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Review article

A review of decreased sound tolerance in autism: Definitions, phenomenology, and potential mechanisms

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ABSTRACT

Atypical behavioral responses to environmental sounds are common in autistic children and adults, with 50–70 % of this population exhibiting decreased sound tolerance (DST) at some point in their lives. This symptom is a source of significant distress and impairment across the lifespan, contributing to anxiety, challenging behaviors, reduced community participation, and school/workplace difficulties. However, relatively little is known about its phenomenology or neurocognitive underpinnings. The present article synthesizes a large body of literature on the phenomenology and pathophysiology of DST-related conditions to generate a comprehensive theoretical account of DST in autism. Notably, we argue against conceptualizing DST as a unified construct, suggesting that it be separated into three phenomenologically distinct conditions: hyperacusis (the perception of everyday sounds as excessively loud or painful), misophonia (an acquired aversive reaction to specific sounds), and phonophobia (a specific phobia of sound), each responsible for a portion of observed DST behaviors. We further elaborate our framework by proposing preliminary neurocognitive models of hyperacusis, misophonia, and phonophobia that incorporate neurophysiologic findings from studies of autism.

1. Introduction

Autism spectrum disorder (hereafter referred to as “autism”) is a heterogeneous, lifelong neurodevelopmental condition characterized by difficulties with social communication and the presence of restricted, repetitive patterns of behavior, interests, and activities (American Psychiatric Association, 2013). In addition to these cardinal features, autistic¹ people commonly find a number of everyday sensory stimuli to

be quite aversive (Ben-Sasson et al., 2009, 2019; Cascio et al., 2016; Schauder and Bennetto, 2016), now considered a core feature of the condition (American Psychiatric Association, 2013). Although this so-called “sensory hyperreactivity” can be present in any modality (Ausderau et al., 2014; Crane et al., 2009; Hazen et al., 2014; Leekam et al., 2007; Tavassoli et al., 2014), decreased sound tolerance (DST; i.e., an inability to tolerate everyday sounds) is among the most prevalent, persistent, and disabling sensory features of autism (Gomes et al., 2008;

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¹ The terms ‘autistic person’ and ‘person on the autism spectrum’ are the preferred language of the majority of people diagnosed with autism (Bury et al., 2020; Kenny et al., 2016). Out of respect for these preferences, we use these terms to refer to individuals on the spectrum rather than exclusively using person-first language.

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O'Connor, 2012; Stefanelli et al., 2020; Stiegler and Davis, 2010). A recent meta-analysis estimated that the current prevalence of DST in the autistic population is 38–45 %, with 50–70% of individuals on the autism spectrum having experienced DST at some point in their lives (Williams, Suzman, et al., 2020b). In the largest single study investigating this phenomenon, Law et al. (2016) reported current and lifetime DST prevalence rates of 77.6 % and 86.6 %, respectively, in an online sample of 814 autistic children. The majority of children exhibited DST-related challenging behaviors daily or weekly, and over one third had physically injured themselves or others as a result of these behaviors (Law et al., 2016). Even when not a safety concern, DST contributes significantly to autism-related functional impairment, as many caregivers report that their children's reactions to sounds prevent them from participating in a wide range of family, school, and community activities (Hussein et al., 2019; E. K. Jones et al., 2020; Law et al., 2016). Furthermore, aversions to sensory stimuli, such as DST, are often cited as reasons that autistic individuals find it difficult to seek medical care (Carter et al., 2017; Giarelli et al., 2014; Muskat et al., 2015; Nicholas et al., 2016). DST symptoms in autism are known to persist into adulthood (Elwin et al., 2013; Kuiper et al., 2019; Landon et al., 2016; A. E. Robertson and Simmons, 2015; Tavassoli et al., 2014), contributing to workplace difficulties (Hayward et al., 2019; Hedley et al., 2018; Lorenz et al., 2016; A. E. Robertson and Simmons, 2015), anxiety (Landon et al., 2016; Simonoff, 2020), avoidance behavior (Landon et al., 2016), and general distress (Griffith et al., 2011; R. S. P. Jones et al., 2003; Smith and Sharp, 2013). Notably, although autism is also associated with *hyporeactivity* to everyday auditory stimuli (Ben-Sasson et al., 2009, 2019; Law et al., 2016; Watts et al., 2016), this response pattern is far less prevalent than DST in the autistic population, and its effects on activity participation and functional impairment appear to be less pronounced (Law et al., 2016). Thus, we choose to focus this review solely on DST in autistic individuals, which we believe to be the sensory feature of autism with the largest overall impact on quality of life in this population.

Despite the prevalence and impact of DST in autism, there is currently insufficient evidence to support recommendations of any behavioral or pharmacologic treatment to reduce the severity or functional impact of this symptom (Fung et al., 2012; Sandbank et al., 2020; Schoen et al., 2019; Sinha et al., 2006; Weitlauf et al., 2017). One potential reason for the lack of evidence-based intervention in this area is the fact that the underlying mechanisms of autism-associated DST are still largely unknown, hindering the development of targeted interventions. Though a number of physiological and psychological processes have been suggested as potential sources of DST in autism (Marriage and Barnes, 1995; McCullagh et al., 2020; Pillion et al., 2018; Stiegler and Davis, 2010), there is still debate in the literature over whether DST behaviors reflect a disturbance in low-level auditory processing, abnormally strong emotional reactions to specific auditory stimuli, or a combination of the two. The purpose of the present article is to review the literature on DST in autism, incorporating published experimental and clinical observations into a unified theoretical framework. Synthesizing findings from the clinical and neuroscientific literature, we propose several potential neurocognitive models to explain the phenomenon of DST in autism. By doing so, we aim to generate testable hypotheses about the relationships between physiology, perception, and behavior, setting the stage for future research on DST mechanisms and bringing the field one step closer to the development of targeted interventions.

2. Definitions

The terminology used to describe DST in the medical literature has been extremely varied, with the words hyperacusis (Fagelson and Baguley, 2018; Tyler et al., 2014), misophonia (P. J. Jastreboff and Jastreboff, 2015; Schröder et al., 2013), phonophobia (Møller, 2011; Phillips and Carr, 1998), auditory over-responsivity (Tavassoli et al.,

2019; Van Hulle et al., 2012, 2018), noise sensitivity (Stansfeld, 1992), auditory defensiveness (Goldsmith et al., 2006; Kern et al., 2006), noxacusis (Auerbach, 2019), and auditory hypersensitivity (Gomes et al., 2008) all used to describe specific patterns of sound intolerance across populations. The terminology used to describe DST as a symptom of autism specifically has also been highly inconsistent (Gomes et al., 2008; Landon et al., 2016; Stefanelli et al., 2020; Stiegler and Davis, 2010; Tavassoli et al., 2019), and thus we seek to provide definitions of several key terms before reviewing the literature on these topics. Although there is no unified standard of nomenclature for disorders of sound tolerance, we align our terminology with the first major academic text on this topic (Fagelson and Baguley, 2018), separating disorders of DST into the specific conditions of *hyperacusis*, *misophonia*, and *phonophobia* (Table 1; see also Tyler et al., 2014 for a similar framework).

2.1. Hyperacusis

Hyperacusis is defined here as a hearing disorder involving an increased sensitivity or decreased tolerance to sound at levels that would not trouble most individuals. For the person experiencing hyperacusis, everyday sounds can be unpleasant, intense, painful, and/or overwhelming, and these sounds are often perceived as much louder than they actually are (Fackrell et al., 2019). This definition is more expansive than many that have previously been proposed, which have tended to focus exclusively on the perception of moderate-intensity sounds as overly loud (Fackrell et al., 2017; Phillips and Carr, 1998; Tyler et al., 2014). In their pivotal review on the topic, Tyler et al. (2014) proposed that hyperacusis could be separated into four subtypes characterized by loudness, annoyance, fear, and pain, occurring either singly or in combination. A more recent consensus definition of hyperacusis (Fackrell et al., 2019) differentiates hyperacusis from both misophonia (an acquired aversive reaction to specific “trigger” sounds characterized by anger, extreme annoyance, and disgust) and phonophobia (a persistent, abnormal and unwarranted fear of certain sounds). Thus, within our framework, hyperacusis refers specifically to *loudness hyperacusis* and *pain hyperacusis*, whereas the terms *misophonia* and *phonophobia* are proposed to refer to the constructs of *annoyance hyperacusis* and *fear hyperacusis* proposed by Tyler et al., respectively. Furthermore, despite the consensus definition of hyperacusis including the words “increased sensitivity,” it is well established that patients with hyperacusis do not have increased sensitivity to sounds in the psychoacoustic sense (i.e., lower auditory detection thresholds), and that many non-autistic individuals with hyperacusis exhibit some degree of hearing loss (Anari et al., 1999; Sheldrake et al., 2015; Tyler et al., 2014). Within the framework proposed by Ward (2019), a distinction is made between *subjective* sensory sensitivity (i.e., higher self-reported intolerance of sensory stimuli), *neural* sensory sensitivity (i.e., increased neural responses evoked by a given sensory stimulus), and *behavioral* sensory sensitivity (i.e., lower thresholds for stimulus detection and/or discrimination). However, as these three types of “sensory sensitivity” are generally unrelated to each other within the autistic population (Donkers et al., 2015; Dunlop et al., 2016; Gravel et al., 2006; Hudac et al., 2018; C. R. G. Jones et al., 2009; Kuiper et al., 2019; Millin et al., 2018; Tharpe et al., 2006), we believe the use of this single term to describe constructs at the behavioral, perceptual, and neural levels will lead researchers to commit the “jingle fallacy” (Dang et al., 2020), in which measures of “sensory sensitivity” at different levels are thought to tap the same construct. Thus, in accordance with Tyler et al. (2014) we refrain from using the term “hypersensitivity” to describe hyperacusis or any other form of DST, and we encourage autism researchers to use the term “sensory sensitivity” only when referring to *behavioral* stimulus detection or discrimination thresholds.

Loudness hyperacusis is a condition in which the threshold for loudness discomfort is reduced and sounds of moderate intensity are judged to be very loud (Phillips and Carr, 1998). Psychoacoustically, loudness hyperacusis can be thought of as an increased slope of the

Table 1
Comparison of the Hyperacusis, Misophonia, and Phonophobia.

	Hyperacusis	Misophonia	Phonophobia
Definition	A hearing disorder in which sound of moderate intensity is perceived as excessively loud, painful, and/or overwhelming.	A neuropsychiatric condition in which individuals have excessive and inappropriate emotional responses to specific “trigger” sounds (e.g., chewing, tapping, sniffing), even when presented at a low level.	A specific phobia of particular sounds or classes of sounds, resulting in anticipatory responses and avoidance of potential sound sources.
Limited to specific sounds	No	Yes	Yes
Primary response to sound	Excessive loudness sensation and/or pain in ears/head	Anger, disgust, and/or extreme irritation. Idiosyncratic physical symptoms.	Fear and/or panic, anticipatory anxiety
Psychoacoustic loudness perception	Steeper loudness growth, reduced LDL	Normal	Unknown (possibly reduced LDL)
Influence of contextual factors	Low	High	High
Results in avoidance behavior	Yes	Yes	Yes
Associated with psychopathology	Yes	Yes	Yes
Occurs secondarily to	Cochlear hearing loss, noise trauma, brain injury	Unknown	Hyperacusis, reactive tinnitus, misophonia, posttraumatic stress disorder, other anxiety disorders
Proposed cognitive mechanism	Amplification of low-level sensory information resulting in a steeper growth of subjective loudness with increasing sound level.	Attribution of excess salience to particular sounds or associated perceptual phenomena (e.g., sights), resulting in conditioned aversive emotional response and heightened sympathetic arousal.	Pathological fear learning, combining excess attribution of threat to specific sounds with poor experience-dependent extinction. Maintained by avoidance of feared stimulus.
Implicated brain regions	Primary/secondary auditory cortex, inferior colliculus, auditory brainstem (superior olivary complex)	Salience network (anterior insular cortex, dorsal anterior cingulate cortex), ventromedial prefrontal cortex, posteromedial cortex, hippocampus, amygdala	Amygdala, hippocampus, anterior cingulate cortex, ventromedial prefrontal cortex, anterior insular cortex, bed nucleus of the stria terminalis/extended amygdala
Increased prevalence in autism	Yes	Unknown	Yes
Unique pathophysiology in autism	Yes	No	No

Note. LDL = loudness discomfort level (the decibel level at which a sound starts being perceived as uncomfortably loud).

loudness growth function (i.e., steeper growth of perceived loudness as a function of sound intensity; Brandy and Lynn, 1995; Hébert et al., 2013; Noreña and Chéry-Croze, 2007). This condition is distinguishable from *loudness recruitment*, a steepening of the loudness growth function that occurs in the setting of cochlear hearing loss due to outer hair cell damage (Fowler, 1965; B. C. J. Moore et al., 1985; Preyer and Gummer, 1996). Notably, in loudness recruitment, the loudness of a sound “catches up” to that of a normal hearing listener, and at high levels the loudness growth functions of recruiting and normal-hearing ears will again overlap (B. C. J. Moore et al., 1985). This is in contrast to loudness hyperacusis, where the loudness growth curve diverges from that of a normal hearing listener without again merging with the normal loudness function (Brandy and Lynn, 1995; Noreña and Chéry-Croze, 2007).

Pain hyperacusis (Auerbach, 2019; Pollard, 2019; Tyler et al., 2014), also referred to as *noxacusis*, is a less well understood form of the condition in which an individual perceives physical pain in the ear when exposed to certain sounds at levels far below those needed to cause pain in a typical listener (i.e., approximately 120 dB sound pressure level [SPL], as loud as the front row of a rock concert; Plutchik, 1963). Although the character of the pain varies greatly across individuals (e.g., dull ache, burning, sharp, stabbing, or throbbing), 62 % of hyperacusis patients responding to an online survey reportedly experienced ear pain at least daily (Pollard, 2019). It is currently unclear whether the pain experienced in this condition is the same pain experienced by typical listeners at extremely high sound levels or an entirely separate phenomenon with distinct neurophysiologic substrates. Recent discoveries have implicated the population of type II cochlear afferent neurons in mediating the perception of noxious or painful auditory stimuli (Flores et al., 2015; Liu et al., 2015; Zhang and Coate, 2017), but the role of these cells in pain hyperacusis remains to be determined.

Throughout this review, the term “hyperacusis” will be used to refer generally to both loudness and pain hyperacusis, regardless of

neurological, psychiatric, otologic, or idiopathic etiology (Tyler et al., 2014). The specific terms “loudness hyperacusis” and “pain hyperacusis” will be utilized when referring to only one of the subtypes.

2.2. Misophonia

Misophonia, also called selective sound sensitivity syndrome (Neal and Cavanna, 2013) or annoyance hyperacusis (Danesh and Aazh, 2020; Tyler et al., 2014), is a newly described neuropsychiatric condition in which individuals have excessive and inappropriate emotional responses to specific “trigger” sounds (e.g., chewing, tapping, sniffing), even when presented at a low level (Brout et al., 2018; Claiborn et al., 2020; Jager et al., 2020; Palumbo et al., 2018; Potgieter et al., 2019; Schröder et al., 2013). The specific triggers and their elicited responses vary greatly across individuals and may change over time, although the predominant emotional response tends to involve some form of anger, disgust, or irritation (Jager et al., 2020) and increased autonomic arousal (Edelstein et al., 2013; Kumar et al., 2017). This emotional response is often accompanied by an idiosyncratic set of physical symptoms (e.g., muscle tension, paresthesias, abdominal discomfort, or other physical sensations; Claiborn et al., 2020; Dozier and Morrison, 2017). Moreover, misophonic reactions are in some cases evoked by specific visual stimuli as well (e.g., the sight of a person chewing can trigger anger and physical sensations, even in the absence of a sound), a phenomenon that has been termed “misokinesia” (Potgieter et al., 2019). Interestingly, the context in which these triggers are encountered modulates the response substantially, with more intense responses being reported when triggers are experienced in a familiar context (Potgieter et al., 2019) and fewer or less intense responses occurring when the triggering sound is made by a toddler or an adult with cognitive impairment (Jager et al., 2020). Triggering sounds also do not seem to typically evoke a response when produced by the individuals with

misophonia themselves (Potgieter et al., 2019).

Compared with hyperacusis, misophonia is a relatively new concept, first described in the academic literature in 2002 (M. M. Jastreboff and Jastreboff, 2002). However, it was not until 2013, when diagnostic criteria for this disorder were proposed (Schröder et al., 2013), that misophonia began to attract the attention of researchers in psychology, psychiatry, and audiology. Although misophonia research remains in its infancy, there is sufficient evidence to indicate that misophonia is a distinct behavioral syndrome that can result in substantial distress and functional impairment (Brout et al., 2018; Jager et al., 2020; Potgieter et al., 2019; Schröder et al., 2013).

2.3. Phonophobia

The term phonophobia, literally meaning “fear of sound,” is commonly used in neurology to describe the sound intolerance that often accompanies migraine headaches (Ashkenazi et al., 2009; Irimia et al., 2008; Vingen et al., 1998; Woodhouse and Drummond, 1993). However, in the current framework, we define phonophobia as a specific phobia of particular sounds or classes of sounds, resulting in anticipatory responses and avoidance of potential sound sources (Baguley and McFerran, 2011; Landgrebe and Langguth, 2011; Möller, 2011; Stiegler and Davis, 2010). Our definition of phonophobia is nearly synonymous with that of Tyler’s (2014) “fear hyperacusis,” whereas the “phonophobia” described in migraine could be better classified within this framework as episodic loudness hyperacusis (Suhnan et al., 2017). Although a fear of loud noises is common in childhood (Meltzer et al., 2009; Ollendick et al., 2002), a diagnosis of phonophobia would require an amount of fear and impairment out of proportion to what one would expect for that individual’s developmental level (American Psychiatric Association, 2013). Furthermore, while both misophonia and phonophobia can involve inappropriate emotional reactions to specific sounds, the misophonic reaction primarily involves anger and/or disgust, whereas phonophobia is characterized by fear and/or anxious preoccupation. Notably, phonophobia as defined here often develops secondary to other forms of DST, as some patients with hyperacusis or misophonia may develop excessive anxiety with respect to situations in which they may encounter painful or otherwise distressing sounds (Blasing and Kroener-Herwig, 2012; Goebel and Floezinger, 2008; Jager et al., 2020; Jüris et al., 2014; Landgrebe and Langguth, 2011).

2.4. Noise sensitivity

Unlike the previous terms, noise sensitivity is not a diagnosable medical condition but is instead a stable personality trait that moderates one’s reactions to noise. It is not, however, a true “sensory sensitivity,” as this trait is unrelated to auditory detection thresholds (Stansfeld et al., 1985). Defined by Job (1999, p. 58), noise sensitivity refers to “the internal states (be they physiological, psychological [including attitudinal], or related to life style or activities conducted) of any individual which increase their degree of reactivity to noise in general.” Noise sensitivity is thought to moderate the degree to which a person finds any given noise annoying, irrespective of overall noise exposure (Kliuchko et al., 2016; van Kamp et al., 2004). Compared to the general population, noise-sensitive individuals attend more to noises, find noises more threatening and out of their control, and adapt to noises more slowly (Stansfeld, 1992; Stansfeld and Clark, 2019). Unlike hyperacusis, noise sensitivity is not associated with changes in loudness functions (Ellermeier et al., 2001; Stansfeld et al., 1985), although self-reports of hyperacusis symptoms and noise sensitivity may correlate highly in some populations (Viziano et al., 2017). Notably, although most noise-sensitive individuals do not have hyperacusis, patients with hyperacusis report high levels of noise sensitivity (Paulin et al., 2016), likely as a result of the discomfort they experience in response to many everyday sounds.

2.5. Decreased sound tolerance

We define decreased sound tolerance (DST) as an umbrella term encompassing hyperacusis, misophonia, and phonophobia (P. J. Jastreboff and Jastreboff, 2014, 2015). This term is preferred over equally general terms such as “auditory defensiveness” and “auditory over-responsivity,” as it refers to the subjective percept of the sound as intolerable without describing any particular behavioral reaction. The personality trait of noise sensitivity is *not* included within this definition, though high levels of noise sensitivity may be seen in those with DST (Paulin et al., 2016). Similarly, individuals with chronic subjective tinnitus are not necessarily classified as having DST, although comorbid hyperacusis (Tyler et al., 2014) and phonophobia (Blasing and Kroener-Herwig, 2012; Landgrebe and Langguth, 2011) are commonly observed in this population and can be diagnosed separately. While the labels of hyperacusis, misophonia, and phonophobia are better able to describe the phenomenology of an individual’s sound intolerance, the label of DST is useful when there is a lack of certainty about the underlying reasons for an individual’s sound-induced distress or discomfort (e.g., in nonverbal individuals who cannot describe why certain sounds are aversive). Thus, we use DST to refer to the behavioral hyperreactivity to auditory stimuli seen in individuals on the autism spectrum, as it is currently unclear whether these behaviors are due to hyperacusis, misophonia, phonophobia, or some combination thereof (Stiegler and Davis, 2010). As we argue in the following section, all three conditions likely contribute to the high rates of DST behavior seen in autistic individuals, and further research is needed to determine their relative contributions to the autistic DST phenotype.

3. Phenomenology of decreased sound tolerance in autism

Although a sizable body of literature has been published on DST in autism (Gomes et al., 2008; Moossavi and Moallemi, 2019; O’Connor, 2012; Stefanelli et al., 2020; Stiegler and Davis, 2010), there has been relatively little research to date systematically examining the specific sounds that autistic individuals find distressing or which aspects of the stimuli these individuals find difficult to tolerate. Although some first-person accounts of autistic people contain descriptions of subjective DST (Bemporad, 1979; Cesaroni and Garber, 1991; DePape and Lindsay, 2016; Elwin et al., 2012, 2013; Howe and Stagg, 2016; R. S. P. Jones et al., 2003; Kirby et al., 2015; Landon et al., 2016; Preece and Jordan, 2010; A. E. Robertson and Simmons, 2015; Smith and Sharp, 2013; Stiegler and Davis, 2010; Volkmar and Cohen, 1985), these accounts often do not provide enough detail of the individual’s perception of sound to confidently classify the reported DST as hyperacusis, misophonia, or phonophobia. An exception is the qualitative study by Landon and colleagues, which focused exclusively on the phenomenology of DST in autistic adults (Landon et al., 2016). In this study, researchers interviewed 10 adults with diagnosed autism and self-reported DST, asking questions about the participants’ experiences of sounds, the qualities of sounds that they felt caused their distress, specific events that produced aversive reactions, and strategies employed to cope with sounds in everyday life. Participants consistently regarded loud, sharp, or otherwise high-pitched sounds to be the most distressing, although several also indicated that specific sounds elicited strong emotional reactions regardless of level. The authors concluded that the participants reported experiences were consistent with both hyperacusis and “an intolerance to specific sounds” (i.e., misophonia). Anxiety and avoidance also played a prominent role in the participants’ responses to noise, indicating that a number of participants likely would be considered to have phonophobia as well.

Another frequently reported symptom in the Landon study was a tendency to be easily distracted by noises, even in relatively innocuous or quiet situations (Landon et al., 2016). Although auditory distractibility is pertinent to the overall sensory phenotype of autism, this process is distinct from DST as it is typically defined (Fagelson and Baguley,

2018; P. J. Jastreboff and Jastreboff, 2015). Moreover, auditory distractibility is likely mediated by higher-order cognitive factors such as working memory capacity and selective attention (Sörqvist, 2010; Sörqvist and Marsh, 2015; Sörqvist and Rönnerberg, 2014), which are known to differ in the autistic population (Habib et al., 2019). Individuals with attention-deficit/hyperactivity disorder (ADHD) are also particularly susceptible to the effects of auditory distractions (Micoulaud-Franchi et al., 2015; Pelletier et al., 2016; Zentall and Shaw, 1980), and thus the high prevalence of co-occurring ADHD in autistic children and adults (Lai et al., 2019; Lugo-Marín et al., 2019) may contribute to the high rates of auditory distractibility seen in this population. A failure to habituate to low-level sounds may also play a role, as preliminary work has demonstrated reductions in simple loudness adaptation in autistic adults relative to neurotypical controls (Lawson et al., 2015). Alternatively, this symptom may be related to the ability of individuals on the autism spectrum to simultaneously process a larger amount of auditory information than neurotypical controls, a difference supported by data from laboratory-based auditory detection tasks (Brinkert and Remington, 2020; Remington and Fairnie, 2017). Auditory distractibility is also a known correlate of noise sensitivity (Belojević et al., 1992; Kjellberg et al., 1996; Sandrock et al., 2008), and the enhanced distractibility seen in autism could potentially contribute to more autistic individuals developing noise sensitivity. However, as the correlates of auditory distractibility in autism have yet to be empirically tested, these relationships remain purely speculative at this time.

In sum, the most detailed phenomenological account of DST in autism indicates that the auditory challenges in this population encompass hyperacusis, misophonia, phonophobia, and potentially noise sensitivity as well (Landon et al., 2016). Accordingly, questions of whether the DST seen in autism is physiological or psychological in origin (Stiegler and Davis, 2010) present a false dichotomy, as abnormalities in lower-level perceptual processes (i.e., hyperacusis) and higher-level cognitive processes (i.e., misophonia and phonophobia) each likely contribute to DST in a portion of autistic individuals (Danesh et al., 2015; Demopoulos and Lewine, 2016; Khalfa et al., 2004; Landon et al., 2016; B. Y. Lau et al., 2020; A. E. Robertson and Simmons, 2015). Still, it remains possible that a “dominant” pattern of sound intolerance (e.g., loudness hyperacusis) exists in this population. Thus, in sections 3.1–3.3, we review the published literature suggesting that DST in autism is characterized by (a) hyperacusis, (b) misophonia, and (c) phonophobia.

3.1. Hyperacusis in autism

An aversion to loud stimuli is one of the most prominent forms of DST reported in both personal accounts and clinical descriptions of autism (O'Connor, 2012; Phillips and Carr, 1998; Stiegler and Davis, 2010; Tyler et al., 2014). Furthermore, when autistic people complete standardized self-report questionnaires assessing hyperacusis symptoms, they routinely endorse higher symptom levels than neurotypical controls (Danesh et al., 2015; Dunlop et al., 2016; Keith et al., 2019). Though such reactions are highly consistent with hyperacusis, it remains unclear whether individuals on the autism spectrum are more likely to manifest the loudness or pain subtype. Personal accounts of autism often describe certain sounds as physically painful (Elwin et al., 2012; Howe and Stagg, 2016; R. S. P. Jones et al., 2003; Kirby et al., 2015; Landon et al., 2016; A. E. Robertson and Simmons, 2015; Smith and Sharp, 2013); however, there are no empirical studies quantifying the number of autistic individuals who experience physical pain in response to everyday sounds. Alternatively, several studies indicate that loudness growth functions assessed via categorical loudness scaling are steeper in persons on the autism spectrum (Dunlop et al., 2016; Khalfa et al., 2004; Ohmura et al., 2019), confirming the presence of loudness hyperacusis in those participants. Notably, an unpublished study by our group of 243 patients with self-reported hyperacusis contained four individuals on the autism spectrum (Williams, Suzman, et al., 2020a), two of whom

reported pain hyperacusis (one with comorbid misophonia and the other with comorbid phonophobia) and two of whom reported loudness hyperacusis (one with comorbid phonophobia and the other reporting no other DST conditions). Three of these individuals (two loudness, one pain) had also received diagnoses of hyperacusis from physicians or audiologists. These data, although preliminary, support the contention that both loudness and pain hyperacusis are present in some individuals on the autism spectrum, although the portion of individuals experiencing each subtype has yet to be precisely determined.

As further evidence of hyperacusis in autism, individuals on the autism spectrum also tend to exhibit lower loudness discomfort levels (LDLs) than neurotypical controls (Demopoulos and Lewine, 2016; Khalfa et al., 2004; Rosenhall et al., 1999; Steigler and Ruhlin, 2014). During LDL testing, a discrete sound stimulus (typically about one second in duration) is repeatedly presented with increasing intensity until the participant verbally or behaviorally indicates that the sound has become uncomfortably loud (Punch et al., 2004). In one of the first studies objectively assessing sound tolerance in autism, Rosenhall et al. (1999) reported that 18 % of autistic children were unable to tolerate an 80 dB nHL broadband click stimulus as part of an auditory brainstem testing protocol (although all could tolerate be tested at 70 dB nHL). Notably, only one autistic child with sound tolerance problems had a sensorineural hearing loss, indicating that loudness recruitment could not account for this phenomenon in the majority of the sample. A smaller but more comprehensive study by Khalfa et al. (2004) confirmed the presence of enhanced loudness perception in autism, reporting that 63 % of their autism group had LDLs for pure tones below 80 dB HL. In a higher-IQ group of autistic children, Demopoulos and Lewine (2016) tested LDLs for speech stimuli, finding that 37 % of their autism group reported LDLs three or more standard deviations below the neurotypical group's mean in at least one ear. Steigler and Ruhlin (2014) also reported the case of an autistic man with profoundly reduced tolerance of low-frequency sounds, confirmed by abnormally low LDLs to tones in the low frequencies and normal LDLs in the high frequencies (≥ 2000 Hz). Two additional studies have used behavioral observations to test sound tolerance in autistic children, finding that only a small minority of individuals exhibited behavioral signs of distress when exposed to high-level sounds (Gomes et al., 2004; Lucker, 2013). However, both of these studies were limited by their reliance solely on observable behavioral reactions; they were unable to rule out the possibility that additional participants experienced the sounds as uncomfortable but failed to communicate that discomfort in a “typical” way (Keating and Cook, 2020; D. J. Moore, 2015). Despite mixed results concerning behavioral loudness tolerance, multiple studies demonstrating reduced LDLs in autism suggest that loudness hyperacusis is prevalent in this population, although other forms of DST (i.e., pain hyperacusis or phonophobia) may also contribute to these abnormalities.

To further assess the role of loudness in autism-associated DST, we also consider the literature on intensity discrimination in this population. In persons with cochlear hearing loss and loudness recruitment (increased loudness growth due to outer hair cell damage), it has been hypothesized that steepened loudness functions translate into superior intensity discrimination ability (Buus et al., 1982; although see Huettel and Collins, 2004; Schroder et al., 1994 for an alternative explanation based on spread of excitation). Thus, based on the steeper loudness functions observed in autism, it would stand to reason that autistic people may also possess superior intensity discrimination ability compared to neurotypical listeners. However, the literature on psychophysical intensity discrimination in autism has not confirmed this hypothesis, with the majority of studies finding intensity discrimination abilities in persons on the autism spectrum to be normal (Alcántara et al., 2012; Bonnel et al., 2010; C. R. G. Jones et al., 2009) or even impaired (Kargas et al., 2015) relative to neurotypical controls. While these data are inconsistent with the theory that abnormal loudness growth in autism leads to enhanced intensity discrimination, it is

notable that none of these studies concomitantly measured loudness functions and intensity discrimination thresholds. It is therefore still possible that the subset of individuals on the autism spectrum with steep loudness growth curves *would* exhibit superior intensity discrimination when compared to typical controls. Further work on loudness and intensity processing in autism is necessary to extend these findings, specifically addressing whether subjective reports of hyperacusis can be linked to psychoacoustic disturbances of loudness perception.

3.2. Misophonia in autism

As misophonia has only recently been recognized as a distinct DST condition, far fewer studies have considered it as a potential explanation for observed behavioral reactions to auditory stimuli in autism (Stiegler and Davis, 2010). Furthermore, no study has specifically been conducted to assess the prevalence of misophonia in autistic individuals. Nevertheless, in the clinical sample of misophonia patients described by Jager et al. (2020), 14 of 575 (3%) were diagnosed with comorbid autism spectrum disorder. Notably, individuals with “primary autism spectrum conditions” referred for misophonia evaluation were excluded from the sample (i.e., misophonia in the aforementioned 14 individuals was judged to be “separate” from autism), indicating that the overlap between these conditions could potentially be substantially larger. Additionally, 38 of 1061 individuals (3.6 %) in a large online sample of adults with self-reported misophonia reported having been diagnosed with autism (Claiborn et al., 2020), a prevalence nearly double that of the general population (Dietz et al., 2020). In another large clinical sample, over one fourth of children referred to a specialist pediatric hyperacusis center (60 % of whom were diagnosed with autism) identified classic misophonia triggers (i.e., “people chewing, breathing, and snoring”) as the specific sounds causing distress (Amir et al., 2018). Lastly, in the survey of DST in autism performed by Law et al. (2016), many parents reported that environmental sounds made their children irritable (61.3 %), frustrated (43.9 %) or annoyed (40.9 %), raising the possibility that some of these episodes may arise from misophonic reactions (Potgieter et al., 2019).

A number of personal accounts also support the contention that autistic individuals with DST may be experiencing misophonia-like symptoms (Cesaroni and Garber, 1991; Grinker, 2007; Landon et al., 2016; A. E. Robertson and Simmons, 2015; Smith and Sharp, 2013). A particularly classic account of an autistic person displaying misophonic reactions comes from anthropologist Roy Grinker, who described his autistic teenage daughter Isabel’s reaction to very specific sounds such as throat-clearing and the sounds of certain words:

...she still hates certain sounds, like a baby crying, the car alarm that tells you your seatbelt isn’t fastened, or the sound of a bathtub draining. When she hears them, she gets agitated, holds her hands over her ears, and vocalizes to block out the sound. She has the same reaction when she hears me clear my throat, or when someone says words associated with bathing, such as “bath,” “shower” or “shampoo.” (Grinker, 2007, p. 299)

Other examples have been published of autistic adults reacting strongly to sounds considered to be common misophonic triggers, “Small noises annoy me, like breathing, crunching food or ... someone whistling ... it makes me ratty” (A. E. Robertson and Simmons, 2015, p. 575) or describing experiences of being emotionally “triggered” by sounds in a way they retrospectively view as excessive:

... there is all this energy racing around inside me out of irritation and thinking about these things... its building up inside and you can’t let it out, you can’t go “ahhhhh be quiet” or whatever and can’t be jumping up and down or doing anything... (Landon et al., 2016, p. 47).

Remarkably, many of these individuals reporting misophonia-like

experiences also seemed to concurrently experience problems tolerating loud noises (Landon et al., 2016), suggesting that a number of autistic individuals with DST may meet criteria for both misophonia and hyperacusis. Overall, these results together provide substantial evidence that at least some cases of DST in autism are likely due to misophonia, although additional research is needed to estimate the prevalence of misophonia, its co-occurrence with other types of DST, and its functional consequences in this population.

3.3. Phonophobia in autism

Comorbid anxiety disorders are exceedingly common in autistic individuals (Hollocks et al., 2019; Lai et al., 2019), presenting as a mixture of “typical” anxiety symptoms and “atypical” fears that are unique to autism (Kerns et al., 2014, 2016; Kerns and Kendall, 2012; B. Y. Lau et al., 2020; Rodgers et al., 2016; Scahill et al., 2019; Wood and Gadow, 2010). Among these autism-specific fears, a number of studies have listed loud noises (either loud noises in general or specific noises such as toilets flushing) as the object of a child’s specific phobia (Gjevik et al., 2011; Kerns et al., 2014, 2016; B. Y. Lau et al., 2020; Leyfer et al., 2006; Mayes et al., 2013; Mukaddes and Fateh, 2010; Ozsivadjian et al., 2012), and multiple autism-specific anxiety questionnaires include items directly assessing a fear of loud noise (Rodgers et al., 2016; Scahill et al., 2019). This particular fear is present in a sizable minority of autistic children, with one large study finding that 23 % had a phobia of loud sounds (e.g., babies crying, hairdryer sounds), and an additional 6% had fears of other specific sounds (B. Y. Lau et al., 2020). In addition, over half of autistic children with DST in the study by Law et al. (2016) were reported to become “scared” (55 %) or “nervous” (54 %) in response to bothersome sounds. No study has investigated the prevalence of phonophobia in adults on the autism spectrum, but qualitative reports indicate that many autistic adults continue to experience anxiety in response to loud noises (Simonoff, 2020), resulting in patterns of avoidance consistent with a specific phobia of these sounds (Bemporad, 1979; Cesaroni and Garber, 1991; Landon et al., 2016; Smith and Sharp, 2013).

Although published studies confirm the presence of phonophobia in many individuals on the autism spectrum, one major unresolved question in this area is whether this phonophobia is secondary to hyperacusis or unrelated to abnormalities in loudness perception. As noted by Jastreboff and Jastreboff (2015), phonophobia is practically inevitable in cases of severe hyperacusis, as anxious apprehension and hypervigilance directed toward everyday sounds can easily develop from repeated exposures to extremely unpleasant/painful stimuli. Kerns et al. (2016) provide a relevant case example, in which an autistic child develops an anticipatory fear of fire alarms as a result of pre-existing hyperacusis. However, these authors argue that the majority of DST-related impairment experienced by this patient is due to hyperacusis, and therefore a diagnosis of specific phobia is not warranted unless a more impairing pattern of avoidance behavior develops. Interestingly, there is some limited evidence that behavioral tolerance of the aversive sound stimulus can be achieved by treating the phobia with graded exposure (Johnston et al., 2020; Koegel et al., 2004). This may indicate a bidirectional relationship between sound-induced discomfort and anxiety, whereby interventions targeting either hyperacusis or phonophobia symptoms have the potential to reduce symptoms in the other domain. As acute stress can decrease LDLs in some individuals (Hasson et al., 2013), reducing phobic anxiety could feasibly improve both the emotional reaction to the feared sound and its perceived loudness. However, as these studies did not include judgments of subjective loudness or pain, any effects of exposure therapy on the perceptual qualities of aversive sounds remain speculative. An alternative possibility is that the participants in these studies did not suffer from hyperacusis at all, and thus treatment of phonophobia was sufficient to eliminate all DST in those individuals. Additional research is necessary to determine whether autistic people with psychoacoustically-confirmed

hyperacusis can experience a reduction in subjective DST from interventions targeting phonophobia or anxiety in general.

4. Potential mechanisms of decreased sound tolerance in autism

While DST in autism is frequently discussed from a clinical perspective, the neurobiological correlates of this symptom cluster remain poorly understood. A wide range of abnormalities in the structure and function of the auditory system have been demonstrated in both autistic individuals and preclinical animal models of autism (Beers et al., 2014; Chin et al., 2013; McCullagh et al., 2020; O'Connor, 2012; Pillion et al., 2018; Williams, Abdelmessih, et al., 2020), but few theoretical models have been constructed to link these findings to behavioral sound intolerance. Instead, current theoretical frameworks for sensory hyper-reactivity in autism tend to focus on multi-modality sensory processing (Mottron et al., 2006; Pellicano and Burr, 2012; C. E. Robertson and Baron-Cohen, 2017; Van de Cruys et al., 2014; Ward, 2019) in an attempt to explain the wide range of sensory differences seen in autistic individuals. Alternatively, a number of theoretical mechanisms of DST have been proposed based on findings in non-autistic individuals (Auerbach, 2019; Auerbach et al., 2014; Brout et al., 2018; Diehl and Schaeffe, 2015; P. J. Jastreboff and Jastreboff, 2014, 2015; Kumar et al., 2017; Palumbo et al., 2018; Pienkowski, 2019; Pienkowski et al., 2014; Sheppard et al., 2020; Suhnan et al., 2017), few of which have been specifically considered in the context of autism-associated DST. Thus, the purpose of this section is to synthesize the literature on these related topics, generating explanatory neurocognitive models to account for the presence of hyperacusis, misophonia, and phonophobia in individuals on the autism spectrum. Although evidence to support our proposed mechanisms of DST in autism is limited at this time, these theoretical models will provide a framework for future research in this area, generating hypotheses about the underlying neurobiology of DST and providing context for findings related to auditory physiology in autism and related conditions.

4.1. Model of hyperacusis: enhanced central gain

Although the underlying biology of hyperacusis is still poorly understood, a growing body of evidence suggests that the symptoms of loudness hyperacusis are generated by a pathological increase in central auditory gain (Auerbach, 2019; Auerbach et al., 2014; Diehl and Schaeffe, 2015; Pienkowski, 2019; Salvi et al., 2020; Sheppard et al., 2020) in which “neural activity from more central auditory structures is paradoxically increased at suprathreshold intensities” (Auerbach et al., 2014, p. 1). In particular, animal models of hyperacusis display steeper neural input-output functions in multiple cortical and subcortical areas, with the largest increases seen in the inferior colliculus (IC) and primary auditory cortex (Auerbach et al., 2019; Y.-C. Chen et al., 2015; Ma et al., 2020; Salvi et al., 2020; Stolzberg et al., 2012; Wong et al., 2020). Although there have been few studies examining sound-evoked neural activity in humans with hyperacusis (J.-H. Hwang et al., 2009), those that have examined hyperacusis in tinnitus patients have typically found increased activity comparable to that seen in these animal models (Gu et al., 2010; Lanting et al., 2008; Melcher et al., 2009). As activity in the primary and secondary auditory cortex is thought to encode loudness rather than intensity (Behler and Uppenkamp, 2016, 2020; Langers et al., 2007; Röhl and Uppenkamp, 2012; Schmidt et al., 2020; Schreiner and Malone, 2015; Uppenkamp and Röhl, 2014), hyperactive responses to sounds in these areas are hypothesized to be the substrate of loudness hyperacusis. While some studies have indicated that this enhanced neural activity may be insufficient to explain hyperacusis-like behavior in animal models (Möhrle et al., 2019; Radziwon et al., 2019), the central gain model remains the most empirically-supported model of hyperacusis pathophysiology proposed to date (Auerbach, 2019; Auerbach et al., 2014; Diehl and Schaeffe, 2015; Pienkowski, 2019; Sheppard et al., 2020).

Given the strong associations between hyperacusis, tinnitus, and noise exposure (Pienkowski et al., 2014; Tyler et al., 2014), the central gain model of hyperacusis typically posits that an increase in central gain is a homeostatic consequence of reduced neural output from the cochlea (i.e., sensorineural hearing loss or potentially “cochlear synaptopathy”; Auerbach et al., 2014; Hickox and Liberman, 2014). However, rates of peripheral hearing loss are not greatly elevated in persons on the autism spectrum (Beers et al., 2014), and the majority of autistic individuals with reduced LDLs have hearing acuity within normal limits (Demopoulos and Lewine, 2016; Dunlop et al., 2016; Khalfa et al., 2004; Rosenhall et al., 1999), indicating that the central gain mechanism that putatively drives hyperacusis in autism may arise via a different mechanism. Though we are only able to speculate about the ways in which aberrant neurodevelopment in autism could contribute to enhanced central auditory gain, multiple plausible mechanisms exist based on current understandings of autism neuropathology (Fig. 1).

One likely source of enhanced central gain in autism is auditory brainstem dysfunction, which has been observed in both idiopathic autism and several neurodevelopmental syndromes that frequently cause autism, such as fragile X syndrome (McCullagh et al., 2020; Pillion et al., 2018). Postmortem human and rodent studies have documented a number of abnormalities in auditory brainstem nuclei, with multiple studies converging on pathology in the superior olivary complex (Eto et al., 2017; Kulesza et al., 2011; Kulesza and Mangunay, 2008; Li et al., 2003; Lukose et al., 2011, 2015; Mansour et al., 2019; Mansour and Kulesza, 2020; McCullagh et al., 2020; Rodier et al., 1997; Rotschafer et al., 2015; Rotschafer and Cramer, 2017; Toyoshima et al., 2009; Zimmerman et al., 2018, 2020), a group of nuclei that mediates aspects of binaural processing and the efferent auditory pathways (Guinan, 2006, 2018; Laumen et al., 2016). Though data are mixed regarding the presence and nature of functional auditory brainstem abnormalities in autism (Bennetto et al., 2017; Dabbous, 2012; Danesh and Kaf, 2012; ElMoazen et al., 2020; Gravel et al., 2006; Kaf and Danesh, 2013; B. K. Lau et al., 2018; Lukose et al., 2013; McCullagh et al., 2020; Mercati et al., 2017; Miron et al., 2018, 2020; Ohmura et al., 2019; Pillion et al., 2018; Santos et al., 2017; Talge et al., 2018; Tharpe et al., 2006; Wilson et al., 2017), preliminary studies have indicated that certain auditory brainstem assays may differentiate autistic individuals with and without concurrent hyperacusis (Mercati et al., 2017; Ohmura et al., 2019; Wilson et al., 2017). In cases where such brainstem dysmorphology does exist, data from animal models suggests that fewer inhibitory axons project from various areas of the auditory brainstem to the IC (Li et al., 2003; Zimmerman et al., 2020). As the central gain model typically posits increased spontaneous and sound-evoked activity in the IC and higher auditory regions (Auerbach et al., 2014), a plausible model of central gain in autism would likely include similar enhancements of activity in these areas, brought on by homeostatic adaptations to aberrant brainstem information transfer. We therefore propose a model wherein structural abnormalities in the auditory brainstem during early neurodevelopment lead to compensatory changes in the IC and auditory cortex in autism, which result in an overall increase in central auditory gain and hyperacusis symptoms (Fig. 1B). As the percept of subjective loudness (rather than sound intensity) is not seemingly represented until auditory cortex (Behler and Uppenkamp, 2016; Langers et al., 2007; Röhl and Uppenkamp, 2012; Schreiner and Malone, 2015; Uppenkamp and Röhl, 2014), increased central gain occurring only in cortical structures may also reasonably explain the phenomenon of hyperacusis in autism. Further research using both animal models and human neuroimaging is thus necessary to validate this model, investigating the presence of increased central auditory gain in autism at either the cortical or subcortical level.

An alternative explanation for increased central auditory gain in autism is the presence of an imbalance in the ratio of excitatory and inhibitory neurotransmission (E/I ratio) in key subcortical and cortical auditory structures (McCullagh et al., 2020), leading to an overall increase in activity of the IC, thalamus, and/or auditory cortex (Fig. 1C).

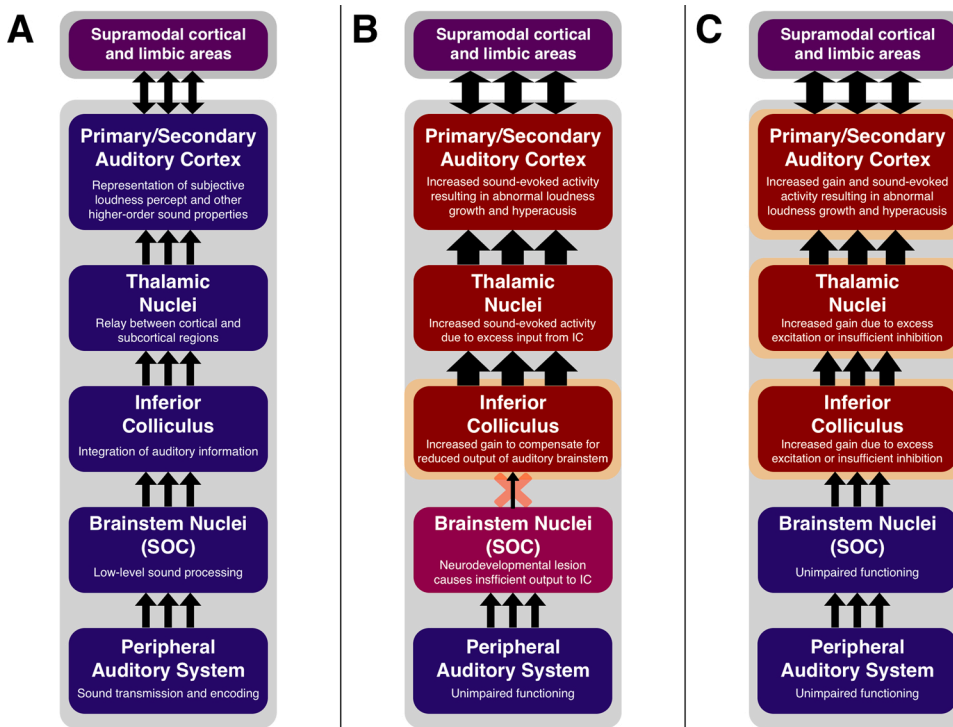


Fig. 1. (A) Schematic of ascending information pathway in the central auditory system. Descending and recurrent connections have been omitted for simplicity. (B) Hypothesized model of enhanced central gain and hyperacusis in autism resulting from impaired brainstem transmission. Homeostatic upregulation of gain in the inferior colliculus (IC) results in excessive sound-evoked activity in the higher structures of the auditory system, including primary/secondary auditory cortex, the putative source of enhanced loudness perception. (C) Alternate model of enhanced central gain and hyperacusis in autism as a result of excitation/inhibition imbalance in the IC, thalamus, and/or auditory cortex. Notably, enhanced auditory cortical activity is likely sufficient to cause hyperacusis, and while other central auditory structures may contribute, pathology could feasibly be limited to cortical areas. SOC = Superior Olivary Complex.

Such an increase in E/I ratio is not inconsistent with the previous hypothesis of brainstem dysfunction, as an imbalanced E/I ratio could feasibly serve as the circuit-level substrate of decreased brainstem information transfer or the homeostatic activity up-regulation seen in the IC and/or auditory cortex (McCullagh et al., 2020; Zimmerman et al., 2020). Furthermore, it is quite likely that an increased E/I ratio is responsible for increases in central gain seen in models of hyperacusis elicited by salicylates (G.-D. Chen et al., 2013; Gong et al., 2008; Lu et al., 2011; W. Sun et al., 2009) or acoustic trauma (Heeringa and van Dijk, 2016; Ma et al., 2020; Salvi et al., 2000; Scholl and Wehr, 2008; Wei Sun et al., 2012).

A model of increased E/I ratio has long been posited as a common final pathway to explain the core features of autism (Culotta and Penzes, 2020; Foss-Feig et al., 2017; Lee et al., 2017; Nelson and Valakh, 2015; Rubenstein and Merzenich, 2003; Sohal and Rubenstein, 2019) as well as some associated conditions such as epilepsy (Bozzi et al., 2018). Although some recent data have suggested that this imbalance is an epiphenomenon of autism rather than its underlying cause (Antoine et al., 2019), this distinction is irrelevant when determining whether E/I imbalance is responsible for hyperacusis and enhanced central gain in some autistic individuals. The E/I imbalance model was further elaborated by Ward (2019) as a potential explanation for the wide range of sensory features seen in autism. In this framework, an increased E/I ratio results in both an increased signal level but also increased noise within a neural circuit's computations. Thus, a given sensory stimulus will elicit a stronger neural response, activating larger areas of cortex and corresponding to a more intense (and in the case of hyperacusis, louder) percept. Although evidence for this model of sensory hyperreactivity is mixed (Dickinson et al., 2016; Ward, 2019), there are no studies specifically investigating the relationship of loudness hyperacusis and E/I imbalance in humans. A single study (Naples et al., 2020) has examined the relationship between self-reported "auditory sensitivity" (as measured by the Glasgow Sensory Questionnaire; A. E. Robertson and Simmons, 2013) and E/I imbalance (as measured by the Hurst exponent of the resting EEG power spectrum) in a sample of adults with and without diagnoses of autism or schizophrenia, finding a moderate correlation between the two metrics. In addition, comorbid epilepsy is

associated with DST in autistic children (Law et al., 2016), implicating E/I imbalance as a potential cause of both co-occurring conditions. Furthermore, both rodent and human studies suggest that the phenotype of DST and increased auditory cortical activity seen in fragile X syndrome (Ethridge et al., 2016; McCullagh et al., 2020; Rotschafer and Razak, 2013) can be attributed to an E/I imbalance in auditory cortex (Ethridge et al., 2017; Lovelace et al., 2020; Wen et al., 2018). Given the plausibility of E/I imbalance as a mechanism for central auditory gain and hyperacusis in autism, future studies on this topic should incorporate human neuroimaging metrics of E/I balance (Bruining et al., 2020; Dickinson et al., 2016; Trakoshis et al., 2020), testing whether psychoacoustically-defined loudness growth is associated with an excess of excitatory neurotransmission.

4.2. Model of Misophonia: conditioned allocation of excess salience

In contrast to hyperacusis, there has been relatively little research seeking to understand the pathological basis of misophonia in non-autistic individuals. Based on neurophysiologic models of tinnitus and hyperacusis, Jastreboff and Jastreboff (2014, 2015) proposed a model of misophonia/phonophobia (considered to be the same construct in their framework) in which the processing of low-level auditory information is intact, but "the functional connections between the auditory and the limbic and autonomic nervous systems are enhanced for specific patterns of sound," (P. J. Jastreboff and Jastreboff, 2014, p. 111). This model suggests that the aversive responses to sounds seen in misophonia are developed and maintained, at least in part, by associative learning mechanisms, and thus that the brain areas most likely implicated in misophonia are those involved in emotion, memory, and learning (Brou et al., 2018). So far, a small number of studies have begun to validate parts of this model. For instance, it is now fairly well established that individuals with misophonia have normal hearing acuity (Jager et al., 2020) and that exposure to misophonic triggers induces a degree of autonomic arousal greater than that seen in healthy controls (Edelstein et al., 2013; Kumar et al., 2017; Schröder et al., 2019). Furthermore, preliminary neuroimaging studies of misophonia indicate that misophonic triggers elicit intense emotional responses that are coupled with

hyperactivation of anterior insular cortex (Kumar et al., 2017; Schröder et al., 2019), a key node of the brain's salience network (Menon and Uddin, 2010; Uddin, 2015). One of these studies also investigated functional connectivity of the anterior insula during the presentation of misophonic trigger sounds (Kumar et al., 2017), finding an increase in connectivity between the insula and ventromedial prefrontal cortex, posteromedial cortex, hippocampus and amygdala, limbic regions involved in emotional processing and regulation. Thus, while misophonic reactions are likely mediated in part by the limbic system, the primary process at work may instead be the attribution of excessive salience to specific sounds.

The attribution of salience to specific auditory stimuli is an important neurocognitive process that allows individuals to efficiently focus attention on important environmental signals (e.g., a fire alarm or police siren) and to enact a timely behavioral response (Huang and Elhilali, 2017; Kaya and Elhilali, 2017). Of particular note, the human auditory system has been evolutionarily primed to detect and respond to the cries of our young (Arnal et al., 2015; Soltis, 2004), and thus, the acoustic properties of an infant's cry cause this sound to be exceptionally salient. Using acoustic analysis, psychophysical experiments, and neuroimaging, Arnal et al. (2015) demonstrated that a wide range of natural and artificial alarm signals (including human screams, air horns, and sports arena buzzers) all contain amplitude modulations in the 30–150 Hz range, which correlate with the psychoacoustic attribute of roughness (see also Trevor et al., 2020). The roughness of a sound is highly predictive of its salience and subjective aversiveness (Arnal et al., 2015, 2019; Zhao et al., 2019), and individuals can localize rough stimuli both more quickly and more accurately than other sounds (Arnal et al., 2015). Notably, the perception of rough sounds is associated with unique patterns of brain activity, including the synchronization of large-scale salience-related networks that include superior temporal regions, subcortical and cortical limbic areas, frontal areas (e.g., inferior frontal gyrus, orbitofrontal cortex), and insular cortex (Arnal et al., 2019). As preliminary neuroimaging studies implicate many of these areas in the pathophysiology of misophonia (Kumar et al., 2017; Schröder et al., 2019), we hypothesize that misophonia is characterized by dysfunctional hyperactivation of this specialized “auditory salience detection” network, causing individuals with misophonia to categorize a number of everyday sounds as disproportionately salient and aversive.

In addition to neuroimaging studies, several other factors suggest that an inappropriate attribution of salience to auditory stimuli could lie at the heart of misophonia. Subjectively, patients with misophonia routinely describe an intense hyper-focus on their various trigger stimuli (da Silva and Sanchez, 2019; Edelstein et al., 2013; Osuagwu et al., 2020; Schröder et al., 2017), which may serve to further amplify the already intense emotional reactions elicited by those stimuli. Moreover, in the first published study to systematically evaluate cognitive behavioral therapy in misophonia, Schröder et al. (2017) targeted hyper-focus on trigger sounds as a core symptom of misophonia in addition to the patients' negative emotional reactions (see also Aazh et al., 2019). The potential interactions between hyper-focus on triggers, intense emotional experiences, and autonomic arousal can be further explained by the large degree of functional overlap between neural circuits responsible for sympathetic arousal, emotion, and salience detection (Beissner et al., 2013). As the salience of an auditory stimulus is highly associated with its perceived emotional intensity (Anikin, 2020), it is quite possible that the intense negative emotional reactions seen in misophonia could be coupled with an over-activation of salience neurocircuitry, along with associated projections to limbic areas. Moreover, as auditory salience attribution is remarkably context dependent (Huang and Elhilali, 2017), a salience mechanism helps account for the variable reactions that individuals with misophonia can have to the same stimulus across different situations. Furthermore, the inability of self-produced sounds to trigger a misophonic reaction can potentially be explained by the reduced salience attributed to self-generated stimuli, a phenomenon known as self-suppression (Hughes et al., 2013; Whitford,

2019). Like other authors, we contend that the idiosyncratic nature of misophonic triggers is the result of each individual's unique learning history; however, as some sounds have been reported to trigger the vast majority of individuals with misophonia (e.g., chewing, nasal/breathing sounds; Jager et al., 2020), we also believe that some acoustic property of these sounds preferentially activates the aforementioned salience attribution neurocircuitry in persons with misophonia, increasing the likelihood that a given individual will find them aversive.

With regard to the neural underpinnings of misophonia, we have no *a priori* reason to expect that the pathophysiology of this condition would differ in autistic and non-autistic individuals. Moreover, the insula and salience network have been heavily implicated in the pathology of autism (Nomi et al., 2019; Uddin, 2015), and changes in insular structure/function may contribute to a higher rate of misophonia in individuals on the autism spectrum. This hypothesis is further supported by neuroimaging studies in autistic children that indicate that nonspecific (auditory-tactile) sensory hyperreactivity is related to increased resting-state connectivity between the salience network and amygdala (Green et al., 2016; Green and Wood, 2019). This finding also raises the question of whether the intolerance of stimuli in other modalities seen in autism could similarly be attributed to the mechanism of excessive salience attribution. Additional research is necessary to understand the manner in which the salience network contributes to sensory processing abnormalities in autism, particularly in the context of comorbid misophonia.

4.3. Model of phonophobia: pathological fear learning and extinction

As a form of specific phobia, the neurobiological underpinnings of phonophobia are far more established than those of either hyperacusis or misophonia. A large body of research has been published on the neural correlates of fear conditioning and anxiety disorders (Chavanne and Robinson, 2020; Garcia, 2017; Herry and Johansen, 2014; Ipser et al., 2013; LeDoux et al., 2017; Tovote et al., 2015), as well as the ways in which auditory stimuli acquire affective valence (Frühholz et al., 2016). While a comprehensive overview of both topics is beyond the scope of this review, we seek to integrate these two lines of research into a neurocognitive model of phonophobia, which can be applied to autistic as well as non-autistic individuals.

The predominant neurocircuitry involved in fear and fear conditioning centers on connections within and between nuclei of the amygdala, hippocampus, and multiple areas of medial prefrontal cortex, including anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC; Chavanne and Robinson, 2020; Fullana et al., 2020; Tovote et al., 2015). The amygdala is essential for the acquisition, storage, and expression of learned fear associations, serving as a major hub in a number of fear- and anxiety-related neural circuits (LeDoux, 2000). Additionally, the amygdala is highly connected to auditory areas of the thalamus and cortex (Frühholz et al., 2016; Frühholz and Staib, 2017; LeDoux et al., 1991), and during sound processing, the amygdala is implicated in both the modulation of auditory cortical activity (Aizenberg et al., 2019) and encoding multiple features of the sound stimulus, including its perceived aversiveness (Kumar et al., 2012; Viinikainen et al., 2012). This hippocampus is primarily involved in the learning, storage, and retrieval of fear memories, as well as inhibiting the retrieval of these memories in specific contexts. The ACC, which plays a role in assessing the salience of a stimulus and regulating emotional responsiveness, has been associated with the expression of conditioned fear responses (Ipser et al., 2013). Via connections with the anterior insula, the ACC also makes up part of a “central autonomic–interoceptive network,” which is responsible for integrating representations of one's cognitive, affective, and physical state to facilitate homeostatic autonomic and behavioral responses (Fullana et al., 2016). The vmPFC plays a role in the inhibition of threat expression by downregulating amygdala activity (Fullana et al., 2020), and this region is also implicated in the generation, storage, and retrieval of “safety”

signals (i.e., extinction memories; Fullana et al., 2016; Milad and Quirk, 2012). Working in concert, this fear conditioning network serves to evaluate the content of a stimulus within the current context, triggering downstream signals of “danger” or “safety” and priming the individual to enact an appropriate behavioral response.

Although appropriate fear learning is key to survival, dysfunctional fear neurocircuitry can lead to phobias, in which the fear experienced by an individual is disproportionate to any potential danger. Neuroimaging studies have indicated that specific phobia is associated with hyperactivation of the amygdala and insular cortex when exposed to a phobic stimulus (Ipser et al., 2013), seemingly indicating that the salience and subjective aversiveness of the stimulus are both exaggerated in this condition. As a fear of loud noises is common during development (Meltzer et al., 2009; Ollendick et al., 2002), phonophobia is considered a nonexperiential or nonassociative phobia (i.e., a phobia not developed through direct experience with the phobic object; Garcia, 2017; Poulton and Menzies, 2002). While for the majority of children, the fear of loud noises is transient, there exists a small group of individuals in whom these fears intensify over time rather than resolving, potentially due to a genetic vulnerability (Muris et al., 2002). According to a recent model proposed by Garcia (2017), nonexperiential phobias are generated and maintained by both a sensitization of the fear response and a deficit in fear extinction learning, resulting in overly exaggerated initial fear responses and a persistence of the irrational fear despite nontraumatic exposure to the feared stimulus. This sensitized fear response is likely due to hyperactive amygdala responses to loud noises, which could result from baseline differences in the extent of sound-evoked auditory cortical activity, amygdala E/I balance, or auditory-limbic connectivity. Individuals with hyperacusis in particular may find specific sounds extremely painful or aversive, leading to a similar avoidant phenotype seen in chronic pain patients with high levels of pain anxiety (Greenberg and Burns, 2003). In addition to this sensitized fear response, individuals with specific phobias display persistent amygdala activity to repeated stimulation that does not habituate effectively (Garcia, 2017). An inability to habituate to repeated exposures likely indicates an underlying deficit in the ability to encode the “safety” signal necessary to extinguish a learned fear response. Thus, abnormalities in neurocircuitry involved in fear extinction, including the vmPFC and hippocampus (Fullana et al., 2016), likely play a role in the pathological persistence of phobic responses. Additionally, the extinction process may be hindered in patients with hyperacusis, whose adverse reactions to loud and/or painful sounds may serve to reinforce their maladaptive responses to phobic stimuli.

Although this model of phonophobia is equally applicable to autistic and non-autistic individuals, neuroimaging studies of autism provide further evidence of its utility in this population. Autistic children and adolescents display elevated amygdala activity in response to mildly aversive auditory stimuli (Green et al., 2013, 2015), with stronger amygdala activation predicting higher levels of parent-reported sensory hyperreactivity (Green et al., 2013, 2015). In addition, autistic individuals with high levels of sensory hyperreactivity demonstrate reduced amygdala habituation over repeated presentations of auditory and tactile stimuli (Green et al., 2015, 2019), which is thought to result from altered functional connectivity of the amygdala with prefrontal regions (Green et al., 2015, 2019). These findings provide preliminary evidence that the pattern of neural activity elicited by sensory stimuli in autistic individuals may be altered in such a way as to predispose these individuals to developing specific phobias, including phonophobia. This hypothesis is further supported by clinical studies demonstrating correlations between self/parent reports of sensory hyperreactivity and anxiety symptoms in autistic children and adults (Glod et al., 2015; Y. I. J. Hwang et al., 2020; Neil et al., 2016, 2017; Pickard et al., 2020; Syu and Lin, 2018; Wigham et al., 2015), with particularly strong relationships between sensory hyperreactivity and symptoms of specific phobia (Bitsika et al., 2016; Black et al., 2017; MacLennan et al., 2020). Longitudinal studies further indicate that increased sensory hyperreactivity

early in development is predictive of later anxiety symptoms, both in autistic children and the general population (Carpenter et al., 2019; Green et al., 2012). This body of research generally supports the theory that hyperreactivity to sensory stimuli in autism may contribute to the high rates of anxiety disorders seen in this population (Green and Ben-Sasson, 2010; Kerns et al., 2016; McVey, 2019; Muskett et al., 2019; South and Rodgers, 2017). However, as sensory reactivity to date has primarily been measured using parent reports of a child’s observable behaviors, it remains possible that many aversive responses to sensory stimuli are actually the manifestations of specific phobia (Koegel et al., 2004). Additional research relating observed sound intolerance behaviors, psychoacoustic loudness growth, and phonophobia symptoms is thus necessary to clarify the relative contributions of hyperacusis and phonophobia to the observable phenotype of DST in autism.

5. Conclusion and future directions

Based on our review of the literature on DST in autism, it is likely that autistic individuals with DST present with a wide range of subjective complaints, including hyperacusis, misophonia, and phonophobia. Evidence from personal accounts, behavioral studies, and psychophysical tests all tend to support the notion that autistic people frequently perceive everyday sounds as unbearably loud or painful, suggesting that a substantial portion of DST behaviors can be explained by the presence of hyperacusis. In addition, many autistic children and adults exhibit clinically significant anxiety directed towards specific sounds (i.e., phonophobia), which may arise on its own or secondary to hyperacusis. However, the interplay between hyperacusis and phonophobia has not been studied in autism, and it remains unclear whether these conditions are comorbid in the majority of cases. Lastly, while much less research has examined the overlap of misophonia and autism, there is moderate evidence to suggest that a minority of autistic individuals with DST complaints likely meet diagnostic criteria for misophonia, regardless of whether hyperacusis is present.

In addition to describing the phenomenology of DST in autism, we propose neurocognitive models to explain each subtype of DST and its occurrence in people on the autism spectrum. Although hyperacusis in non-autistic individuals is typically associated with cochlear damage, we instead hypothesize that an alteration in the subcortical processing of auditory information leads to enhanced central auditory gain, resulting in the same sound-evoked auditory cortex hyperactivity seen in patients with tinnitus and hyperacusis. As opposed to our autism-specific model of hyperacusis, we believe that the neurocognitive processes leading to misophonia and phonophobia are the same regardless of the presence of autism, although certain neurobiological alterations seen in autism may predispose autistic individuals to these conditions. We propose that misophonia is a disorder of excessive salience attribution, in which neural machinery to detect evolutionarily important stimuli is abnormally sensitive to the acoustic properties of certain repetitive sounds, causing widespread neuronal synchronization that results in a disproportionate emotional and autonomic response. This misophonic reaction becomes associated with the “trigger” stimulus through associative learning mechanisms, potentially generalizing to other stimuli over time. Similarly, we hypothesize that phonophobia results from pathological fear learning, including an abnormally strong initial fear response to aversive sound stimuli and a failure to extinguish this response in the presence of non-threatening stimuli. Our model further suggests that hyperacusis strongly predisposes an individual to phonophobia, as aversive reactions to loud or painful sounds sensitize the amygdala to these stimuli, reinforcing and maintaining the fear response in the presence of repeated sound exposures. Though we find preliminary support for these explanatory models in the autism literature, additional behavioral, psychophysical, and neuroimaging research is necessary to validate model predictions and further refine the proposed DST constructs. By developing this theoretical framework, we hope to set the stage for future research on DST in autism, encouraging the field

to move beyond descriptive science and into a new era of hypothesis-driven investigations and mechanism-based therapeutic development.

Although this work represents a major step forward in conceptualizing DST in autism, substantially more research in this area is necessary to improve our theoretical understanding of this construct and its mechanistic underpinnings. The body of literature describing DST in autism is limited by variable and inconsistent terminology and a tendency to group hyperacusis, misophonia, and phonophobia symptoms together into the construct of “auditory over-responsiveness.” Moreover, no study simultaneously assesses multiple types of DST in individuals on the autism spectrum, making it difficult to determine the relative contributions of hyperacusis, misophonia, and phonophobia to DST in this population. Perhaps most importantly, the most widely used measures of sensory responsiveness in autistic children and adults (DuBois et al., 2017; Jorquera-Cabrera et al., 2017; Williams et al., 2018) do not effectively differentiate between DST subtypes, substantially limiting the inferences that can be made about DST using these tools. Important future directions in this area of research include (a) the abandonment of “auditory over-responsiveness” and generalized sensory hyperreactivity as unitary constructs, (b) the establishment of a common nomenclature for DST conditions across disciplines, (c) the development and validation of novel DST questionnaires with adequate content coverage of hyperacusis, misophonia, and phonophobia, (d) the simultaneous assessment of all DST subtypes and their developmental trajectories in autistic individuals, (e) the investigation of DST in relation to other sensory features of autism, such as hyporeactivity and sensory seeking, (f) the comparison of psychoacoustic and neurophysiologic indices of auditory processing between groups of individuals with each form of DST, and (g) the evaluation of candidate interventions specifically targeting individual DST subtypes in controlled clinical trials. By partitioning DST into the distinct conditions of hyperacusis, misophonia, and phonophobia, we can reduce the heterogeneity inherent in autism and potentially derive subgroups of autistic individuals who differ in neuropathology, clinical course, or response to treatment (Feczko et al., 2019; Harris, 2019; Uljarević et al., 2017).

Declaration of Competing Interest

ZJW has received consulting fees from Roche. He is also a member of the Family Advisory Committee of the Autism Speaks Autism Treatment Network site at Vanderbilt University and the Autistic Researcher Review Board of the Autism Intervention Research Network on Physical Health (AIR-P). The remaining authors declare no competing interests, financial or otherwise.

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