., & Winterer, G. (2010). Brain activation patterns underlying fast habituation to painful laser stimuli. *Int J Psychophysiol*, *75*(1), 16-24. https://doi.org/10.1016/j.ijpsycho.2009.10.008

Modabbernia, A., Velthorst, E., & Reichenberg, A. (2017). Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Molecular autism*, *8*, 13-13. https://doi.org/10.1186/s13229-017-0121-4

Montaque, I., Dallos, R., & McKenzie, B. (2018). "It feels like something difficult is coming back to haunt me": An exploration of 'meltdowns' associated with autistic spectrum disorder from a parental perspective. *Clin Child Psychol Psychiatry*, *23*(1), 125-139. https://doi.org/10.1177/1359104517730114

Murphy, J. V., Wheless, J. W., & Schmoll, C. M. (2000). Left vagal nerve stimulation in six patients with hypothalamic hamartomas. *Pediatr Neurol*, *23*(2), 167-168. https://doi.org/10.1016/s0887-8994(00)00170-3

Nakai, M., & Ogino, K. (1984). The relevance of cardio-pulmonary-vascular reflex to regulation of the brain vessels. *The Japanese journal of physiology*, *34*(1), 193-197. https://doi.org/10.2170/jjphysiol.34.193

Namkung, H., Kim, S. H., & Sawa, A. (2017). The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends Neurosci*, *40*(4), 200-207. https://doi.org/10.1016/j.tins.2017.02.002

Napadow, V., Dhond, R., Conti, G., Makris, N., Brown, E. N., & Barbieri, R. (2008). Brain correlates of autonomic modulation: Combining heart rate variability with fMRI. *NeuroImage*, *42*(1), 169-177. https://doi.org/https://doi.org/10.1016/j.neuroimage.2008.04.238

Narayanan, A., White, C. A., Saklayen, S., Scaduto, M. J., Carpenter, A. L., Abduljalil, A., Schmalbrock, P., & Beversdorf, D. Q. (2010). Effect of propranolol on functional connectivity in autism spectrum disorder--a pilot study. *Brain Imaging Behav*, *4*(2), 189-197. https://doi.org/10.1007/s11682-010-9098-8

Neuhaus, E., Bernier, R., & Beauchaine, T. P. (2014). Brief report: social skills, internalizing and externalizing symptoms, and respiratory sinus arrhythmia in autism. *J Autism Dev Disord*, *44*(3), 730-737. https://doi.org/10.1007/s10803-013-1923-7

Nomi, J. S., Farrant, K., Damaraju, E., Rachakonda, S., Calhoun, V. D., & Uddin, L. Q. (2016). Dynamic functional network connectivity reveals unique and overlapping profiles of insula subdivisions. *Hum Brain Mapp*, *37*(5), 1770-1787. https://doi.org/10.1002/hbm.23135

Nomi, J. S., & Uddin, L. Q. (2015). Developmental changes in large-scale network connectivity in autism. *Neuroimage Clin*, *7*, 732-741. https://doi.org/10.1016/j.nicl.2015.02.024

O'Neill, M., & Jones, R. S. (1997). Sensory-perceptual abnormalities in autism: a case for more research? *J Autism Dev Disord*, *27*(3), 283-293. https://doi.org/10.1023/a:1025850431170

Odriozola, P., Uddin, L. Q., Lynch, C. J., Kochalka, J., Chen, T., & Menon, V. (2016). Insula response and connectivity during social and non-social attention in children with autism. *Soc Cogn Affect Neurosci*, *11*(3), 433-444. https://doi.org/10.1093/scan/nsv126

Oppenheimer, S., & Cechetto, D. (2016). The Insular Cortex and the Regulation of Cardiac Function. *Compr Physiol*, *6*(2), 1081-1133. https://doi.org/10.1002/cphy.c140076

Oppenheimer, S. M., & Cechetto, D. F. (1990). Cardiac chronotropic organization of the rat insular cortex. *Brain Research*, *533*(1), 66-72. https://doi.org/https://doi.org/10.1016/0006-8993(90)91796-J

Oppenheimer, S. M., Gelb, A., Girvin, J. P., & Hachinski, V. C. (1992). Cardiovascular effects of human insular cortex stimulation. *Neurology*, *42*(9), 1727-1732. https://doi.org/10.1212/wnl.42.9.1727

Oveis, C., Cohen, A. B., Gruber, J., Shiota, M. N., Haidt, J., & Keltner, D. (2009). Resting respiratory sinus arrhythmia is associated with tonic positive emotionality. *Emotion*, *9*(2), 265-270. https://doi.org/10.1037/a0015383

Paakki, J. J., Rahko, J., Long, X., Moilanen, I., Tervonen, O., Nikkinen, J., Starck, T., Remes, J., Hurtig, T., Haapsamo, H., Jussila, K., Kuusikko-Gauffin, S., Mattila, M. L., Zang, Y., & Kiviniemi, V. (2010). Alterations in regional homogeneity of resting-state brain activity in autism spectrum disorders. *Brain Res*, *1321*, 169-179. https://doi.org/10.1016/j.brainres.2009.12.081

Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian approaches to autism: Towards volatility, action, and behavior. *Psychol Bull*, *143*(5), 521-542. https://doi.org/10.1037/bul0000097

Palmer, R. F., Blanchard, S., & Wood, R. (2009). Proximity to point sources of environmental mercury release as a predictor of autism prevalence. *Health Place*, *15*(1), 18-24. https://doi.org/10.1016/j.healthplace.2008.02.001

Panju, S., Brian, J., Dupuis, A., Anagnostou, E., & Kushki, A. (2015). Atypical sympathetic arousal in children with autism spectrum disorder and its association with anxiety symptomatology. *Molecular Autism*, *6*(1), 64. https://doi.org/10.1186/s13229-015-0057-5

Park, Y. D. (2003). The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism. *Epilepsy Behav*, *4*(3), 286-290. https://doi.org/10.1016/s1525-5050(03)00080-5

Parr, T., Limanowski, J., Rawji, V., & Friston, K. (2021). The computational neurology of movement under active inference. *Brain*, *144*(6), 1799-1818. https://doi.org/10.1093/brain/awab085

Patriquin, M. A., Hartwig, E. M., Friedman, B. H., Porges, S. W., & Scarpa, A. (2019). Autonomic response in autism spectrum disorder: Relationship to social and cognitive functioning. *Biol Psychol*, *145*, 185-197. https://doi.org/10.1016/j.biopsycho.2019.05.004

Paul, L. K., Corsello, C., Tranel, D., & Adolphs, R. (2010). Does bilateral damage to the human amygdala produce autistic symptoms? *Journal of Neurodevelopmental Disorders*, *2*(3), 165-173. https://doi.org/10.1007/s11689-010-9056-1

Paulus, M. P., Feinstein, J. S., & Khalsa, S. S. (2019). An Active Inference Approach to Interoceptive Psychopathology. *Annu Rev Clin Psychol*, *15*, 97-122. https://doi.org/10.1146/annurev-clinpsy-050718-095617

Pellicano, E. (2013). Sensory Symptoms in Autism: A Blooming, Buzzing Confusion? *Child Development Perspectives*, *7*, 143-148.

Penick, S., & Solomon, P. R. (1991). Hippocampus, context, and conditioning. *Behav Neurosci*, *105*(5), 611-617. https://doi.org/10.1037//0735-7044.105.5.611

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat Rev Neurosci*, *11*(11), 773-783. https://doi.org/10.1038/nrn2920

Pezzulo, G., Rigoli, F., & Friston, K. (2015). Active Inference, homeostatic regulation and adaptive behavioural control. *Progress in Neurobiology*, *134*, 17-35. https://doi.org/https://doi.org/10.1016/j.pneurobio.2015.09.001

Picard, R. W. (2009). Future affective technology for autism and emotion communication. *Philos Trans R Soc Lond B Biol Sci*, *364*(1535), 3575-3584. https://doi.org/10.1098/rstb.2009.0143

Pitskel, N. B., Bolling, D. Z., Hudac, C. M., Lantz, S. D., Minshew, N. J., Vander Wyk, B. C., & Pelphrey, K. A. (2011). Brain mechanisms for processing direct and averted gaze in individuals with autism. *Journal of autism and developmental disorders*, *41*(12), 1686-1693. https://doi.org/10.1007/s10803-011-1197-x

Plichta, M. M., Grimm, O., Morgen, K., Mier, D., Sauer, C., Haddad, L., Tost, H., Esslinger, C., Kirsch, P., Schwarz, A. J., & Meyer-Lindenberg, A. (2014). Amygdala habituation: a reliable fMRI phenotype. *NeuroImage*, *103*, 383-390. https://doi.org/10.1016/j.neuroimage.2014.09.059

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology*, *32*(4), 301-318. https://doi.org/10.1111/j.1469-8986.1995.tb01213.x

Porges, S. W. (2001). The polyvagal theory: phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology*, *42*(2), 123-146. https://doi.org/https://doi.org/10.1016/S0167-8760(01)00162-3

Porges, S. W. (2004). Neuroception: A subconscious system for detecting threats and safety. . *Zero to Three*, *24*(5), 19-24.

Porges, S. W. (2005). The Vagus: A Mediator of Behavioral and Physiologic Features Associated with Autism. In M. L. Bauman & T. L. Kemper (Eds.), *The Neurobiology of Autism* (2 ed., pp. 65-78). The Johns Hopkins University Press.

Porges, S. W. (2007). A phylogenetic journey through the vague and ambiguous Xth cranial nerve: A commentary on contemporary heart rate variability research. *Biological Psychology*, *74*(2), 301-307. https://doi.org/https://doi.org/10.1016/j.biopsycho.2006.08.007

Porges, S. W. (2009). The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med*, *76 Suppl 2*(Suppl 2), S86-90. https://doi.org/10.3949/ccjm.76.s2.17

Porges, S. W. (2022). Polyvagal Theory: A Science of Safety. *Front Integr Neurosci*, *16*, 871227. https://doi.org/10.3389/fnint.2022.871227

Porges, S. W., Macellaio, M., Stanfill, S. D., McCue, K., Lewis, G. F., Harden, E. R., Handelman, M., Denver, J., Bazhenova, O. V., & Heilman, K. J. (2013). Respiratory sinus arrhythmia and auditory processing in autism: modifiable deficits of an integrated social engagement system? *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, *88*(3), 261-270. https://doi.org/10.1016/j.ijpsycho.2012.11.009

Quattrocki, E., & Friston, K. (2014). Autism, oxytocin and interoception. *Neuroscience and biobehavioral reviews*, *47*, 410-430. https://doi.org/10.1016/j.neubiorev.2014.09.012

Rajendra Acharya, U., Paul Joseph, K., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: a review. *Medical & biological engineering & computing*, *44*(12), 1031-1051. https://doi.org/10.1007/s11517-006-0119-0

Roberts, A. L., Lyall, K., Hart, J. E., Laden, F., Just, A. C., Bobb, J. F., Koenen, K. C., Ascherio, A., & Weisskopf, M. G. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. *Environ Health Perspect*, *121*(8), 978-984. https://doi.org/10.1289/ehp.1206187

Rodgers, K. M., Benison, A. M., Klein, A., & Barth, D. S. (2008). Auditory, Somatosensory, and Multisensory Insular Cortex in the Rat. *Cerebral Cortex*, *18*(12), 2941-2951. https://doi.org/10.1093/cercor/bhn054

Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S., & Romano, J. (1996). Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *J Comp Neurol*, *370*(2), 247-261. https://doi.org/10.1002/(sici)1096-9861(19960624)370:2<247::Aid-cne8>3.0.Co;2-2

Rogers-Carter, M. M., Varela, J. A., Gribbons, K. B., Pierce, A. F., McGoey, M. T., Ritchey, M., & Christianson, J. P. (2018). Insular cortex mediates approach and avoidance responses to social affective stimuli. *Nature Neuroscience*, *21*(3), 404-414. https://doi.org/10.1038/s41593-018-0071-y

Rotschafer, S. E. (2021). Auditory Discrimination in Autism Spectrum Disorder [Review]. *Frontiers in Neuroscience*, *15*(419). https://doi.org/10.3389/fnins.2021.651209

Ruggiero, D. A., Mraovitch, S., Granata, A. R., Anwar, M., & Reis, D. J. (1987). A role of insular cortex in cardiovascular function. *J Comp Neurol*, *257*(2), 189-207. https://doi.org/10.1002/cne.902570206

Schaaf, R. C., Benevides, T. W., Leiby, B. E., & Sendecki, J. A. (2015). Autonomic dysregulation during sensory stimulation in children with autism spectrum disorder. *Journal of autism and developmental disorders*, *45*(2), 461-472. https://doi.org/10.1007/s10803-013-1924-6

Scheydt, S., Müller Staub, M., Frauenfelder, F., Nielsen, G. H., Behrens, J., & Needham, I. (2017). Sensory overload: A concept analysis. *Int J Ment Health Nurs*, *26*(2), 110-120. https://doi.org/10.1111/inm.12303

Schoen, S. A., Miller, L. J., Brett-Green, B., & Hepburn, S. L. (2008). Psychophysiology of children with autism spectrum disorder. *Research in Autism Spectrum Disorders*, *2*(3), 417-429. https://doi.org/https://doi.org/10.1016/j.rasd.2007.09.002

Seth, A. K., & Friston, K. J. (2016). Active interoceptive inference and the emotional brain. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1708), 20160007. https://doi.org/doi:10.1098/rstb.2016.0007

Sheinkopf, S. J., Levine, T. P., McCormick, C. E. B., Puggioni, G., Conradt, E., Lagasse, L. L., & Lester, B. M. (2019). Developmental trajectories of autonomic functioning in autism from birth to early childhood. *Biological psychology*, *142*, 13-18. https://doi.org/10.1016/j.biopsycho.2019.01.003

Shipp, S. (2016). Neural Elements for Predictive Coding [Review]. *Frontiers in Psychology*, *7*(1792). https://doi.org/10.3389/fpsyg.2016.01792

Shipp, S., Adams, R. A., & Friston, K. J. (2013). Reflections on agranular architecture: predictive coding in the motor cortex. *Trends Neurosci*, *36*(12), 706-716. https://doi.org/10.1016/j.tins.2013.09.004

Shura, R. D., Hurley, R. A., & Taber, K. H. (2014). Insular Cortex: Structural and Functional Neuroanatomy. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *26*(4), iv-282. https://doi.org/10.1176/appi.neuropsych.260401

Sikich, L., Kolevzon, A., King, B. H., McDougle, C. J., Sanders, K. B., Kim, S.-J., Spanos, M., Chandrasekhar, T., Trelles, M. D. P., Rockhill, C. M., Palumbo, M. L., Witters Cundiff, A., Montgomery, A., Siper, P., Minjarez, M., Nowinski, L. A., Marler, S., Shuffrey, L. C., Alderman, C., . . . Veenstra-VanderWeele, J. (2021). Intranasal Oxytocin in Children and Adolescents with Autism Spectrum Disorder. *New England Journal of Medicine*, *385*(16), 1462-1473. https://doi.org/10.1056/NEJMoa2103583

Silani, G., Bird, G., Brindley, R., Singer, T., Frith, C., & Frith, U. (2008). Levels of emotional awareness and autism: an fMRI study. *Soc Neurosci*, *3*(2), 97-112. https://doi.org/10.1080/17470910701577020

Silvani, A., Calandra-Buonaura, G., Dampney, R. A., & Cortelli, P. (2016). Brain-heart interactions: physiology and clinical implications. *Philos Trans A Math Phys Eng Sci*, *374*(2067). https://doi.org/10.1098/rsta.2015.0181

Singletary, W. M. (2015). An integrative model of autism spectrum disorder: ASD as a neurobiological disorder of experienced environmental deprivation, early life stress and allostatic overload. *Neuropsychoanalysis*, *17*(2), 81-119. https://doi.org/10.1080/15294145.2015.1092334

Sklerov, M., Dayan, E., & Browner, N. (2019). Functional neuroimaging of the central autonomic network: recent developments and clinical implications. *Clinical Autonomic Research*, *29*(6), 555-566. https://doi.org/10.1007/s10286-018-0577-0

Skogheim, T. S., Weyde, K. V. F., Engel, S. M., Aase, H., Surén, P., Øie, M. G., Biele, G., Reichborn-Kjennerud, T., Caspersen, I. H., Hornig, M., Haug, L. S., & Villanger, G. D. (2021). Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. *Environ Int*, *152*, 106468. https://doi.org/10.1016/j.envint.2021.106468

Smith, D., Ropar, D., & Allen, H. A. (2015). Visual integration in autism. *Front Hum Neurosci*, *9*, 387. https://doi.org/10.3389/fnhum.2015.00387

Smith Roley, S., Mailloux, Z., Miller-Kuhaneck, H., & Glennon, T. (2007). Understanding Ayres' Sensory Integration. *OT Practice*, *12*(7), CE-1-CE-7.

Smout, C. A., Tang, M. F., Garrido, M. I., & Mattingley, J. B. (2019). Attention promotes the neural encoding of prediction errors. *PLOS Biology*, *17*(2), e2006812. https://doi.org/10.1371/journal.pbio.2006812

Song, R., Liu, J., & Kong, X. (2016). Autonomic Dysfunction and Autism: Subtypes and Clinical Perspectives. *North American Journal of Medicine & Science*, *9*.

Stark, K. H., Barnes, J. C., Young, N. D., & Gabriels, R. L. (2015). Brief Report: Understanding Crisis Behaviors in Hospitalized Psychiatric Patients with Autism Spectrum Disorder—Iceberg Assessment Interview. *Journal of Autism and Developmental Disorders*, *45*(11), 3468-3474. https://doi.org/10.1007/s10803-015-2552-0

Stark, S. M., Reagh, Z. M., Yassa, M. A., & Stark, C. E. L. (2018). What's in a context? Cautions, limitations, and potential paths forward. *Neurosci Lett*, *680*, 77-87. https://doi.org/10.1016/j.neulet.2017.05.022

Süllwold, L. (1991). *Manual zum Frankfurter Beschwerde-Fragebogen (FBF)*. Springer http://proxy.library.cornell.edu/login?url=https://link.springer.com/10.1007/978-3-642-58209-7

Swartz, J. R., Wiggins, J. L., Carrasco, M., Lord, C., & Monk, C. S. (2013). Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*, *52*(1), 84-93. https://doi.org/10.1016/j.jaac.2012.10.012

Szeska, C., Pünjer, H., Riemann, S., Meinzer, M., & Hamm, A. O. (2022). Stimulation of the ventromedial prefrontal cortex blocks the return of subcortically mediated fear responses. *Translational Psychiatry*, *12*(1), 394. https://doi.org/10.1038/s41398-022-02174-8

Tam, F. I., King, J. A., Geisler, D., Korb, F. M., Sareng, J., Ritschel, F., Steding, J., Albertowski, K. U., Roessner, V., & Ehrlich, S. (2017). Altered behavioral and amygdala habituation in high-functioning adults with autism spectrum disorder: an fMRI study. *Sci Rep*, *7*(1), 13611. https://doi.org/10.1038/s41598-017-14097-2

Taylor, A. G., Goehler, L. E., Galper, D. I., Innes, K. E., & Bourguignon, C. (2010). Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. *Explore (NY)*, *6*(1), 29-41. https://doi.org/10.1016/j.explore.2009.10.004

Tecchio, F., Benassi, F., Zappasodi, F., Gialloreti, L. E., Palermo, M., Seri, S., & Rossini, P. M. (2003). Auditory sensory processing in autism: a magnetoencephalographic study. *Biol Psychiatry*, *54*(6), 647-654. https://doi.org/10.1016/s0006-3223(03)00295-6

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. *Annals of Behavioral Medicine*, *37*(2), 141-153. https://doi.org/10.1007/s12160-009-9101-z

Toichi, M., & Kamio, Y. (2003). Paradoxical Autonomic Response to Mental Tasks in Autism. *Journal of Autism and Developmental Disorders*, *33*(4), 417-426. https://doi.org/10.1023/A:1025062812374

Tonhajzerova, I., Mestanik, M., Mestanikova, A., & Jurko, A. (2016). Respiratory sinus arrhythmia as a non-invasive index of 'brain-heart' interaction in stress. *Indian J Med Res*, *144*(6), 815-822. https://doi.org/10.4103/ijmr.IJMR_1447_14

Truijen, J., & Van Lieshout, J. J. (2010). Experimental Physiology –Viewpoints: Parasympathetic control of blood flow to the activated human brain. *Experimental Physiology*, *95*(10), 980-981. https://doi.org/10.1113/expphysiol.2010.054783

Uddin, L., Kinnison, J., Pessoa, L., & Anderson, M. L. (2014). Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *J Cogn Neurosci*, *26*(1), 16-27. https://doi.org/10.1162/jocn_a_00462

Uddin, L., Nomi, J. S., Hébert-Seropian, B., Ghaziri, J., & Boucher, O. (2017). Structure and Function of the Human Insula. *Journal of Clinical Neurophysiology*, *34*(4), 300-306. https://doi.org/10.1097/wnp.0000000000000377

Uddin, L. Q., & Menon, V. (2009). The anterior insula in autism: under-connected and under-examined. *Neuroscience and biobehavioral reviews*, *33*(8), 1198-1203. https://doi.org/10.1016/j.neubiorev.2009.06.002

Valenza, G., Sclocco, R., Duggento, A., Passamonti, L., Napadow, V., Barbieri, R., & Toschi, N. (2019). The central autonomic network at rest: Uncovering functional MRI correlates of time-varying autonomic outflow. *NeuroImage*, *197*, 383-390. https://doi.org/https://doi.org/10.1016/j.neuroimage.2019.04.075

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism. *Psychol Rev*, *121*(4), 649-675. https://doi.org/10.1037/a0037665

Van de Cruys, S., Perrykkad, K., & Hohwy, J. (2019). Explaining hyper-sensitivity and hypo-responsivity in autism with a common predictive coding-based mechanism. *Cogn Neurosci*, *10*(3), 164-166. https://doi.org/10.1080/17588928.2019.1594746

Vasa, R. A., Hagopian, L., & Kalb, L. G. (2020). Investigating mental health crisis in youth with autism spectrum disorder. *Autism Res*, *13*(1), 112-121. https://doi.org/10.1002/aur.2224

Vaughan Van Hecke, A., Lebow, J., Bal, E., Lamb, D., Harden, E., Kramer, A., Denver, J., Bazhenova, O., & Porges, S. W. (2009). Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child Dev*, *80*(4), 1118-1133. https://doi.org/10.1111/j.1467-8624.2009.01320.x

Wacongne, C., Labyt, E., van Wassenhove, V., Bekinschtein, T., Naccache, L., & Dehaene, S. (2011). Evidence for a hierarchy of predictions and prediction errors in human cortex. *Proc Natl Acad Sci U S A*, *108*(51), 20754-20759. https://doi.org/10.1073/pnas.1117807108

Wang, Z., Lü, W., & Qin, R. (2013). Respiratory sinus arrhythmia is associated with trait positive affect and positive emotional expressivity. *Biol Psychol*, *93*(1), 190-196. https://doi.org/10.1016/j.biopsycho.2012.12.006

Watkins, L. L., Grossman, P., Krishnan, R., & Sherwood, A. (1998). Anxiety and vagal control of heart rate. *Psychosomatic medicine*, *60*(4), 498-502. https://doi.org/10.1097/00006842-199807000-00018

Watling, R. L., Deitz, J., & White, O. (2001). Comparison of Sensory Profile scores of young children with and without autism spectrum disorders. *Am J Occup Ther*, *55*(4), 416-423. https://doi.org/10.5014/ajot.55.4.416

Watson, L. R., Roberts, J. E., Baranek, G. T., Mandulak, K. C., & Dalton, J. C. (2012). Behavioral and physiological responses to child-directed speech of children with autism spectrum disorders or typical development. *Journal of autism and developmental disorders*, *42*(8), 1616-1629. https://doi.org/10.1007/s10803-011-1401-z

Wiggins, J. L., Swartz, J. R., Martin, D. M., Lord, C., & Monk, C. S. (2014). Serotonin transporter genotype impacts amygdala habituation in youth with autism spectrum disorders. *Soc Cogn Affect Neurosci*, *9*(6), 832-838. https://doi.org/10.1093/scan/nst039

Williams, L. M., Barton, M. J., Kemp, A. H., Liddell, B. J., Peduto, A., Gordon, E., & Bryant, R. A. (2005). Distinct amygdala-autonomic arousal profiles in response to fear signals in healthy males and females. *NeuroImage*, *28*(3), 618-626. https://doi.org/10.1016/j.neuroimage.2005.06.035

Williamson, J. W., Nobrega, A. C., McColl, R., Mathews, D., Winchester, P., Friberg, L., & Mitchell, J. H. (1997). Activation of the insular cortex during dynamic exercise in humans. *J Physiol*, *503 (Pt 2)*(Pt 2), 277-283. https://doi.org/10.1111/j.1469-7793.1997.277bh.x

Wilson, K. G. (1987). Electrodermal lability and simple reaction time. *Biol Psychol*, *24*(3), 275-289. https://doi.org/10.1016/0301-0511(87)90008-1

Windham, G. C., Zhang, L., Gunier, R., Croen, L. A., & Grether, J. K. (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. *Environ Health Perspect*, *114*(9), 1438-1444. https://doi.org/10.1289/ehp.9120

Woodard, C. R., Goodwin, M. S., Zelazo, P. R., Aube, D., Scrimgeour, M., Ostholthoff, T., & Brickley, M. (2012). A comparison of autonomic, behavioral, and parent-report measures of sensory sensitivity in young children with autism. *Research in Autism Spectrum Disorders*, *6*(3), 1234-1246. https://doi.org/https://doi.org/10.1016/j.rasd.2012.03.012

Wozniak, R. H., Leezenbaum, N. B., Northrup, J. B., West, K. L., & Iverson, J. M. (2017). The development of autism spectrum disorders: variability and causal complexity. *Wiley Interdiscip Rev Cogn Sci*, *8*(1-2). https://doi.org/10.1002/wcs.1426

Yamasaki, T., Maekawa, T., Takahashi, H., Fujita, T., Kamio, Y., & Tobimatsu, S. (2014). Electrophysiology of Visual and Auditory Perception in Autism Spectrum Disorders. In (pp. 791-808). https://doi.org/10.1007/978-1-4614-4788-7_39

Yasui, Y., Breder, C. D., Saper, C. B., & Cechetto, D. F. (1991). Autonomic responses and efferent pathways from the insular cortex in the rat. *J Comp Neurol*, *303*(3), 355-374. https://doi.org/10.1002/cne.903030303

Zalla, T., & Sperduti, M. (2013). The amygdala and the relevance detection theory of autism: an evolutionary perspective. *Front Hum Neurosci*, *7*, 894. https://doi.org/10.3389/fnhum.2013.00894

Zamrini, E. Y., Meador, K. J., Loring, D. W., Nichols, F. T., Lee, G. P., Figueroa, R. E., & Thompson, W. O. (1990). Unilateral cerebral inactivation produces differential left/right heart rate responses. *Neurology*, *40*(9), 1408-1411. https://doi.org/10.1212/wnl.40.9.1408

Zhang, Z., & Oppenheimer, S. M. (1997). Characterization, distribution and lateralization of baroreceptor-related neurons in the rat insular cortex. *Brain Research*, *760*(1), 243-250. https://doi.org/https://doi.org/10.1016/S0006-8993(97)00284-9

Zhang, Z. H., Rashba, S., & Oppenheimer, S. M. (1998). Insular cortex lesions alter baroreceptor sensitivity in the urethane-anesthetized rat. *Brain Res*, *813*(1), 73-81. https://doi.org/10.1016/s0006-8993(98)00996-2

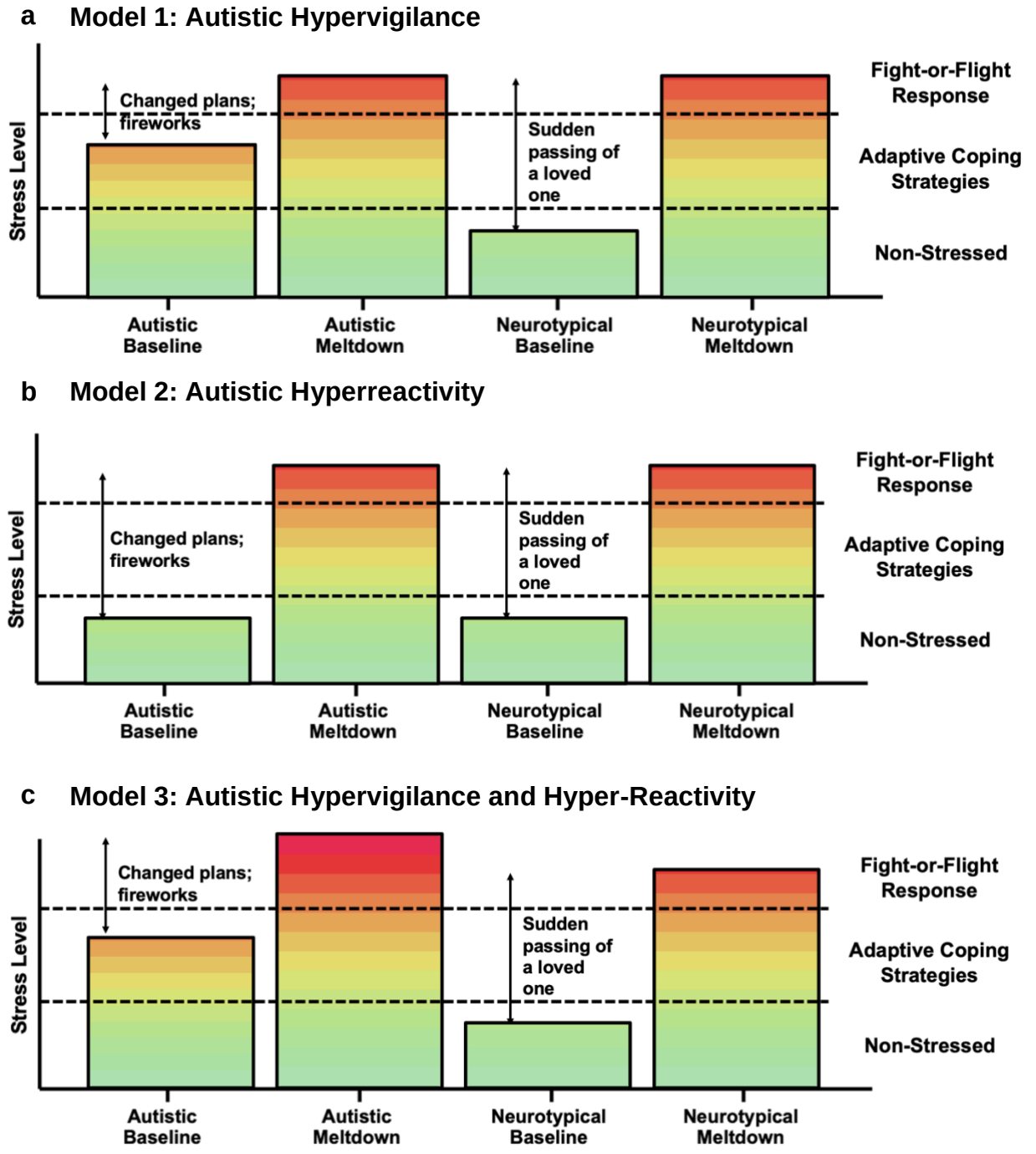

Figure 1. Modeling autistic hypervigilance and hyperreactivity (a-c) Schematic graphs comparing the relative stress levels (in arbitrary units) of neurotypicals and autistic individuals at baseline and during a behavioral meltdown that would be expected for three models of meltdowns. The graph in (a) represents autistic hypervigilance, which models autistic meltdowns as a product of baseline autonomic hypervigilance that reduces the threshold of additional stressors they can tolerate before experiencing a fight-or-flight (meltdown-like) response. The graph in (b) models autistic hyperreactivity, arguing that autistic individuals interpret the cognitive or sensory stressors that trigger meltdowns as being much more dangerous or

threatening than they appear to neurotypicals. (c) frames autistic meltdowns as a product of both hypervigilance and hyperreactivity. In each model, the meltdown trigger for autistic individuals is either fireworks (sensory stressor) or changed plans (cognitive stressor), while that for neurotypicals is a more obviously stressful major life events, such as the sudden passing of a loved one. Created with BioRender.com.

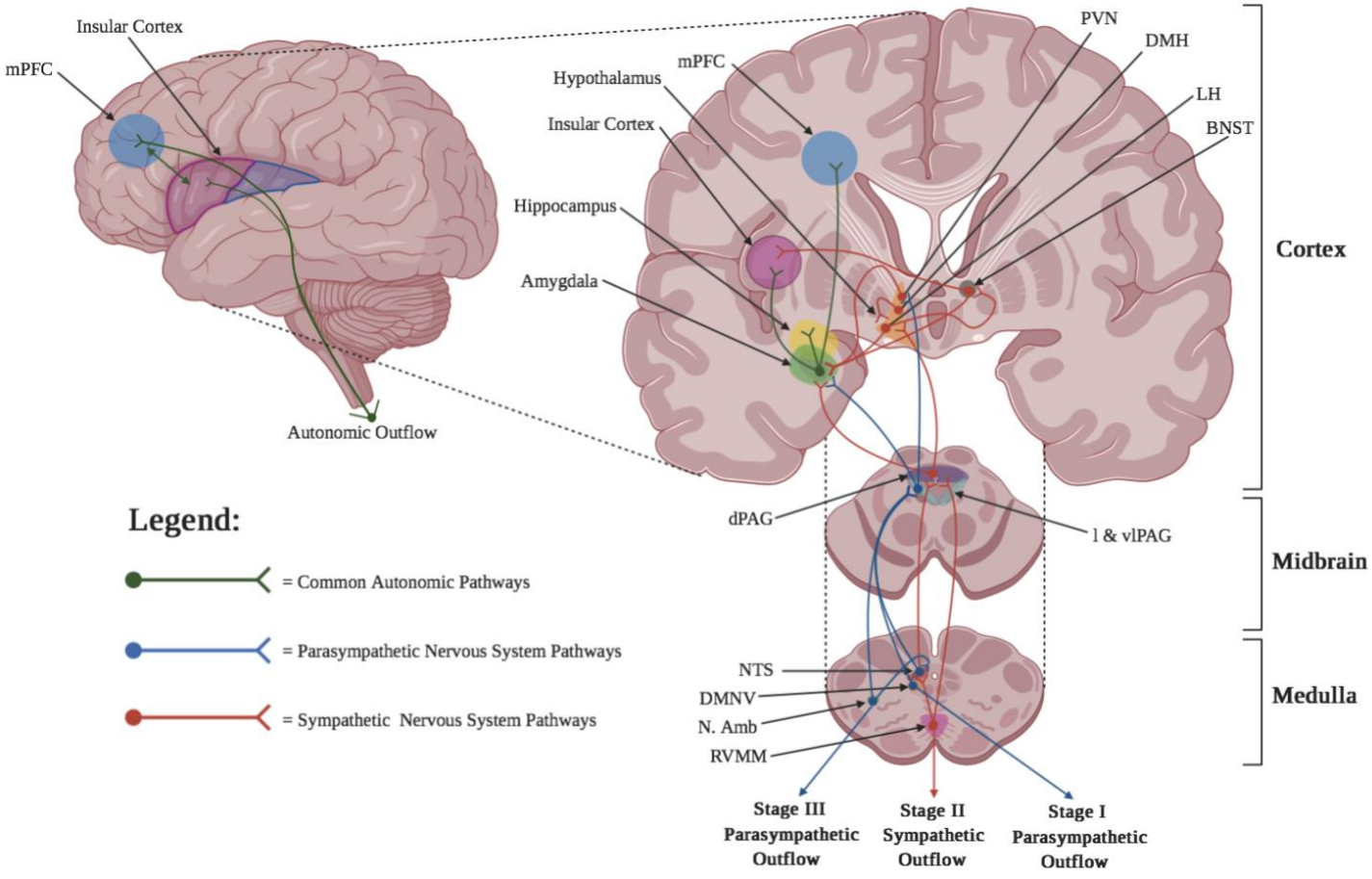

Figure 2. The Central Autonomic Network: A schematic illustrating the descending autonomic pathways involved in regulating stage I, II, and III polyvagal responses. Note that there are additional connections between each structure that are not depicted in the figure. **Abbreviations:** mPFC, medial Pre-Frontal Cortex; PVN, Paraventricular Nucleus of the Hypothalamus; DMH, Dorsomedial Nucleus of the Hypothalamus; LH, Lateral Hypothalamus; BNST, Bed Nucleus of the Stria Terminalis; PAG, Periaqueductal Gray; NTS, Nucleus Tractus Solitarius; DMNV, Dorsal Motor Nucleus of the Vagus; N. Amb, Nucleus Ambiguus; RVMM, Rostral Ventromedial Medulla; d, dorsal; l, lateral; vl, ventrolateral. Created with BioRender.com.

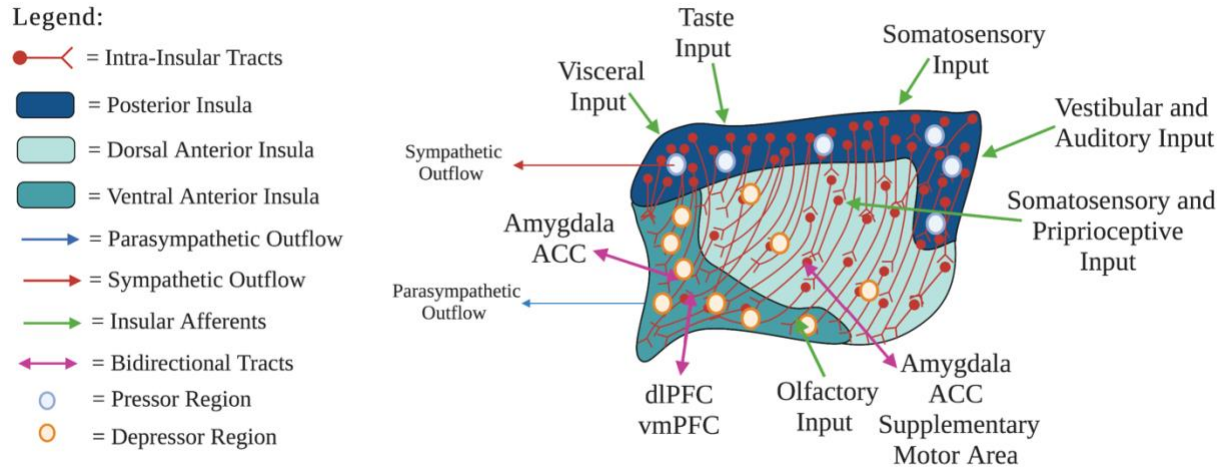

Figure 3. Neuroanatomy of the primate insular cortex: A schematic illustrating the efferent, afferent, and bidirectional tracts linking the insular cortex with the rest of the brain. In the neurotypical insula, intra-insular tracts process incoming interoceptive data along an anterior-to-posterior gradient. The integration of these data with cognitive and emotional cues in the mid and anterior insula gives rise to adaptive autonomic and behavioral states. The construction of this figure was heavily informed by the information presented in Figure 1C of Benarroch (2019). **Abbreviations:** ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Created with BioRender.com.

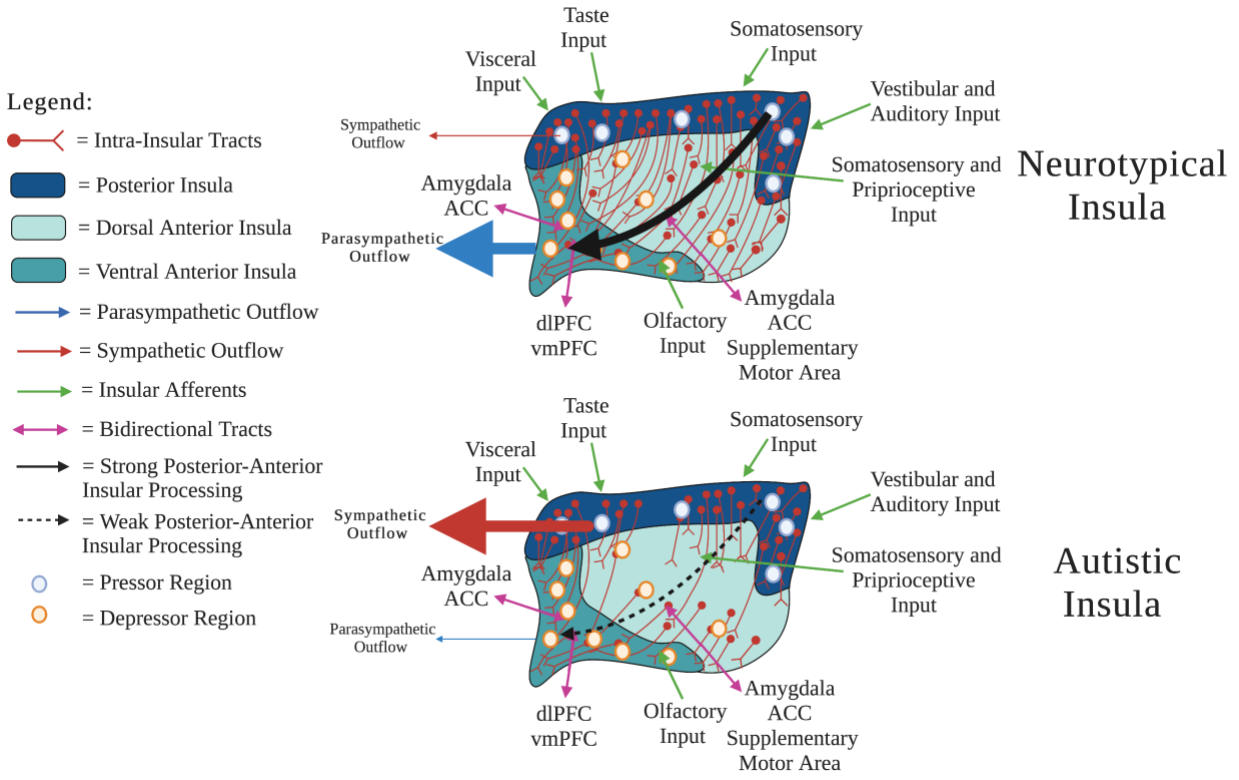

Figure 4. The Meltdown Pathway: A neurophysiological model of autistic hypervigilance: Interoceptive data arriving in the posterior insula progresses from the posterior to the anterior insula along intra-insula tracts. The integration of these data with exteroceptive data, limbic cues and cognitive cues in the mid and anterior insula contextualizes internal body states within the outside world. The insula uses this integrated interoceptive and exteroceptive data to select the appropriate autonomic and behavioral response (either stage I, II, or III polyvagal responses) to novel, potentially threatening external stimuli. The parts of the insula that initiate stage II and III responses are termed pressors (preferentially localized to the posterior insula) and depressors (preferentially localized to the anterior insula), respectively. In autism, hypo-connectivity between the anterior and posterior insula prevents the delivery of integrated sensory data to the anterior insula. This, we argue, augments pressor activity and diminishes depressor activity chronically—leading to autistic hypervigilance. **Abbreviations:** ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Created with BioRender.com.

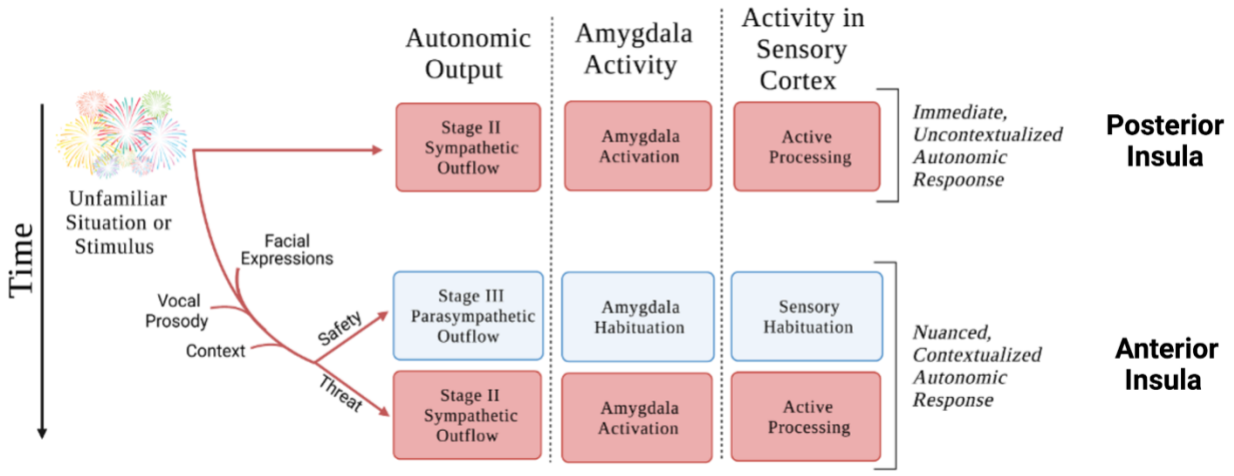

Figure 5. A basic model of neuroception in the anterior and posterior insula: The insula is uniquely positioned to evaluate and control whether an individual's autonomic and behavioral state prepares them to meet environmental challenges. Changes in the environment which are unfamiliar and potentially (but not necessarily) threatening will first be processed by the posterior insula, which will initiate an initial stage II autonomic and behavioral response. The anterior insula then contextualizes multiple safety and danger cues from the environment and draws from prior experiences to make a more nuanced, context-sensitive threat assessment. Depressor or pressor regions in the anterior insula can then either maintain the stage II response (for situations deemed threatening) or deploy the vagal break (for situations deemed safe). When a situation is deemed safe, the onset of stage III autonomic and behavioral states is often coordinated with amygdalar and sensory habituation.

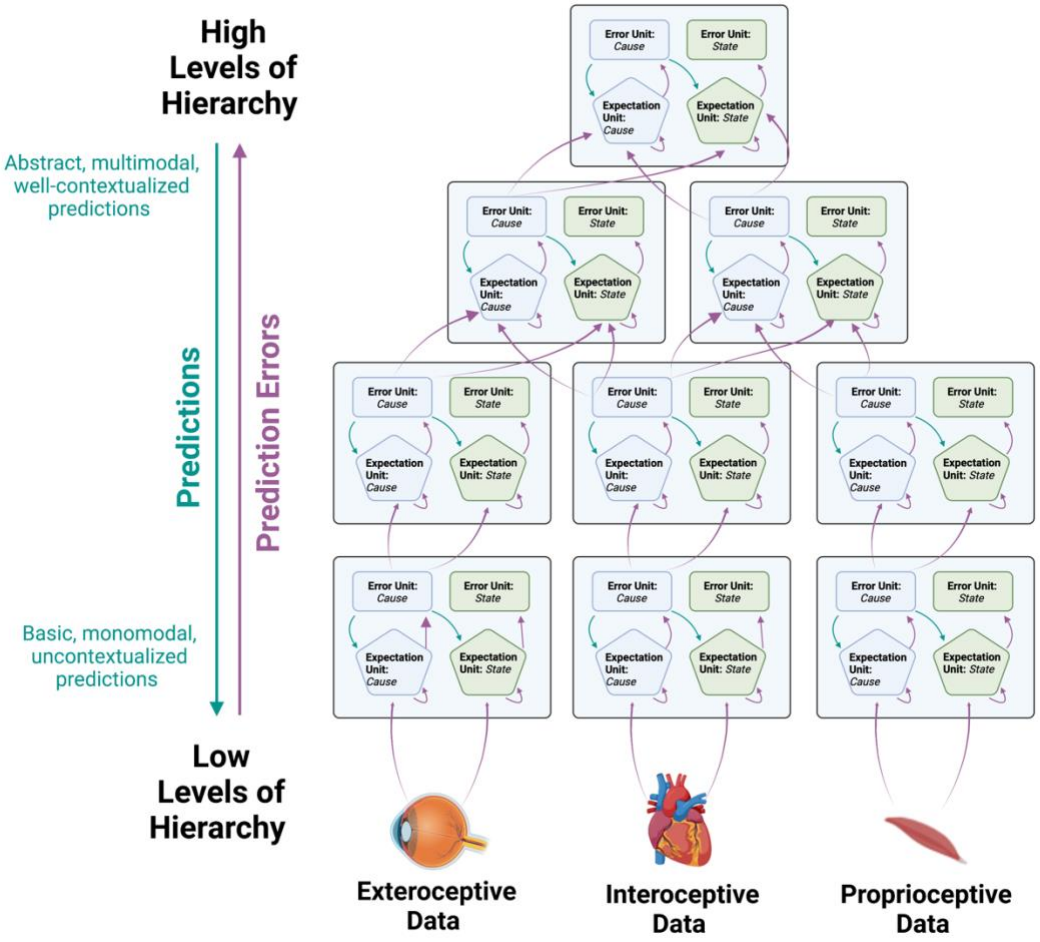

Figure 6. A generalized predictive coding hierarchy: A simplified schematic of a predictive coding hierarchy in the central nervous system. Parallel streams of exteroceptive, interoceptive, and proprioceptive sensory data entering the nervous system are compared with top-down priors of increasing complexity. At low levels of the hierarchy, predictions are basic, monomodal, and uncontextualized. At high levels of the hierarchy, prediction errors encounter abstract, multimodal, and well-contextualized predictions which assimilate data across modalities into a coherent portrait of the environment. Each level contains separate expectations and error units to process 'causes'—objects in the environment which create predictable streams of sensory data (ie. a smiling face, a bird chirping, etc.)—and 'states'—the time and context-dependent dynamics of causes (Shipp, 2016). Created with BioRender.com.

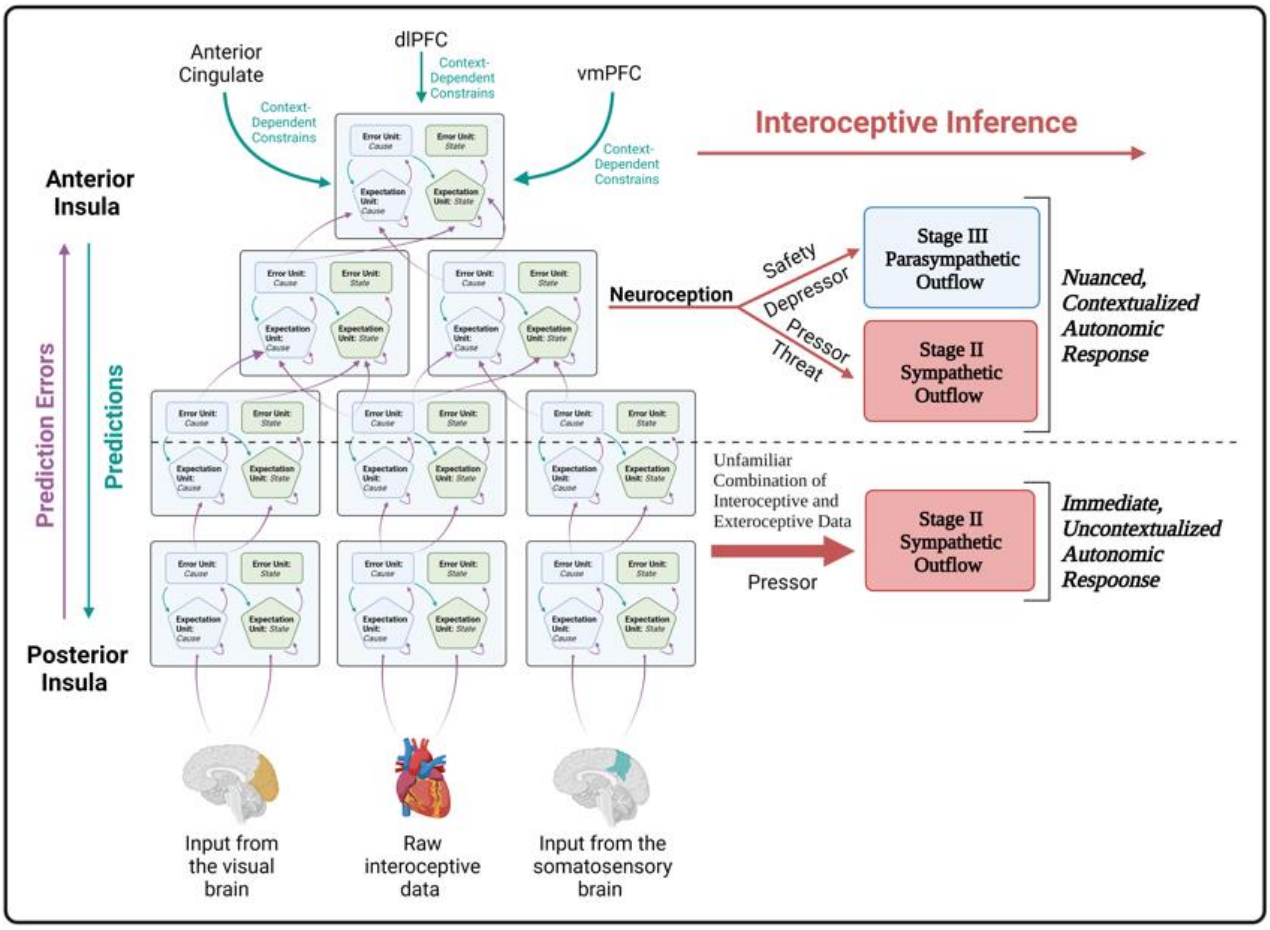

Figure 7. Our model of predictive coding in the neurotypical insula: Raw interoceptive inputs from the viscera along with well-processed exteroceptive context clues from the sensory corticies (e.g., the visual or auditory brain) arrive in the posterior insula. As these data are progressively processed and integrated along the posterior-to-anterior axis, they are compared with generative models of increasing complexity and multimodality. The posterior insula contains more rudimentary generative models, which function like high-level coincidence detectors between an exteroceptive sign of danger (e.g., a loud public venue) and a given allostatic state (e.g., sympathetic arousal and fight-or-flight behaviors). By contrast, generative models in the anterior insula co-represent autonomic state, multiple environmental cues, and social cues, allowing interoceptive information to be unpacked in the context afforded by every other modality the brain has to offer. This enables context-sensitive threat appraisal and ensures that a person's specific context (whether threatening or safe) is matched with an appropriate allostatic plan (e.g., stage I, II, or III polyvagal responses). Created with BioRender.com.

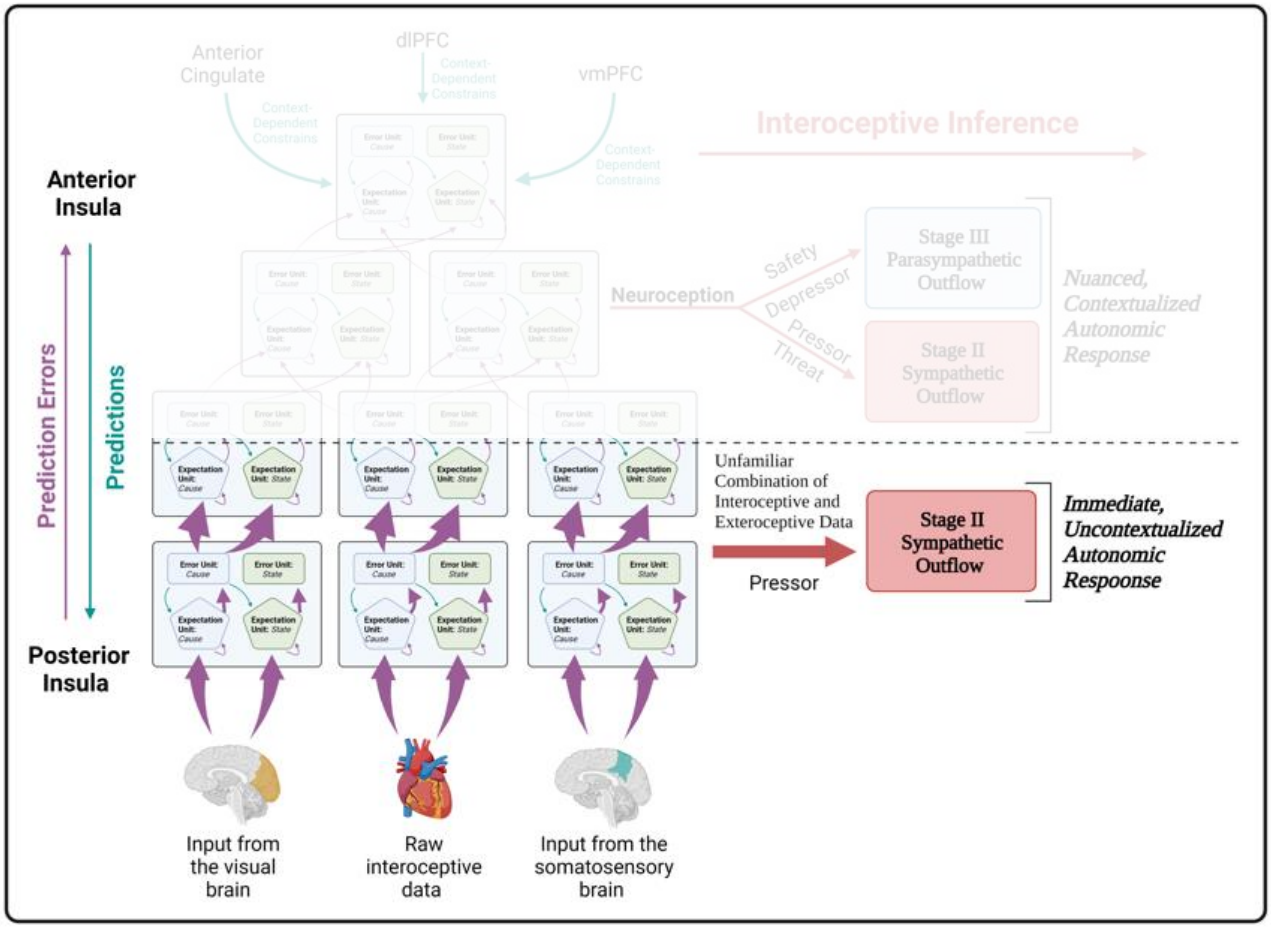

Figure 8. Unattenuated sensory precision and failures of deep processing in the insular predictive coding hierarchy engender meltdowns: Aberrant precision accounts of autism argue that *all* incoming sensory data, including sensory noise, is afforded a uniformly high precision in those with autism (Lawson et al., 2014; Van de Cruys et al., 2014; Palmer et al., 2017). As a consequence, uninformative, irrelevant sensory details in the environment are constantly reported to levels of the cortex capable of organizing an allostatic plan—like the insula. We speculate that these extemporaneous and confusing inputs are likely labelled as ambiguous danger signals that must be resolved through an allostatic plan. Unattenuated sensory precision is represented by the over-weighted purple prediction error arrows shown in this figure. Compounding this, we argue that those with autism also experience impairments of deep processing within the interoceptive hierarchy, leading to meltdowns. Building on Quattrocki and Friston (2014)'s model, we propose that early oxytocin deficiency impairs acquisition of the high-level generative models required to 1) assimilate interoceptive feedback with exteroceptive context clues and 2) select context-appropriate allostatic plans (e.g., stage I, II, or III polyvagal responses). This is represented by the covered anterior insula in the above figure. The result of these two changes in interoceptive predictive coding leads those with autism to display immediate autonomic and behavioral responses to ambiguous, but objectively harmless, environmental stressors that can never be contextualized by high-level processing in the mid and anterior insula. Created with BioRender.com.