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Cardiac Autonomic Regulation in Autism and Fragile X Syndrome: A Review

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Abstract

Despite the significance of efforts to understand the biological basis of autism, progress in this area has been hindered, in part, by the considerable heterogeneity in the disorder. Fragile X syndrome (FXS), a monogenic condition associated with high risk for autism, may pave the way for the dissection of biological heterogeneity within idiopathic autism. This paper adopts a cross-syndrome biomarker approach to evaluate potentially overlapping profiles of cardiac arousal dysregulation (and broader autonomic dysfunction) in autism and FXS. Approaches such as this, aimed at delineating shared mechanisms across genetic syndromes, hold great potential for improving diagnostic precision, promoting earlier identification, and uncovering key systems that can be targeted in pharmaceutical/behavioral interventions. Biomarker approaches may be vital to deconstructing complex psychiatric disorders, and are currently promoted as such by major research initiatives such as the NIMH Research Domain Criteria (RDoC). Evidence reviewed here supports physiological dysregulation in a subset of individuals with autism, as evidenced by patterns of hyperarousal and dampened parasympathetic vagal tone, which overlap with the well-documented physiological profile of FXS. Moreover, there is growing support for a link between aberrant cardiac activity and core deficits associated with autism, such as communication and social impairment. The delineation of physiological mechanisms common to autism and FXS could lend insight into relationships between genetic etiology and behavioral endstates, highlighting *FMR1* as a potential candidate gene. Research gaps and potential pitfalls are discussed to inform timely, well-controlled biomarker research that will ultimately promote better diagnosis and treatment of autism and associated conditions.

Keywords

autism; fragile X syndrome; vagal tone; heart rate; cardiac activity; autonomic nervous system; physiological arousal; hyperarousal; *FMR1*; FMRP; biomarker; endophenotype

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In recent years, autism spectrum disorder has emerged as a major public health concern. Autism is a serious, lifelong condition that affects an astounding 1 in 68 children in the United States (1 in 42 boys and 1 in 189 girls; Autism Developmental Disabilities Monitoring Network, 2014). The disorder is defined by deficits in social interaction/communication and the presence of stereotyped and repetitive behaviors and interests (American Psychiatric Association, 2013). Impairments persist throughout life, with only a minority of individuals with autism finding work or living independently as adults (Howlin, Goode, Hutton, & Rutter, 2004). This highly prevalent disorder comes with substantial economic consequences; the societal burden of each individual with autism is estimated at 3.2 million dollars (Ganz, 2007). These serious economic and public health consequences underscore the significance of efforts to understand the biological basis of autism; yet, despite major initiatives promoting biomarker approaches for improving the identification and treatment for neuropsychological disorders (i.e., the National Institute of Mental Health's Research Domain Criteria [RDoC]; Insel, 2014), reliable and valid biomarkers for autism have not been identified. This line of research is crucial, as deconstructing clinical groups at the biological level may lead to new diagnostic methods that can be implemented earlier in development, and with increased accuracy and precision. Detection of autism at an earlier age is critical to timely enrollment in early intervention, which has been proven to enhance developmental outcomes for individuals with autism (Lord & McGee, 2001). Thus, early and valid diagnosis not only has potential to improve lives at the level of the individual and family, but may also ease the broader societal and economic burden of autism. Despite improvements seen with early intervention, treatment efforts have been hindered by the fact that no single approach has been proven effective for all individuals with autism (Reichow, 2012). It is currently unclear what individual factors predict "what works for whom and why", and efforts to identify behavioral predictors of treatment response have generally been unfruitful (Vivanti, Prior, Williams, & Dissanayake, 2014). Biomarker approaches present a fresh opportunity to parse out the heterogeneity in autism to identify biologically meaningful subtypes, thus facilitating the implementation of treatments that are uniquely targeted and potentially more effective. Such an approach could also prove useful to discovering new, targeted pharmaceutical interventions and promoting the clinical translation of these drug targets by identifying markers that may more sensitively index treatment response. Cross-syndrome research focused on delineating shared or divergent mechanisms across genetic conditions has promise to unveil biological and genetic subtypes of autism, ultimately improving the diagnosis, treatment, and characterization of autism and related conditions.

Physiological dysregulation has been put forth in causal models of autism (Belmonte & Yurgelun-Todd, 2003; Dalton, Nacewicz, Alexander, & Davidson, 2005; Hutt, Hutt, Lee, & Ounsted, 1964; Marshall & Fox, 2006; Porges, 2004), although this line of research, and attempts to understand the biological basis of such deficits more generally, have been hindered by the significant heterogeneity in the disorder (Jeste & Geschwind, 2014). Fragile X syndrome (FXS), a well-defined monogenic disorder that has substantial phenotypic overlap with autism, serves as a promising gateway for delineating biological mechanisms across etiologic subgroups of autism. Given that FXS is a single-gene disorder (caused by a mutation on the *Fragile X Mental Retardation-1* gene, located on the long arm of the X chromosome), studies of biomarkers for social and related behavioral impairments in this

condition can provide insights into gene-behavior relationships relevant to understanding the roots of complex human traits. Such knowledge would provide insight into mechanisms underlying the continuum of social behaviors seen in typical and atypical development, aiding efforts to ameliorate symptoms of disorders involving social impairment, such as autism and FXS.

The present review article examines theoretical and empirical evidence for a role of autonomic dysfunction in impairments associated with autism and FXS. First, a brief overview of the normal functions of the autonomic nervous system is presented, leading into a detailed review of cardiac indices of heart rate and vagal tone as sensitive peripheral markers of autonomic nervous system functioning in autism and FXS. Group comparisons with controls are presented to establish areas of physiological divergence, followed by review of within-group behavioral correlates. Additionally, we provide a critical evaluation of cardiac autonomic activity in disorders of distinct genetic etiologies that are joined together through common risk for autism (Williams syndrome, Down syndrome, Rett syndrome, and Prader-Willi syndrome). Defining and distinguishing intermediate phenotypes that may lead to shared behavior across genetic disorders can help clarify complex links between genetic etiology and behavioral endstates. Here we discuss cardiac autonomic activity in other neurogenetic disorders associated with autism, both to characterize physiological underpinnings that may be specific to autism and/or FXS, as well as to capture those that may potentially generalize to other syndromes associated with autism. Finally, a summary of findings and evaluation of the literature are presented, with a discussion of implications for future research and clinical practice.

Overview of the Autonomic Nervous System and Its Functions

The primary function of the autonomic nervous system is to maintain homeostasis (i.e., allow the body to preserve a controlled, functional physiological condition while adapting to continuous change; Cannon, 1929). Homeostasis is maintained through the combined interchange of the sympathetic and parasympathetic subsystems of the autonomic system. These subsystems work in a complementary manner in order to attend to external demands while supporting the needs of many internal organs and bodily systems. The sympathetic nervous system is responsible for activating the arousal response that prepares the body for action by increasing metabolic output, including broad activation of the cardiovascular system and the endocrine glands, and physiological responses such as pupil dilation and increased heart rate (Lacey, 1967; Porges, 1992). This autonomic defense mechanism, often referred to as the “fight or flight” response, is an adaptive strategy that allows the body to maximize physical reserves to defend against danger (Porges, 1995a; Thayer & Sternberg, 2006). In contrast, the parasympathetic system is associated with growth and restoration; when not challenged, its primary role is to optimize the function of the internal organs and bodily systems for which it is responsible, which includes the stomach, lungs, and heart (Porges, 1992). The parasympathetic system works in a manner that is often antagonistic with the sympathetic system, acting as a restraint (or “brake”) to counteract sympathetic activity. When the body is at rest, the parasympathetic system promotes a calm physiological state that supports internal needs, such as slowing heart rate to conserve energy (Porges, 1992). Alternatively, when the body is challenged, the parasympathetic

system responds by releasing the brake to allow for reciprocal increases in sympathetic tone and accompanying physiological excitation.

The dynamic balance between the parasympathetic and sympathetic subsystems promotes adaptability and health. When this delicate balance goes awry, with either the sympathetic or parasympathetic subsystem governing the other, the body becomes vulnerable to pathology (Thayer & Lane, 2007). Autonomic dysfunction is implicated in a range of psychological disorders, such as panic disorder (Yeragani et al., 1993), anxiety (Friedman, 2007), schizophrenia (Valkonen-Korhonen et al., 2003), anorexia (Mazurak, Enck, Muth, Teufel, & Zipfel, 2011), post-traumatic stress disorder (Sahar, Shalev, & Porges, 2001), social phobia (Schmitz, Kramer, Tuschen-Caddier, Heinrichs, & Blechert, 2011), and attention-deficit/hyperactivity disorder (Rash & Aguirre-Camacho, 2012). It also plays an important role in the development of social behaviors such as affective expressiveness, empathy, attachment, and social approach (see Beauchaine, 2001). Because of its role in social development and broad association with pathology, dysfunction of the autonomic system can serve as an index of stress vulnerability and is hypothesized to play a role in autism (Marshall & Fox, 2006; Porges, 2004).

Autism and Fragile X Syndrome

Although the etiology of autism is not fully understood, evidence clearly indicates a genetic component; twin studies support heritability at 70–80%, and multiple genes have now been identified as conferring risk to autism (Ronald & Hoekstra, 2014). Additional support for genetic involvement comes from family studies of autism showing elevated sibling and half-sibling recurrence rates (Constantino et al., 2012; Ozonoff et al., 2011) and a milder phenotype among unaffected family members, believed to reflect underlying genetic liability (Losh, Childress, Lam, & Piven, 2008; Piven et al., 1994). Despite such strong evidence for genetic influence, there currently exist no reliable biological markers for autism and diagnosis remains based on the aggregation of behavioral symptoms in the domains of social/communication competence and stereotyped behaviors (American Psychiatric Association, 2013). Some of the earliest mechanistic theories of autism focused on physiological dysregulation and subsequent suboptimal processing of environmental input as causes of atypical behavior (Hutt et al., 1964; Kootz & Cohen, 1981; Rimland, 1964), and these theories are still considered in contemporary research (Helt et al., 2008; Lord & McGee, 2001; Rogers & Ozonoff, 2005). Hutt et al. (1964) was the first to propose this theory, contending that autism is characterized by abnormally elevated physiological arousal that prevents habituation to environmental stimuli and eventually leads to avoidance of novel situations. Others have put forth that individuals with autism are underaroused, causing hyporesponsiveness to environmental input (Schoen et al., 2008). Arousal hypotheses provide a physiological explanation to account for atypical attention, processing, and interaction with the external environment that is characteristic of autism. Importantly, arousal dysregulation has a clear theoretical tie with social impairment, which is hypothesized by some to constitute the primary domain of impairment in autism (Charman et al., 2005; Chevallier, Troiani, Brodkin, & Schultz, 2012; Dawson & Bernier, 2007; Pelphrey, Shultz, Hudac, & Vander Wyk, 2011). Reduced and inefficient engagement with environmental input, including social stimuli, would prevent optimal processing of social

information (such as the ability to process language or recognize familiar faces) and broadly hinder social learning over time.

Approximately 2–8% of autism cases can be traced to FXS, which is the most common known monogenic condition associated with autism and the most common inherited form of intellectual disability (Cohen, Pichard, & Tordjman, 2005). FXS affects approximately 1 in 2,500 individuals (Fernandez-Carvajal et al., 2009; Hagerman, 2008). The disorder is caused by a mutation in the *Fragile X Mental Retardation-1* (*FMR1*) gene that halts the production of Fragile X Mental Retardation Protein (FMRP), a protein that plays a critical role in brain development and functioning (Loesch, Huggins, & Hagerman, 2004; Tassone et al., 1999). The neurobehavioral profile of FXS includes intellectual disability, communication difficulties, hyperactivity, social deficits, and impairments in executive functions such as attention and impulse control (Schneider, Hagerman, & Hessl, 2009). Owing to the fact that individuals with FXS show over-reactive responses to environmental and social stimuli, arousal dysregulation and related processes of anxiety have been hypothesized to underlie the behavioral phenotype of FXS (e.g., Belser & Sudhalter, 1995; Cornish, Sudhalter, & Turk, 2004; Miller et al., 1999).

Because the genetic basis of FXS is relatively well-understood, FXS has been studied as a more homogeneous genetic context that can lend insight into core features that are shared across all etiologic subtypes of autism (syndromic or idiopathic) and which may be linked to specific etiologic pathways (e.g., Abrahams & Geschwind, 2010; Belmonte & Bourgeron, 2006; Hagerman, Narcisa, & Hagerman, 2011). The study of FXS provides a means for linking a known genetic mutation with core behavioral and biological features associated with autism. In line with this approach, research has focused on defining behavioral phenotypes that are common in autism and FXS, with the goal of identifying shared underlying biological pathways. Autistic features are common in FXS, with about 60% of males with FXS meeting diagnostic criteria for autistic spectrum disorder using gold standard diagnostic instruments (Garcia-Nonell et al., 2008; Klusek, Martin, & Losh, 2014b). Furthermore, almost all individuals with FXS, even those who do not meet diagnostic thresholds, exhibit autistic-like behaviors such as abnormalities in eye contact and impairments in social communication (Hernandez et al., 2009; Kaufmann et al., 2004; Klusek, Martin, & Losh, 2014a). Similarities are also seen in performance on direct-assessment measures of social-communication ability and social cognition (i.e., the ability to understand the thoughts and feelings of others), with performance in these domains associated with longer CGG repeat lengths at the *FMR1* locus and greater gene methylation (i.e., decreased function; Losh, Martin, Klusek, Hogan-Brown, & Sideris, 2012). Furthermore, women who carry the *FMR1* premutation present with subtle social communication and personality features of the broad autism phenotype (or, subclinical characteristics resembling some features of autism but that are much milder in expression and believed to reflect genetic liability to autism; Losh, Klusek, et al., 2012). Overall, direct comparison studies of fragile X-associated and idiopathic autism support strong behavioral overlap, which suggests that dysregulation of the *FMR1* gene can give rise to autism symptomatology.

Several studies have directly explored associations between the protein encoded by the *FMR1* gene (FMRP) and autism symptom severity. Indices of *FMR1* function (e.g., repeat length, methylation) have in some cases been shown to relate to features associated with autism, such as social communication and social cognition (Losh, Martin, et al., 2012). Socialization difficulties, such as internalizing problems and withdrawn behaviors, have also been linked with FMRP reduction in females with FXS (Hessl et al., 2001). Additionally, reduced FMRP is associated with alterations in brain activity that are linked with autism, including reduced amygdala activation (Hessl et al., 2011). However, FMRP as typically measured (i.e., indirectly, via count of the number of cells producing FMRP rather than direct measurement of protein levels; see Schutzius et al., 2013) is not associated with autism symptomatology after controlling for intellectual ability (Bailey, Hatton, Skinner, & Mesibov, 2001; Harris et al., 2008; Loesch et al., 2007). Consequently, it has been proposed that the autistic behaviors seen in FXS are simply a consequence of cognitive deficits that occur in the absence of FMRP (e.g., Clifford et al., 2007; Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). It is notable, however, that IQ accounts for only a small percentage of the variance in the autistic behaviors of individuals with FXS (8% in females and 18% in males; Hall et al., 2010). Moreover, despite normal intelligence and only mildly reduced levels of FMRP (Tassone, Hagerman, Mills, & Harris, 2000), individuals with premutation alleles on *FMR1* also show elevated rates of autism (Clifford et al., 2007; Farzin et al., 2006; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004) and the broad autism phenotype (Losh, Klusek, et al., 2012). While intellectual disability may heighten risk for autism in FXS, this causal model ignores broader etiologic factors that include, but are not limited to, psychobiological and environmental factors coupled with genetic vulnerability associated with *FMR1* (e.g., Dykens, 2000).

FMR1 has been proposed to increase risk for autism through interaction with multiple background genes, thereby lowering the genetic threshold for producing autism (Bailey, Hatton, Skinner, et al., 2001; Harris et al., 2008; Rogers, Wehner, & Hagerman, 2001). Indeed, molecular-genetic research suggests that FMRP is responsible for translational regulation of a considerable number of genes (estimated at 842), and reduced FMRP causes widespread primary and secondary changes in the expression of other proteins (Darnell & Klann, 2013; Darnell et al., 2011). A number of well-studied proteins implicated in autism, including neurexin, neuroligin$_3$, neuroligin$_4$, and CYFIP, become dysregulated in the absence of FMRP (see Bagni, Tassone, Neri, & Hagerman, 2012; Darnell & Klann, 2013; Darnell et al., 2011; De Rubeis & Bagni, 2011; Hagerman, Hoem, & Hagerman, 2010; Iossifov et al., 2012). Highly significant overlap has been documented between FMRP targets and autism susceptibility genes, with 24% of the 117 autism candidate genes from the SFARI database identified as FMRP targets, such as NLGN3, NRXN1, SHANK3, PTEN (Basu, Kollu, & Banerjee-Basu, 2009). In a meta-analysis of exome sequencing studies of autism, FMRP was found to control the translation of one-third to one-half of genes associated with autism (Iossifov et al., 2012). FMRP is also involved in the regulation of a significant proportion (25 of 196) of overexpressed copy number variants (CNV's) that have been identified as autism susceptibility factors (Darnell et al., 2011). Evidence of interactions between *FMR1* and autism susceptibility loci provides insight into the molecular process by which *FMR1* begets autism symptoms.

Because *FMR1* has been relatively well studied, with mouse and fly models developed and a number of targeted drug therapies in progress, studies of phenotypic and biological overlap of FXS and autism can help inform the pathophysiology of both conditions. A key step in such work is the identification of quantitative endophenotypes that are more proximally related to underlying biology than downstream clinical and behavioral outcomes. Given that arousal modulation has been hypothesized to underlie the behavioral phenotypes of both autism and FXS (e.g., Cohen, 1995; Hutt et al., 1964; Kootz & Cohen, 1981; Rimland, 1964), and considering the strong behavioral overlap in these disorders, cardiac dysregulation (indexing broader autonomic nervous system dysfunction) may be a promising candidate endophenotype common to autism (or subgroups of individuals with autism) and FXS. Endophenotypes are hypothesized to bear a closer relationship to underlying biological processes than the full clinical presentation of a disorder, and thus can be valuable in elucidating gene-behavior relationships within the context of complex neuropsychological disorders such as autism (Gottesman & Gould, 2003; Gottesman & Shields, 1973; Leboyer et al., 1998). Several criteria have been proposed for evaluating candidate endophenotypes; namely, a trait must be heritable, show association with illness, present at elevated rates among both affected and unaffected family members, and show reliable measurement (Almasy, 2012; Almasy & Blangero, 2001; Gershon & Goldin, 1986; Gottesman & Gould, 2003; Gottesman & Shields, 1973). Physiological arousal has been shown to be heritable, with twin studies supporting substantial heritability at .65–.82 for resting heart rate (Boomsma & Plomin, 1986; Ditto, 1993) and .50 for vagal tone (Kupper et al., 2005). Arousal markers also show good short and long term test-retest reliability over time: cardiac measures sampled within short time periods are highly correlated (*r*'s range from about .60–.70; Doussard-Roosevelt, Montgomery, & Porges, 2003; Fracasso, Porges, Lamb, & Rosenberg, 1994; Kleiger et al., 1991) and heart activity patterns are stable across the developmental shift from infancy to childhood (Calkins & Keane, 2004; El-Sheikh, 2005). Moreover, cardiac indices are non-invasive, reliable, quantitative indices of biological functions, making them optimal candidates for studies of complex traits and disorders. Should measures of physiological arousal prove related to both autism and FXS, they could therefore constitute important endophenotypes tied to a known genetic mutation (i.e., *FMR1*). Below, we consider such evidence, beginning with an overview of cardiac indicators of autonomic nervous system function, followed by a detailed review of case-control comparisons of cardiac activity in autism and FXS and behavioral correlates of physiological profiles in these disorders.

Cardiac Vagal Tone as an Index of Parasympathetic Function

Cardiac vagal tone provides a non-invasive measure of parasympathetic autonomic activity via the quantification of heart rate variability patterns. Briefly, the tenth cranial nerve, the vagus, provides bidirectional communication between the brain and heart (Porges, 2001). Parasympathetic cardiac responses to environmental challenge are regulated via vagal efferent pathways, which project to the sinoatrial node of the heart (the heart's natural pacemaker). Activation of vagal efferent fibers slows the firing of the node, causing a rapid decrease in heart rate (Levy & Warner, 1994; Porges, 2003). Because the heart is innervated by both parasympathetic and sympathetic projections to the sinoatrial node, measures of

heart rate (i.e., inter-beat-interval) reflect both parasympathetic and sympathetic autonomic influences (Bernston, Cacioppo, & Quigley, 1993; see Table 1).

Respiratory Sinus Arrhythmia (RSA), on the other hand, provides a specific estimate of parasympathetic vagal control (Bernston et al., 1997; Eckberg, 1983; Katona & Jih, 1975; Porges, 2007). At rest, heart rate varies with respiratory parameters, quickening upon inhalation and slowing upon exhalation. These cyclical patterns of heart rate variability are linked with sympathetic and parasympathetic influences; expiratory slowing of heart rate is mediated by the parasympathetic system via the vagus, whereas inspiratory quickening of the heart reflects transitory release of the vagal brake (Bernston et al., 1993; Berntson et al., 1994). Therefore, the beat-to-beat variability in heart rate patterns that occurs with spontaneous breathing allows for the estimation of vagal cardiac influences (Porges & Byrne, 1992). Specifically, larger variability in the rise and fall of heart rate (i.e., higher RSA amplitude) indexes greater vagal cardio-inhibitory influences on the heart, and increased parasympathetic control. For detailed review of methods for quantifying RSA, see Denver, Reed, and Porges (2007), Grossman and Taylor (2007), Lewis, Furman, McCool, and Porges (2012), and the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996).

Several models have been proposed to account for the connection between autonomic functioning and psychobiological health, and more specifically, social behavior. Among these is the Central Autonomic Network model (Benarroch, 1993; Benarroch, 1997), which identifies a functional network of cortical structures and pathways within the central nervous system that appear to support behavior and adaptability. This proposed network (which includes the amygdala and hypothalamus, among other structures) is hypothesized to control sympathetic and parasympathetic motorneurons, as well as respiratory and neuroendocrine outputs. The primary output of the Central Autonomic Network is mediated through sympathetic and parasympathetic projections that innervate the heart via the vagus nerve, directly linking the output of the network with heart rate variability. Dysfunction of multiple systems in the network can result in psychological conditions, such as anxiety disorders, which are associated with reduced vagal control. More recently, the Neurovisceral Integration model has been proposed by Thayer and colleagues (Thayer & Lane, 2000, 2009) in attempt to integrate the functional network identified by the Central Autonomic Network model with other models of neural substrates that function in the service of social, affective, and motivated behavior (such as the “Emotion Circuit” model, Damasio, 1998). The Neurovisceral Integration Model proposes a core set of neural structures that allow for adaptive use of psychophysiological resources to regulate attention and affective information processing, and which are associated with autonomic control of the heart. In this model, vagal control of the heart provides an index of system flexibility; dampened vagal tone is a marker for system imbalance, leading to reduced adaptive responsivity to environmental input (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012).

A theory that has gained traction in recent years is Porges’ Polyvagal theory (e.g., Klusek, Martin, & Losh, 2013; Quintana, Guastella, Outhred, Hickie, & Kemp, 2012; Watson, Roberts, Baranek, Mandulak, & Dalton, 2012). This theory provides an evolutionary framework to support physiological regulation (and the broader autonomic system as

regulated by central mechanisms through the vagal nerve) as a mediator of social behavior (Porges, 2001, 2003, 2007; Porges & Furman, 2011). From an evolutionary perspective, social engagement is an adaptive behavior that promotes survival. Polyvagal theory posits that the phylogenetically newer branch of the vagal nerve, the ventral vagus, evolved over time to include myelinated pathways that allow for adaptive, transitory responses to environmental challenge, thereby facilitating either social engagement or mobilization and defense (Porges, 2001). Quick, momentary adjustments to the vagal brake via the ventral pathway conserves metabolic resources by allowing sympathetic tone to be expressed without activating the sympathetic-adrenal system (Porges, 2001, 2007). In this way, the evolution of the myelinated vagus permits fine-tuned autonomic regulation via the vagal brake, in the service of adaptive social behavior. Unlike other autonomic theories, Polyvagal theory is notable in that it explicitly incorporates autistic-like social dysfunction into its framework, using the vagus as an “organizing principle” to explain behavioral and psychological features associated with autism (e.g., Marshall & Fox, 2006; Porges, 2004; Porges et al., 2013). In this paper, evidence is examined to extend links between autonomic dysfunction and social and related behavioral impairments associated with autism.

Cardiac Indices of Autonomic Function in Autism and FXS: Case-Control Comparisons

Taken as a whole, physiological dysregulation is a well-replicated feature of FXS. This includes general patterns of hyperarousal as indexed by elevated heart rate, as well as reduced vagal tone and atypical cardiac reactivity that are consistent with broader autonomic nervous system dysfunction. While physiological dysregulation has also been documented in autism, findings have proven less consistent than those in studies of FXS. For instance, while elevated heart rate and diminished vagal tone have been documented in some investigations of autism, other studies have found arousal regulation to be on par with developmental or age-based expectations. Discrepant findings across studies of autism may be a reflection of the heterogeneity of this population (Betancur, 2011; Geschwind & Levitt, 2007). Below, the extant research on physiological activity in individuals with autism and FXS is discussed, first with a focus on differences between these groups and control populations, followed by a discussion of behavioral and genetic correlates documented to date.

In appraising this literature, the following methodological considerations should be noted. First, existing research is somewhat limited by small samples and it is possible that some null findings are due to underpowered statistical tests. To aid interpretation, sample sizes are provided and, when possible, effect sizes are reported when discussing null findings (effect sizes are also provided in Tables 2 and 3).

Second, research has focused on participants with a wide range of age and ability levels, which likely accounts for some inconsistencies across findings. Vagal activity is known to increase with age (Alkon et al., 2003; Bar-Haim, Marshall, & Fox, 2000; Longin, Gerstner, Schaible, Lenz, & Konig, 2006; Porges, Doussard-Roosevelt, Portales, & Suess, 1994; Sahni et al., 2000), although it is unclear whether this vagal maturation is influenced by developmental factors, such as cognitive growth, in addition to physical growth that comes

with age. Because developmental influences on cardiac indices of autonomic functioning are not well understood, the impact of different participant characteristics and matching procedures (e.g., chronological versus mental age) is unknown at this time. Most reports have included chronological age matched typically developing controls, with only a few utilizing comparison groups comprised of individuals with other developmental disabilities. Matching procedures and participant characteristics are described throughout, and their apparent impact on findings is discussed in detail when relevant. Sample size, effect size, matching procedures and other relevant participant descriptives are provided in Tables 2 and 3.

Third, cardiac activity has been measured across a range of experimental conditions that vary in the type and intensity of stressor. Careful consideration of condition effects is essential to interpreting this complex literature, as heart activity is known to vary according to context and even small changes in environmental context might elicit divergent responses (Alkon et al., 2003). To assist the reader in parsing context effects, studies are grouped into the broad categories of baseline, cognitive stressors, and social stressors. While an emphasis is placed on the interface between physiological activity and social engagement, cardiac activity during nonsocial contexts (e.g., at baseline or during cognitive stressors) is also discussed to provide breadth, inform chronic versus context-specific patterns, and to illustrate the ways that cardiac responses may vary across social and nonsocial conditions. A well-established literature on typically developing individuals demonstrates that cardiac activity measured in cognitively-demanding conditions is predictive of social ability (e.g., Calkins & Keane, 2004; Gentzler, Santucci, Kovacs, & Fox, 2009; Graziano, Keane, & Calkins, 2007; Stifter & Corey, 2001). Thus, the ability to make subtle adjustments to the physiological system in order to optimize attentional resources during cognitively taxing conditions yields information about autonomic flexibility and capacity for regulated social responsiveness.

Fourth, psychotropic medication is known to impact cardiovascular activity and should be considered as a potential confound (e.g., O'Brien & Oyebode, 2003; Rechlin, 1995; Silke, Campbell, & King, 2002). The majority of studies of autism and FXS have controlled for medication use by excluding individuals who were taking medications, although some studies have controlled for medication use statistically (e.g., Van Hecke et al., 2009) or analyzed groups separately based on medication status (e.g., Daluwatte et al., 2013; Mathewson et al., 2011). The handling of medication use may account for some inconsistencies across findings, although no clear patterns emerge when grouping studies by the inclusion or exclusion of individuals taking medications. Medication status for individual reports is described in Tables 2 and 3.

Finally, because there is little available evidence on gender effects, cardiac activity specifically in females is not discussed here. In autism, most studies have included only a very small number of females and none have tested gender effects. While some emerging research has addressed cardiac activity among females with FXS, these investigations are too few in number to draw meaningful conclusions. Findings based on males likely do not generalize to females, given that clear gender differences are seen in the physiological

profiles of typically developing individuals (with females generally showing higher heart rate and vagal tone than males; Saab, 1992).

Case-Control Comparisons of General Arousal Level Indexed by Heart Rate

Heart rate, commonly measured as the interval between heart beats, or the inter-beat-interval, provides an estimate of one's overall arousal level as influenced by both the parasympathetic and sympathetic subsystems (Bernston et al., 1993). The study of heart rate provides a complementary index of autonomic functioning that, in conjunction with estimates of vagal activity, can shed light on sympathetic influences. When the body is stressed, heart rate generally increases and becomes more stable (Porges & Raskin, 1969) and transitory heart rate acceleration marks an aversive physiological reaction (Sroufe & Waters, 1977). Heart rate that is limited in flexibility and does not vary according to task demands is associated with pathology (Peng et al., 1994; Pincus, Gladstone, & Ehrenkranz, 1991). Below, studies of heart rate in autism and FXS are reviewed; see Tables 2 and 3 for a summary of this research.

Heart Rate in Autism

Early investigations of heart rate in autism date back to the 1960's and were primarily focused on validating theoretical accounts that atypical sensory responses in autism were rooted in physiological reactivity (e.g., Bernal & Miller, 1970; Hutt et al., 1964; MacCulloch & Williams, 1971; Rimland, 1964). While these first reports provide historical context to physiological investigations of autism and have laid the foundation for more recent work, results are not reviewed given the significant advances in techniques for indexing cardiac activity and changes in autism diagnostic nosology since these earliest investigations have been published.

Heart rate during baseline conditions in autism—A number of group comparison studies have been conducted to determine whether hypoarousal or hyperarousal is characteristic of individuals with autism. Evidence is mixed. In calm baseline conditions, eight studies have found heart rate in autism to be elevated in comparison to typically developing children of a similar chronological age (Bal et al., 2010; Daluwatte et al., 2013; Guy, Souders, Bradstreet, DeLussey, & Herrington, 2014; Kushki et al., 2013; Mathewson et al., 2011; Porges et al., 2013; Watson et al., 2012; Woodard et al., 2012; see Table 2 for participant details and effect sizes). In contrast, six studies have not found differences in the baseline heart rate of adult (Toichi & Kamio, 2003; see Table 2 for participant details and effect sizes), adolescent (Bink et al., 2013), school-aged (Althaus, Mulder, Mulder, Aarnoudse, & Minderaa, 1999; Klusek, Martin, et al., 2013) and preschool-aged (Corona, Dissanayake, Arbelle, Wellington, & Sigman, 1998; Sheinkopf, Neal-Beevers, Levine, Miller-Loncar, & Lester, 2013) individuals with autism compared to controls of a similar chronological age. It seems unlikely that the null findings from this latter group of studies were related to insufficient power, as effect sizes were small in most investigations, ranging from .06–.20 (see Table 2). Only one report found hypoarousal in children with autism (n = 152), in comparison to a sample of 36 children with other neurodevelopmental disabilities (Daluwatte et al., 2013). Discrepancies across studies could be related to a number of

factors, including varying participant characteristics such as age, level of functioning, and general symptom heterogeneity that is characteristic of autism. These factors are considered in greater detail in *Summary of Findings and Key Considerations for Future Research.*

Cognitive stressors and heart rate in autism—Increased heart activity during cognitively demanding tasks has been reported in autism samples. In an investigation of 32 children with autism and typical controls, Porges et al. (2013) found that the children with autism had faster heart rates during a dichotomous listening task. Kushki et al. (2013) also detected elevated arousal in children with autism (n = 12) compared with typically developing children while completing a color Stroop task. Likewise, Guy et al. (2014) detected increased heart rate in school-aged children with autism (n = 14) compared to age and IQ matched typical controls during cognitive testing. Notably, each of these studies found that the individuals with autism also exhibited elevated heart rate at baseline, perhaps pointing toward generalized hyperarousal rather than task-specific patterns.

Social stressors and heart rate in autism—A number of studies have investigated social interaction as an elicitor of exaggerated physiological responses in autism, with overall evidence failing to support such a relationship. In a study of 40 boys with autism compared with typically developing boys of a similar mental and chronologic age, Klusek, Martin, et al. (2013) did not find differences in the heart rate of the groups during conversation with an examiner, and the reactivity (i.e., change from baseline) of the groups was similar in magnitude. Sigman, Dissanayake, Coronoa, and Espinosa (2003) also reported similar mean heart rate across children with autism (n = 22) and children with other intellectual disabilities (matched on language, chronological age, and mental age) during interactions with a stranger and with the child's mother. Likewise, Willemsen-Swinkels, Bakermans-Kranenburg, Buiteaar, Ijzendoorn, and Engeland (2000) found that children with autism (n = 32) responded to separation from and reunion with their caregiver with heart rate reactivity that was similar to children with typical development and children with language disorders who were matched on mental age. Finally, in a study of 15 young children with autism and eight age and IQ matched children with typical development, Sheinkopf et al. (2013) did not detect group differences in heart rate during "stranger approach" situations (effect sizes also supported null effects, d's < .11).

Some reports have detected hyperarousal during social interaction, although arousal was chronically elevated across both social and nonsocial conditions in these studies. For instance, Watson, Roberts, Baranek, Mandulak, and Dalton (2012) found that young children with autism (n = 20) showed faster heart rate than chronological age matched controls, regardless of the social or nonsocial content of the stimuli. Similarly, Guy et al. (2014) reported that the heart rate of school-aged children with autism (n = 14) was elevated in comparison to age and IQ matched typical controls at rest, during cognitive testing, and during social conversation. Thus, overall, evidence suggests that social interaction conditions are not specific elicitors of hyperarousal in individuals with autism.

In contrast to social interaction tasks, social *performance* conditions appear to be associated with blunted arousal responses in individuals with autism. Jansen, Gispen-de Wied, van der Gaar, & van Engeland (2003) examined the heart rate of 10 children with autism in the time

preceding a public speaking task and found that, unlike typically developing children, the children with autism failed to increase heart rate in anticipation of the task. Hollocks, Howlin, Papadopoulos, Khondoker, & Simonoff (2014) also found blunted heart rate elevation in children with autism compared to typically developing children during the transition from rest to psychosocial stress related to public performance in the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993). Finally, Smeekens, Didden, and Verhoeven (2013) reported that adult males with autism (n = 16) failed to increase heart rate in response to a social role playing task, whereas typically developing controls of a similar age and IQ increased heart rate in response to the task. Dampened responsivity in these studies may support failure of the individuals with autism to react physiologically to psychosocial stress. However, careful consideration of the cognitive, attentional, and emotional significance of a given experimental condition is key, particularly given the idiosyncratic responses exhibited by individuals with autism. As proposed by Levine, Conradt, Goodwin, Sheinkopf, & Lester (2014), individuals with autism, who have known deficits in social-cognition (e.g., Baron-Cohen, Leslie, & Frith, 1985), may fail to understand the social significance of public performance tasks and thus may not react to these conditions with a physiological stress response. Concurrent measurement of the subjective experience of stress could clarify the meaning of aberrant cardiac responses in future work.

In conclusion, evidence of atypical general arousal level in autism is inconsistent, with findings split between elevated or typical baseline heart rate in autism. Discrepancies in the extant literature may be related to etiologic and phenotypic heterogeneity that is inherent to autism as well as participant characteristics (such as age) and differences across experimental conditions. Hyperarousal or exaggerated reactivity in response to social interaction is generally not supported, although blunted responses to social *performance* tasks suggest that individuals with autism may fail to react physiologically to tasks designed to induce psychosocial stress.

Heart Rate in FXS

Heart rate during baseline conditions in FXS—Cardiac hyperarousal is a well-replicated, hallmark feature of the FXS physiological profile. At rest, faster heart rate has been consistently detected among school-aged and adolescent males with FXS in comparison to typically developing chronological age matched peers (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Heilman, Harden, Zageris, Berry-Kravitz, & Porges, 2011; Klusek, Martin, et al., 2013; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001; Roberts, Tonnsen, Robinson, & Shinkareva, 2012). Only two reports, focusing on very young (i.e., one-to-two year old) infants with FXS, have not detected increased arousal at baseline (Roberts, Hatton, Long, Anello, & Colombo, 2012; Tonnsen, Shinkareva, Deal, Hatton, & Roberts, 2013), consistent with evidence of a non-linear shift from hypo- to hyperarousal in the first two years of life in FXS (Roberts, Tonnsen, et al., 2012).

Cognitive stressors and heart rate in FXS—Cardiac activity during cognitive stressors has not been examined extensively in FXS, although existing work supports hyperarousal in these contexts as well. A landmark study by Boccia and Roberts (2000)

implemented an A-B-A-B-A experimental design to test patterns of arousal during alternative passive (watching a video) and active (IQ testing) conditions. The boys with FXS (n = 20) were hyperaroused in comparison to age matched typically developing boys throughout both conditions, and did not show phase-related cardiac modulation. These findings point toward chronic hyperarousal in FXS that is present across both resting and cognitively taxing contexts. Consistent with this report, Heilman et al. (2011) also detected faster heart rate without significant condition effects in a study of 18 children and adolescent males with FXS during baseline and an auditory word repetition task.

Social stressors and heart rate in FXS—Compared to typically developing children of a similar age, males with FXS demonstrate elevated heart rate during social stressors. It is notable, however, that hyperarousal documented in these studies appears to be a systemic physiological condition rather than a socially-induced state. First, Hall and colleagues (2009) examined heart activity among 26 males with FXS at baseline (video watching) and in response to an unstructured conversation with an examiner with regular prompts to make eye contact, considered a social stressor. Compared to their typically developing brothers, the boys with FXS showed faster heart rates during conversation as well as at baseline. Both groups increased heart rate in response to the conversation task, suggesting that the social task elicited a normal arousal response in the males with FXS. No relationship was detected between arousal and gaze avoidant behavior during the conversational task (Hall et al., 2009). In a second study examining arousal during conversation, Klusek, Martin, et al. (2013) found that school-aged boys with FXS (n = 39) showed faster heart rates than typically developing boys of a similar chronological age, both during conversation with an examiner and at baseline (video watching), suggesting chronic hyperarousal. The direction and magnitude of heart rate reactivity (i.e., change from baseline) in response to the task did not differ across groups.

Finally, Tonnsen et al. (2013) implemented a standardized social stressor task, the Stranger Approach episode of the Laboratory Temperament Assessment (Goldsmith & Rothbart, 1996), to examine physiological responses to social stress in 21 young males with FXS and age matched typically developing boys. The boys with FXS demonstrated faster mean heart rate across all conditions (which consisted of a resting phase followed by various phases of stranger approach), although group differences were not statistically significant after controlling for mental age (a medium effect size of d = .48 suggests that the study may have been underpowered). Notably, no phase-by-group interactions were detected, indicating that the boys with FXS showed arousal responsivity to the social stressor that was similar to controls. In fact, both groups *decreased* arousal in response to the stranger's approach, further demonstrating that social approach does not elicit atypically elevated arousal in FXS.

In summary, existing research supports hyperarousal as a chronic autonomic state of males with FXS that is seen in baseline (Hall et al., 2009; Heilman et al., 2011; Klusek, Martin, et al., 2013; Roberts et al., 2001; Roberts, Tonnsen, et al., 2012), cognitive stressor tasks (Boccia & Roberts, 2000; Heilman et al., 2011), and social stressors (Hall et al., 2009; Klusek, Martin, et al., 2013). Although males with FXS may exhibit hyperarousal during social stressor tasks, this does not appear to represent a context-dependent physiological response. Evidence that social stressors do not evoke atypically elevated arousal in FXS,

which has now been replicated by three independent research groups, is notable because it counters a prevalent theory-- that social impairments are rooted in the inability to modulate arousal during social situations, leading to anxiety and inadequate social engagement (e.g., Belser & Sudhalter, 1995; Cornish et al., 2004; Miller et al., 1999). It may be the case, however, that nonspecific heightened arousal (i.e., hyperarousal that is present regardless of social or nonsocial context) may nonetheless hinder the ability to process and interact with one's environment, including the social environment. In interpreting these findings the "principle of initial values" (Wilder, 1931) should also be considered, which presumes that the higher the prestimulus arousal, the smaller the potential increase in physiological response to a given stimulus, similar to a "ceiling effect". Thus, it is possible that the magnitude of the potential reactivity in FXS is truncated by elevated generalized arousal observed in baseline conditions. The principle of initial values, however, is not universally observed across all physiological systems and is influenced by a number of variables, making its applications to physiological work challenging.

Case-Control Comparisons of Parasympathetic Functioning Indexed by Vagal Tone

Static measures of vagal tone index parasympathetic control of the heart, with higher vagal tone reflecting the maintenance of homeostasis, increased capacity for self-regulation and engagement with the environment, and broader psychophysiological health and autonomic integrity (Porges, 1992; Porges, 1995a; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Porges & Furman, 2011). In typical development, high baseline vagal tone in infancy is associated with greater behavioral reactivity to the environment (an adaptive skill that provides more opportunities for interactive social learning) and is a positive predictor of emotional and behavioral outcomes in toddlerhood and childhood (see Beauchaine, 2001). A number of pro-social behaviors, including emotional expression, self-regulation, empathy, social initiation, and overall social competence, are linked with high vagal tone in childhood (Blair & Peters, 2003; Calkins, 1997; Calkins & Keane, 2004; Eisenberg et al., 1996; Fabes, Eisenberg, & Eisenbud, 1993; Fabes, Eisenberg, Karbon, Troyer, & Switzer, 1994; Fox & Field, 1989; Kagan, Reznick, & Snidman, 1987; Patriquin, Lorenzi, Scarpa, & Bell, 2014). This relationship extends into adulthood, with documented links between vagal tone and complex social regulatory behaviors such as adaptive processing of threatening social stimuli (Miskovic & Schmidt, 2010; Park, Van Bavel, Vasey, & Thayer, 2012), the regulation of facial affect (Demaree, Robinson, Everhart, & Schmeichel, 2004), and social cognitive ability (Quintana et al., 2012).

Some investigations reviewed below have also focused on vagal reactivity, or the change in vagal tone from baseline following exposure to a stressor. As opposed to steady-state parasympathetic function, vagal reactivity reflects the capacity to organize metabolic resources to respond to external demands (Porges et al., 1996). Reduction in vagal tone, or "vagal suppression", permits greater sympathetic influences, allowing the body to respond to external demands with increased attention and behavioral arousal (Lovallo, 2005; Porges, 1995b, 2001; Porges et al., 1996). In typical development, vagal suppression in response to cognitive or attention-demanding challenges is an adaptive response that predicts enhanced

social and emotional competence in other situations (e.g., Calkins & Keane, 2004; Gentzler et al., 2009; Graziano et al., 2007; Stifter & Corey, 2001). On the other hand, vagal suppression in response to social interaction is likely to represent a maladaptive response associated with the perception of threat, and is associated with poorer social outcomes. For example, young children who show greater vagal suppression in response to social interaction have increased anxiety, depression, and internalizing problems (Heilman et al., 2008) and reduced language and play skills (Suess & Bornstein, 2000). Case-control comparisons of vagal tone in autism and FXS are outlined below and are summarized in Tables 2 and 3, respectively.

Vagal Activity in Autism

Vagal activity during baseline conditions in autism—Evidence for atypical resting vagal tone in autism is mixed, with nine investigations reporting typical resting vagal estimates and six reports supporting diminished vagal tone of large effects (see Table 2 for summary). Reduced baseline vagal tone has been detected in children (Bal et al., 2010; Guy et al., 2014; Neuhaus, Bernier, & Beauchaine, 2014; Van Hecke et al., 2009) and adults (Mathewson et al., 2011) with autism, compared with typically developing individuals of a similar age and IQ. Using a device that indexes cardiac parasympathetic tone through real-time measurement of the brainstem activity, Ming, Julu, Brimacombe, Connor, & Daniels (2005) detected reduced resting vagal tone among 15 children with autism compared with 17 healthy controls. This study found that the children with autism who showed other symptoms of autonomic dysfunction (e.g., sleep disturbance, gastrointestinal problems) demonstrated the lowest levels of vagal activity, supporting reduced vagal control as a physiological marker for pervasive autonomic dysfunction. In contrast, eight investigations have not detected group differences in baseline vagal tone. Five reports found similar baseline vagal estimates among age and IQ/mental age matched controls and adolescents with autism (n = 20; Toichi & Kamino, 2003), school-aged children with autism (n = 18; Althaus et al., 1999; n = 40; Klusek, Martin, et al., 2013; n = 19; Levine et al., 2012) and preschoolers with autism (n = 14; Sheinkopf et al., 2013). Baseline vagal estimates of children with autism also do not differ from typical controls who are not matched on IQ (n = 59; Schaaf, Benevides, Leiby, & Sendecki, 2013) or from children with attention-deficit/hyperactivity disorder (n = 20; Bink et al., 2013). This effect holds across individuals with autism who do or do not have comorbid anxiety; Hollocks et al. (2014) detected no differences in baseline vagal tone across children with autism without anxiety (n = 20), children with autism with anxiety (n = 32), and typically developing children. In an investigation of a large sample of children with autism (n = 152), Daluwatte et al. (2013) found no differences in the baseline vagal tone (measured with descriptive statistics of heart rate variability) of the children with autism and 116 typically developing children of a similar chronological age, although there was a trend for lower mean estimates in the autism group. Baseline vagal tone of the children with autism was also compared to a group of 36 children with other neurodevelopmental disabilities, with no group differences detected (Daluwatte et al., 2013).

Cognitive stressors and vagal activity in autism—Reduced vagal tone has been detected in conditions that may be considered cognitively taxing, such as auditory

processing tasks (Porges et al., 2013), cognitive testing (Guy et al., 2014), watching video clips (Van Hecke et al., 2009), and during an emotional Stroop task (Mathewson et al., 2011). Notably, all investigations that have detected reduced vagal tone during cognitive stressors also found vagal tone in the individuals with autism to be reduced at rest (e.g., Guy et al., 2014; Mathewson et al., 2011; Porges et al., 2013; Van Hecke et al., 2009). Likewise, when diminished vagal tone in autism has not been detected during cognitive stressors, vagal estimates were similar to controls at baseline as well (i.e., Bink et al., 2013). Altogether, it appears that some individuals with autism may exhibit chronically dampened parasympathetic tone, rather than parasympathetic dysregulation that is specific to cognitive task demands.

Measuring vagal reactivity to cognitive stressors (the change in vagal tone from baseline) may more directly map task-related parasympathetic regulation. For example, Porges et al. (2013) found reduced vagal tone in children with autism (n = 79) across both baseline and dichotomous listening conditions, consistent with chronic parasympathetic dampening in this sample. However, the reactivity patterns revealed atypical vagal increases in autism whereas the typically developing individuals maintained baseline levels, lending support for atypical reactivity to the cognitive stressor in autism. Similarly, Toichi and Kamio (2003) found a lack of vagal suppression among 20 adolescents and young adults with autism in response to an arithmetic task, whereas age and IQ matched controls decreased vagal activity in accordance with the increased task demands. The groups did not differ in baseline vagal tone or vagal tone during the task, again supporting impaired reactivity in this sample as opposed to chronic parasympathetic dysregulation. Notably, individual response patterns revealed significant individual variability that was not captured in the group-level analysis. While all of the control participants decreased vagal tone in response to the stressor, half of the individuals with autism actually showed *increased* vagal tone, suggesting that a subgroup of individuals with autism found the “challenging” arithmetic task to be less demanding than the resting baseline condition (Toichi & Kamio, 2003).

In another study, Althaus and colleagues (1999) examined vagal change in response to a visual memory search task in 36 school-aged children with autism, who were divided into subgroups according to the presence of hyperactivity. Compared to typically developing children of similar age and IQ, the children with autism showed less vagal suppression than typically developing children, with the most pronounced differences seen among the subgroup of children with autism who showed symptoms of hyperactivity. Interestingly, the groups did not differ in resting vagal tone, which suggests that atypical parasympathetic activity in this group of children was specific to the process of responding to increased environmental demand. Consistent with the notion that attention deficit/hyperactivity symptoms impact cardiac reactivity in autism, a report by Bink et al. (2013) found that task-related vagal suppression in children with autism was not impaired relative to children who are matched on attention deficit/hyperactivity symptom severity. In summary, evidence suggests that individuals with autism fail to suppress parasympathetic tone in response to cognitive stressors, with some emerging evidence that the efficiency of parasympathetic modulation is influenced by symptoms of inattention and hyperactivity. Failure to modulate

parasympathetic tone is considered a maladaptive response that prevents the body from rousing the resources needed to meet task demands.

Social stressors and vagal activity in autism—While the physiological profile of autism may be aberrant at baseline and in response to cognitive stressors, there is mixed support for atypical vagal tone and reactivity in response to social stressors. In an investigation of vagal reactivity of 19 children with autism and a comparison group of typically developing children of a similar age, Van Hecke et al. (2009) found that the children with autism showed significantly reduced vagal tone in response to unfamiliar social stimuli (a video of an unfamiliar person reading a story), but not to familiar social stimuli (a video of a caregiver reading a story). Typically developing children, on the other hand, did not show any reactionary changes in vagal tone across either social condition. Other studies have not detected atypical vagal activity during social stressors. For example, Hollocks et al. (2014) detected similar vagal estimates in children with autism (n = 42) and typical during public performance tasks of the Trier Social Stress Test (Kirschbaum et al., 1993). Similarly, no group differences in vagal tone were detected by Watson et al. (2012) in a study of 20 young children with autism (29–42 months) and age matched controls during viewing of live or recorded “child-directed speech” conditions. Klusek, Martin, et al. (2013) also did not find differences in vagal activity during conversation with an examiner in a study of 40 school-aged boys with autism and 27 typically developing boys of a similar chronological and mental age. Further, the groups did not differ in the magnitude or direction of vagal reactivity (i.e., change from baseline), with a trend in both groups for vagal increases in response to conversation. Guy et al. (2014) also examined the vagal tone of children with autism (n =14) and age and IQ matched controls during rest, cognitive testing, and conversation. Although vagal tone in the autism group was significantly reduced during the conversational condition, it was also reduced at baseline and during the cognitive stressor, suggesting that dampened parasympathetic tone was not specific to the social task (supporting this interpretation, effect sizes were relatively similar across conditions, with the most robust group differences observed at baseline; see Table 2). Consistent with the findings of Klusek, Martin, et al. (2013), Guy and colleagues also found that both the autism and typical groups exhibited significantly increased vagal tone during conversation relative to baseline.

Although atypical vagal activity during social stressors has not been consistently detected, individual differences in the physiological responses of the children with autism have been reliably associated with social outcomes. Children with autism who demonstrated higher vagal tone during the social conditions had better social-communication and expressive language outcomes, both concurrently (Klusek, Martin, et al., 2013) and at a one-year follow-up (Watson, Baranek, Roberts, David, & Perryman, 2010). In interpreting these studies, it is important to consider the risk of circular interpretation, where elevated vagal tone may predict superior language, or conversely, where children with superior language skills approach social-language tasks differently than do children with inferior language (perhaps with less physiological defensiveness, thus explaining the link between language outcomes and vagal tone). Longitudinal investigations, such as that by Watson and

colleagues, can help avoid circularity in discriminating these complex predictive relationships.

In an investigation of social stress to unfamiliar people, Sheinkopf et al. (2013) did not find differences in the vagal tone or reactivity of young children with autism (n = 14) and age and IQ matched typically developing children (n = 8) during a stranger social approach task which involved a "distal approach" where the examiner stood near the door and talked with the child's parent while the child played nearby, and "proximal approach" where the examiner sat near the child and interacted with them in a friendly manner (consistent with this conclusion, the effect size was minimal at d < .01). Contrary to evidence linking vagal withdrawal during social situations with poor social outcomes in typical development (e.g., Heilman et al., 2008; Suess & Bornstein, 2000), the children with autism who reduced vagal tone during social approach showed *better* socialization scores on the Vineland Adaptive Behavior Scale (Sparrow, Balla, & Cicchetti, 1984). This association was not detected in the typical group (S. Sheinkopf, personal communication). Similar counter-intuitive behavioral associations have been reported by Jansen and colleagues (2006), who found that increased heart rate in response to a public speaking task (which was the "normal" response exhibited by controls) was associated with greater social and communication impairments in a sample of ten adults with autism. Given that the significance of social stimuli may be different for typically developing individuals than individuals with autism, who may lack innate attentional preference for social stimuli (Pierce, Conant, Hazin, Stoner, & Desmond, 2011), it may be misguided to expect "adaptive" physiological responses to overlap across these populations. For example, the additional attentional resources afforded by increased arousal may help individuals with autism compensate for innate attentional biases, whereas typically developing individuals may not require increased arousal to adequately attend to social input. Indeed, other atypical yet presumably adaptive neurophysiological responses have been documented in autism, such as abnormal task-related cortical activity in the presence of intact behavioral performance (Belmonte & Yurgelun-Todd, 2003). The possibility that some atypical autonomic responses in autism may reflect compensatory processes hasn't been adequately addressed in prior research.

In summary, resting parasympathetic vagal control is impaired in at least a subset of individuals with idiopathic autism. Clinical heterogeneity likely accounts for some inconsistencies across studies, a possibility that is supported by the findings of Ming et al. (2005), who detected the most diminished vagal tone among the subset of individuals who showed other signs of autonomic dysfunction. Dampened vagal tone in response to cognitive stressors has been more consistently reported, although findings are consistent with patterns of chronically dampened parasympathetic tone rather than task-specific dysregulation. The ability to make physiological adjustments to cognitive demands may be more precisely mapped through measures of vagal reactivity than through static physiological estimates. Evidence remains too limited to make definitive conclusions about physiological modulation in social contexts. As a group, individuals with autism do not differ from controls in static vagal estimates during social conditions, although individual autonomic differences during these contexts do appear to be an important predictor of social outcomes (e.g., Klusek, Martin, et al., 2013; Watson et al., 2010). Atypical physiological reactivity to some types of

social stimuli has been documented (e.g., Van Hecke et al., 2009), although more research is needed to replicate findings and explore the possibility of atypical yet compensatory physiological mechanisms in autism.

Vagal Activity in FXS

Vagal activity during baseline conditions in FXS—A number of investigations encompassing a wide age range of males with FXS have detected decreased vagal tone as compared to age matched typically developing children during resting conditions (Boccia & Roberts, 2000; Hall et al., 2009; Heilman et al., 2011; Roberts et al., 2001; Roberts, Boccia, Hatton, Skinner, & Sideris, 2006; Tonnsen et al., 2013). Although reduced vagal tone is not universally replicated, overall, dampened parasympathetic activity appears to be a robust feature of males with FXS.

Cognitive stressors and vagal activity in FXS—Vagal tone in FXS is also reduced during cognitive tasks, such as arm restraint (Roberts, Tonnsen, et al., 2012), word repetition (Heilman et al., 2011), and cognitive assessment (Boccia & Roberts, 2000). Additionally, males with FXS demonstrate absent or reduced vagal suppression in response to cognitively-challenging tasks (e.g., academic testing), whereas typically developing peers show clear vagal suppression in response to these same tasks (Boccia & Roberts, 2000; Roberts et al., 2001; Roberts et al., 2006). One recent study by Heilman and colleagues (2011) examined vagal reactivity among 12 males with FXS (aged 6–23 years) and 21 typically developing males of similar ages in response to a word repetition task. While the typically developing boys suppressed vagal tone in response to the increased task demands, the boys with FXS responded with atypical increases in parasympathetic vagal tone, indicating a failure to release the vagal brake in response to challenge. Taken together, findings appear to support diminished or absent vagal suppression among males with FXS under conditions of cognitive challenge.

Social stressors and vagal activity in FXS—Whereas males with FXS exhibit atypical vagal reactivity in response to cognitive challenges, *social* challenges do not appear to elicit atypical vagal response. Hall and colleagues (2009) examined vagal reactivity among 26 males with FXS at baseline and in response to an unstructured conversation with an examiner with regular prompts to make eye contact (considered a social stressor). Similar responses were observed among the boys with FXS and their typically developing brothers (who served as a control group), with no reactionary changes in vagal tone across conditions. Furthermore, neither heart rate nor vagal tone were associated with the extent of gaze aversion exhibited during the conversation task, suggesting that gaze avoidance, which has been hypothesized to be rooted in social anxiety (e.g., Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1989), does not interface with physiological modulation. Overall, the Hall et al. findings suggest that conversation with an examiner did not prompt parasympathetic modulation in either group, a conclusion which is substantiated by Klusek, Martin, et al. (2013), who also examined vagal activity in school-aged boys with FXS (n = 39) at rest and during naturalistic conversation with an examiner. Both the boys with FXS and a control group of typically developing boys maintained baseline levels of vagal tone during conversation. In fact, a trend was detected for *increased* vagal tone in response to

conversation in both groups, a finding that suggests that social interaction is not a catalyst for hypervigilance and physiological stress in boys with FXS. Finally, Tonnsen and colleagues (2013) found that although preschool boys with FXS (n = 21) showed decreased vagal activity during the Stranger Approach episode of the Laboratory Temperament Assessment Battery (Goldsmith & Rothbart, 1996) compared to age matched typically developing peers, the vagal estimates of the boys with FXS did not vary significantly between the resting and stranger approach phases of the task. Thus, even when boys with FXS were exposed to a protocol specifically designed to induce social stress, parasympathetic tone did not differ from baseline and showed phase-related changes that were similar to that of controls.

Behavioral and Genetic Correlates of Cardiac Activity: Within-Group Associations

Relationship between Autism Symptom Severity and Cardiac Activity

Most studies have failed to detect a relationship between cardiac indices of arousal and continuous measures of autism symptom severity in autism. Klusek, Martin, et al. (2013) measured vagal tone and heart rate during baseline and conversational conditions in 40 school-aged boys with autism and did not detect significant associations with autism severity, which was directly assessed with the Autism Diagnostic Observation Scale (Lord et al., 2000). In an investigation of ten individuals with autism, Jansen and colleagues (2006) did not find associations between the overall symptom score of the Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994) and heart rate reactivity to a public speaking task. Similarly, parent-reported symptoms of autism have not been found to relate to measures of vagal tone (Guy et al., 2014; Patriquin, Scarpa, Friedman, & Porges, 2013; Van Hecke et al., 2009) or heart rate (Guy et al., 2014; Louwerse et al., 2013; Patriquin et al., 2013) in children with autism. Notably, while these studies failed to detect relationships between overall autism symptom severity and cardiac arousal, many of these reports did detect significant associations with specific symptoms of autism, such as social communication deficits (Klusek, Martin, et al., 2013), social skill deficits (Van Hecke et al., 2009), decreased sharing, communicative gestures and receptive language (Patriquin et al., 2013), and the social and communication subdomains of the Autism Diagnostic Interview-Revised (Jansen et al., 2006). This suggests that omnibus measures of autism symptomatology may be too broad to tap the component features of autism that relate to physiological dysfunction. It is also possible that some tools may yield a range of scores that are too restricted in range to detect associations. For example, the scores from the Autism Diagnostic Observation Scale are restricted to a 6-point range for children who meet criteria for autism spectrum disorder.

Three studies have examined associations with continuously distributed autism symptoms in FXS, with mixed findings. In an investigation of school-aged boys with FXS (n = 39), Klusek, Martin, et al. (2013) did not detect significant associations between autism symptom severity, measured with the Autism Diagnostic Observation Schedule (Lord et al., 2000), and heart rate or vagal tone measured in resting and conversational conditions. In contrast, Roberts, Tonnsen, et al. (2012) examined cardiac activity of 31 infants and toddlers with

FXS during the Toy Play task of the Laboratory Temperament Assessment Battery (Goldsmith & Rothbart, 1996). Developmental interactions were detected where dampened vagal tone emerged as a correlate of autism symptoms in toddlers older than two years of age, but not in younger infants. Elevated heart rate during Toy Play was linked with greater autism severity in children older than three years, but with reduced severity in infants less than a year old. In another study of infants with FXS (n = 12), Roberts, Hatton, Long, Annello, and Colombo (2012) found that shallower heart rate decelerations during the Toy Play task (thought to reflect reduced attention engagement) were marginally associated with autism symptom severity. Overall, these preliminary findings suggest a relationship between autism symptom severity and physiological activity in boys with FXS, although further investigation is needed to clarify developmental effects. Given the scant work including infants, we know little regarding the infant phenotype of FXS. Existing work suggests that nonlinear trajectories may be present, such as a shift from hypo- to hyper-responsivity (Baranek et al., 2008; Roberts et al., 2013; Roberts, Tonnsen, et al., 2012). It is clear that the phenotypic expression of neurodevelopmental disorders is not predetermined from birth, but rather emerges and transforms across the lifespan (Cornish, Roberts, & Scerif, 2012). Mechanistic foundations of behavior likely show developmental interactions as well, although we are just beginning to understand the nature of these complex trajectories.

Relationship between Social-emotional Skills and Cardiac Activity

A number of reports have detected correlations between cardiac activity and social-emotional abilities. Individuals with autism with higher baseline vagal tone show better parent-reported social skills (Neuhaus et al., 2014; Van Hecke et al., 2009), fewer problem behaviors (Van Hecke et al., 2009), increased acts of sharing during play-based assessment (Patriquin et al., 2013), and faster identification of facial emotions (Bal et al., 2010). Medium-to-large correlations (r's = .45–.58) have also been reported between heart rate (measured at rest and during a social role play task) and observed social skills in high-functioning adult males with autism (n = 16), although associations did not reach statistical significance (Smeekens et al., 2013).

Relationship between Communication and Cardiac Activity

Relationships have also been reported with communication, which is a skill that is inherently tied to the ability and motivation to engage socially (Chapman, 2000). First, Patriquin et al. (2013) found that children with elevated baseline heart rate demonstrated decreased use of communicative gestures. A positive relationship was also detected between baseline vagal tone and directly-assessed receptive language skills. In a subsequent study, Patriquin et al. (2013) replicated this finding using parent-report measures; parents of children with low baseline vagal tone were more likely to endorse receptive language delays and the absence of verbal language in their child with autism. Similar patterns were detected by Watson et al. (2010), who found that elevated vagal tone during a social context predicted later expressive language outcomes in 15 young children with autism. In a study of 40 school-aged boys with autism, Klusek, Martin, et al. (2013) did not replicate the finding of associated receptive/expressive language and vagal activity, although the change in heart rate in response to social stress was significantly associated with expressive language skill (with greater arousal reactivity corresponding to better language ability). Only one study has

examined associations between cardiac activity and language skills in FXS; Klusek, Martin, et al. (2013) found that less vagal change in response to a conversational task was correlated with poorer receptive and expressive vocabulary skills. Despite some inconsistencies across studies, evidence appears to support the interface between physiological regulation and structural language competence in autism and FXS, which is consistent with studies of typical development (e.g. Suess & Bornstein, 2000).

Beyond structural language, relationships have also been detected with broader social communication skills. In a prospective study of 15 young boys with autism, higher vagal tone during a social context (listening to child-directed speech) accounted for significant variance in parent-reported social communication adaptive skills at a one-year follow-up, even after accounting for receptive and expressive language skills (Watson et al., 2010). Interestingly, vagal tone measured during a nonsocial context (watching a nonsocial video) was not predictive of later social communication outcomes, a finding that was replicated by Klusek et al. (2013) in a study of 40 school-aged boys with autism. Klusek and colleagues found that, after accounting for receptive and expressive language skills, vagal tone specifically during social interaction (conversation with an examiner), but not at rest, predicted social communication ability in the boys with autism. As suggested by Watson and colleagues, children who can optimally regulate parasympathetic tone specifically during social contexts may be more able to make the physiological adjustments necessary to adapt to social demands. Over time, this may lead to increased social engagement, and, consistent with transactional theories of social learning, greater opportunities for social learning and, consequently, better social communication skills (Chapman, 2000; Dickinson & McCabe, 1991). These findings suggest that the cardiac measurement during social contexts may more sensitively index physiologically mediated social behaviors than the measurement during rest or other contexts. Similar findings have also been reported in typical development, where the language skills of preschoolers were specifically related to vagal tone during social interaction as opposed to baseline (Suess & Bornstein, 2000).

Although Klusek, Martin, et al. (2013) found vagal activity to be a significant predictor of social communication skills in boys with autism, they did not detect this association in a group of boys with FXS (n = 39). In fact, simple correlations revealed different patterns across syndrome groups, with heart rate reactivity corresponding with *better* social communication skills in autism and *poorer* skills in FXS. The authors speculated that differences in the baseline arousal of the groups (the boys with FXS were hyperaroused at baseline compared to typical peers, unlike the boys with autism) may have accounted for discrepant findings. In other words, while increased arousal may have assisted the boys with autism in meeting the demands of the conversational task, further increases in arousal may have hindered the performance of the boys with FXS, who were already hyperaroused prior to the initiation of the stressor (Klusek, Martin, et al., 2013). Again, this study and those reviewed above highlight the need to move beyond viewing arousal as a fixed trait to implement carefully designed experiments that can account for systematic change in arousal across experimental conditions. Arousal is not a static trait; without teasing apart environmental triggers that evoke relative change, we are limited in our understanding of the role of autonomic regulation in socially related behavior.

Relationship between Self-Stimulatory Behavior and Cardiac Activity

Aberrant self-stimulatory acts such as motor stereotypies and self-injurious behaviors have been hypothesized to function as regulatory mechanisms to assist in boosting or dampening arousal level to regulate internal physiological states (Edelson, 1984; Hutt & Hutt, 1965; Romanczyk & Matthews, 1998). For example, self-stimulatory behaviors may assist hyperaroused individuals in blocking out incoming environmental signals to avoid further increases in arousal, or may be used by underaroused individuals to increase external input and stimulate the physiological system. Despite decades of theoretical work, there are few scientific investigations on this topic and most existing work has been limited to descriptive case designs and visual data inspection methods. Thus, although relationships between arousal level and engagement in self-stimulatory behaviors have been reported, evidence is lacking to allow for strong claims to be made to inform clinical practice.

A number of observational studies have noted patterns of heart rate change that are temporally linked with self-stimulatory behaviors. For instance, an early report by Hutt, Forrest, and Richer (1975) observed decreased arousal following motor stereotypies during the play of nine children with autism. Dips in heart rate following self-injury were also detected by Barrera, Violo, and Graver (2007) in a study of two adult females with autism and one adult male with Cornelia de Lange syndrome; visual inspection of the data supported patterns of peak heart rate immediately preceding self-injury and decreased heart rate following self-injury across all three participants. Others have identified patterns of increased arousal following self-stimulatory behaviors. In a naturalistic study of three school-aged boys with autism, Lydon et al. (2013) found that the majority of self-injurious behaviors across participants were followed by heart rate elevation, with no clear arousal pattern immediately preceding the initiation of the behavior. Similarly, Freeman, Horner, and Reichle (1999) found that self-injurious behavior was followed by increased heart rate in a descriptive study of two adults with severe intellectual disabilities, and no clear arousal patterns immediately preceded the behavior. Inconsistent findings may reflect the fact that self-stimulatory behaviors can serve varying functions. Willemsen-Swinkels et al. (1998) found that occurrence of stereotypies was differentially linked with arousal patterns across moods (distress, elation, composure) in an investigation of 18 children with developmental disorders (including children with autism, attention deficit/hyperactivity disorder, and language delay). During periods of distress, stereotyped behaviors were immediately preceded by a peak in heart rate followed by decreased heart rate after engagement in the behavior; during elation stereotypies were followed by increased heart rate (Willemsen-Swinkels et al., 1998).

While the above reports suggest a link between self-stimulatory behaviors and arousal, most scientific evidence in this domain has been limited by a lack of experimental control over the variable of interest (i.e., self-stimulatory behavior) and reliance on visual inspection methods to identify patterns in the data. An innovative single subject study by Jennett, Hagopian, and Beaulieu (2011) experimentally manipulated the ability to engage in self-injurious behavior through the use of arm restraints in a 17-year-old female with autism. Removal of the arm restrains was associated with a replicable increase in heart rate, followed by high rates of self-injury. When restraints were re-applied, self-injury was not

possible and resting heart rate was re-established. While the manipulation of restraints in this study takes a novel first step towards experimentally controlling the occurrence of self-injurious behaviors, the restraints themselves are a confound as it is difficult to determine whether the observed changes in arousal were related to the process of being restrained as opposed to the presence or absence of self-injurious behaviors (particularly given that the participant's extensive history of self-imposed restraint behavior suggests a preference for this condition).

Assertions regarding sequential dependencies between arousal reactivity and the occurrence of self-injurious behavior could also be strengthened through statistical modeling, such as the sequential analyses employed in recent reports by Hoch and colleagues. Using a time lag sequential analysis, Hoch, Moore, McComas, and Symons (2010) did not detect statistically significant relationships between self-injurious behavior and arousal during an activity choice task, although a trend was found for increased self-injurious behavior during periods of high versus low arousal. In another report, Hoch, Symons, and Sng (2013) examined self-injurious behavior and heart activity in three children (two with autism and one with cerebral palsy). Sequential data analysis indicated that, after controlling for confounds related to movement, self-injurious behaviors were significantly more likely to occur following increases in heart rate in one child with autism, but were unrelated in the other child with autism. A correlation was detected between vagal tone and self-injurious behavior in the child with cerebral palsy, although sequential analysis did not support distinctive temporal patterns between the two variables.

In conclusion, preliminary evidence suggests a link between arousal and atypical self-stimulatory behaviors, although well-controlled studies utilizing statistical hypothesis testing and accounting for relevant confounds (e.g., the impact of physical exertion on arousal) are lacking in number. Further decomposition of behaviors in future research may also clarify relationships; in a recent single-case study of a boy with Prader-Willi syndrome, Hall, Hammond, and Hustyi (2013) found that skin picking behavior was reliably tied to elevated arousal only when it resulted in tissue damage. Given the popularity of clinical treatments that aim to reduce self-stimulatory behaviors by achieving an "arousal equilibrium", further scientific understanding of the interplay between arousal level and self-stimulatory behaviors is critical.

Relationship between Sensory Reactivity and Cardiac Activity

Some accounts of autism have focused on physiological hypo- and hyperarousal as an aberrant internal state that leads to inefficient processing of incoming sensory information in autism. For example, individuals who are physiologically hyperaroused may be less able to habituate to environmental stimuli, leading to impaired ability to interact with the environment (Hutt et al., 1964; Rogers & Ozonoff, 2005). In the same vein, hypoarousal may cause lethargy and reduced attention to the surrounding environment, thereby hindering capacity for learning through engagement with the external environment (Leekam, Nieto, Libby, Wing, & Gould, 2007; Schoen, Miller, Brett-Green, & Hepburn, 2008). Physiological dysregulation has also been conceptualized as a consequence, rather than a cause, of atypical sensory processing. In this framework individuals with autism are so inundated with

environmental signals that they are unable to efficiently process incoming stimuli, causing hyperarousal and subsequent disengagement from the environment (Helt et al., 2008).

While empirical research in this area is relatively limited, overall findings do not support a direct relationship between arousal level and behavioral indicators of sensory reactivity (i.e., atypical response to visual, tactile, auditory, olfactory, and gustatory information). In one large study, Schaaf et al. (2013) examined vagal activity of 59 children with autism and 30 typical controls in response to a variety of sensory stimuli, such as auditory, tactile, and olfactory signals. The vector of means across stimuli differed across the groups, with a flatter vector of mean scores in the autism group suggesting that these individuals demonstrated blunted autonomic change from one condition to the next. However, there was little evidence of atypical arousal level in response to the sensory conditions; the groups did not differ on vagal tone averaged across conditions and no differences were detected within individual conditions. Consistent with this finding, two smaller studies have also reported typical autonomic reactivity to sensory input. Woodard et al. (2012) exposed eight young children with autism to a series of potentially aversive sensory sensations (pungent odors, loud sounds, etc.) and did not find any relationship between hyper- or hyposensitive behavioral reactions and heart rate. In an investigation of responses to pleasant and unpleasant odors, Legiša, Messinger, Kermol, and Marlier (2013) found that although children with autism (n = 8) responded to olfactory information with different facial reactions, they did not differ from age matched typically developing children in autonomic responses (heart rate and skin conductance).

Similar conclusions can be drawn from preliminary work in FXS. Baranek and colleagues (2008) reported that neither heart rate nor vagal tone was a significant predictor of the hypo- and hyper-responsive sensory profiles of 12 young boys with FXS. Likewise, Roberts et al. (2013) did not detect a relationship between behavioral and physiological responses (measured with heart rate and vagal tone) in a study of auditory startle responses in 22 young boys with FXS. Overall, there is little compelling support for a relationship between atypical physiological response patterns and behavioral reactivity to sensory stimuli, although additional work including larger samples and incorporating idiosyncratic sensory sensitivities is needed.

Relationship between Anxiety and Cardiac Activity

Anxiety is frequently reported in autism and FXS (Cordeiro, Ballinger, Hagerman, & Hessl, 2011; Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998) and presumably underpins atypical behaviors in these conditions. Studies of both autism and FXS have explored the hypothesis that anxiety is rooted in abnormal arousal regulation. To date, strong associations between cardiac activity and anxiety have not been supported in these populations, although research in this area has been limited by small samples. Reports also vary in characterization of anxiety, with some focusing on generalized or “trait” anxiety and others focusing on “state” anxiety, or the stimulus-bound perception of anxiety.

Those studies focusing on state anxiety have generally found incongruent relationships between the participant-reported appraisal of stress and cardiac indicators. For instance, Kushki et al. (2013) measured the perceived anxiety of children with autism (n =12) and

typically developing children before and after completing a Stroop task. Heart rate was elevated in the children with autism despite similar levels of self-reported anxiety across groups, suggesting that the physiological and subjective experiences of anxiety were not closely coupled. Similarly, Jansen et al. (2006) found that high-functioning adults with autism (n = 10) showed significantly blunted heart rate change in response to a public speaking task compared to typical controls, despite similar subjective ratings of stress across the groups. Additional research is needed, although this emerging literature is not inconsistent with studies of anxiety disorders that demonstrate that the perception of anxiety is not reliably tied to arousal (Anderson & Hope, 2009; Hoehn-Saric & McLeod, 2000; Kelly, Brown, & Shaffer, 1970; McLeod, Hoehn-Saric, Zimmerli, de Souza, & Oliver, 1990; Tyrer & Alexander, 1980). Future research might also better control for the possibility that the individuals studied did not experience situational anxiety in response to the investigator-identified “stressors”. In a single-subject study of three children with autism, Moskowitz et al. (2013) examined cardiac responses to anxiety-provoking contexts that were idiosyncratic to that child per parental report (e.g., singing happy birthday, making left turns in the car). In the idiosyncratic high-anxiety contexts the children exhibited significant behavioral evidence of anxiety, accompanied by elevated heart rate and reduced vagal tone, supporting a physiological component of the anxiety response.

Other investigations have examined trait anxiety in relation to cardiac functioning. Self-reported anxiety among adults with autism was not associated with heart rate or vagal tone in reports by Mathewson et al. (2011) and Smeekens et al. (2013). Guy et al. (2014) also found that parent-reported anxiety in children with autism (n =14) was not significantly related to baseline heart rate or vagal tone. Two investigations have examined relationships between cardiac activity and parent-reported anxiety on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000). Klusek et al. (2013) did not detect significant associations between the DSM-IV-oriented anxiety scale of the CBCL and heart rate or vagal tone (measured at baseline and during conversation) in either boys with autism (n = 32) or boys with FXS (n = 26). In contrast, Neuhaus et al. (2014) did find a significant association between the baseline vagal tone of 18 boys with autism and the anxious/depressed syndrome subscale of the CBCL (r = −.36). However, it is unclear whether this association may have been driven by symptoms of depression that are encompassed in this CBCL subscale, rather than symptoms of anxiety (a strong association between baseline vagal tone and withdrawn/depressed symptoms was also detected in this sample, r = −.53). Associations with the DSM-IV-oriented anxiety scale, which corresponds to anxiety symptoms as described by the DSM-IV, were not examined in this study (Neuhaus et al., 2014).

An informative investigation by Hollocks et al. (2014) examined cardiac responses to the Trier Social Stress Test (Kirschbaum et al., 1993) in typically developing children (n = 23), children with autism without anxiety (n = 20), and children with autism with a comorbid anxiety disorder (n = 32). Blunted heart rate reactivity in response to the public performance task was detected in both autism groups, regardless of the presence of co-occurring anxiety. Interestingly, significant associations between heart rate reactivity and anxiety symptoms were only observed in the subgroup of children who had comorbid anxiety, with greater

physiological reactivity corresponding to lower trait anxiety. Additionally, the children with autism and comorbid anxiety exhibited significantly lower heart rate prior to the stressor than did the children with autism without anxiety and the controls. While at first glance it may seem counter-intuitive that *lower* arousal level and arousal reactivity was observed in children with autism who had co-occurring anxiety, evidence from the study of other vulnerable populations supports blunted physiological responses among individuals who experience chronic stress (Gunnar & Vazquez, 2001). For example, chronic stress in mothers of children with disabilities is associated with lower levels of the stress hormone cortisol upon awakening and blunted cortisol reactivity to daily stressors (Hartley et al., 2012; Seltzer et al., 2012; Wong et al., 2012). Similar patterns of blunted cortisol reactivity are observed in other traumatized or chronically stressed groups, such as paramedics, prisoners of war, parents of children with terminal illnesses, and individuals suffering from chronic pain disorders (see Heim, Ehlert, & Hellhammer, 2000). While this phenomenon has not been investigated in relation to cardiac indicators, it is possible that the autonomic system may also respond to chronic stress with patterns of blunted reactivity.

This research highlights the complexity of adaptive physiological response systems, which interact with multiple endogenous and exogenous factors in a manner that is not completely understood. Moving forward, thoughtful skepticism is needed to avoid applying overly simplistic models to account for the complex interplay between arousal and anxiety. Although it is reasonable to expect heart rate elevation and vagal withdrawal under challenging conditions (including anxiety-provoking conditions), it may be that the anxiety hypothesis is too narrow a framework to account for how disruption in the physiological system creates vulnerability to social impairment. The anxiety/hyperarousal hypothesis emphasizes immediate, stimulus-bound responses of the physiological system and largely ignores the role of cardiac regulation as a broader indicator of psychobiological health. The evidence reviewed above better supports cardiac physiological activity in autism and FXS as an index of general adaptive capacity, as opposed to a measure of stimulus-bound reactive behavior. For example, vagal activity has been fairly consistently linked to broad social-developmental outcomes such as communication ability or social skills (e.g., Klusek et al., 2013; Patriquin et al., 2013; Watson et al., 2010; Van Heck et al., 2009) while associations with task-dependent behavioral responses, such as gaze avoidance, have been less consistently detected (e.g., Hall et al., 2009).

Relationship between Attention and Cardiac Activity

Aberrant attentional profiles are a hallmark feature of autism, with atypical gaze fixation and disengagement latency presenting in the first months of life (Merin, Young, Ozonoff, & Rogers, 2007; Zwaigenbaum et al., 2005). Attentional problems, including marked behavioral features of hyperactivity and impulsivity, are a prominent feature of FXS (Cornish et al., 2004). Attention also has a well-documented relationship with cardiac indicators. Disengaging attention from one stimulus to re-focus on another stimulus (i.e., “orienting”) is accompanied by a transitory decrease in heart rate reflecting attention engagement (Graham & Clifton, 1966; Suess, Porges, & Plude, 1994; Weber, van der Molen, & Molenaar, 1994). In contrast with the studies of heart rate reviewed above, which measured heart rate in conditions lasting several minutes (reflecting general arousal level),

the orienting response is accompanied by a brief (i.e., lasting only seconds) deceleration in heart rate that specifically taps attentional focus (Turpin, Schaefer, & Boucsein, 1999).

There is some support for dampened cardiac orienting to social stimuli in autism, potentially reflecting reduced attentional focus on salient social signals. Corona and colleagues (1998) found that children with autism (n = 22) showed shallower heart rate deceleration (reflecting substandard engagement of attention) than mental, language, and age matched children with developmental delays in response to an examiner feigning pain. Consistent with the physiological findings, behavioral data showed that the children with autism took longer to look at the examiner and looked for a shorter duration. In contrast, three recent studies of adults with autism did not detect atypical orienting to inanimate social stimuli. Louwerse, Tulen et al. (2013) found that adolescents with autism (n = 37) and typical controls both showed heart rate deceleration to unpleasant pictures, regardless of the social content of the pictures. Similarly, Mathersul and colleagues reported similar physiological orienting responses in high-functioning adults with autism and typical controls while viewing a series of faces exhibiting varying degrees of trustworthiness (Mathersul, McDonald, & Rushby, 2013b) and unpleasant and pleasant social images (Mathersul, McDonald, & Rushby, 2013a). Cardiac orienting has not been examined extensively in FXS, although a report by Roberts, Hatton et al. (2012) detected shallower heart rate decelerations (reflecting suboptimal attention) in infant males with FXS (n = 12) compared with age matched typically developing boys in response to auditory stimuli. A trend-level association was detected between cardiac responses and the severity of autism symptoms, suggesting that infants with FXS who are the least physiologically reactive to the environment exhibited the most autism symptoms. Further study of heart-defined attention in autism and FXS may be useful for understanding the potential role of aberrant attention in core impairments of these disorders. For instance, verbal perseveration is a prominent feature of the FXS communication phenotype (Martin et al., 2012), and emotional regulation strategies such as perseverative thinking have been linked with difficulties with attention disengagement (Koster, De Lissnyder, Derakshan, & De Raedt, 2011).

Relationship between *FMR1*-Related Genetic Variation and Cardiac Activity

The protein encoded by *FMR1*, FMRP, is needed for the modification and elimination of synaptic structures; in its absence neural plasticity is affected, disrupting normal brain development and functioning (Reiss & Dant, 2003; Schneider et al., 2009). As reviewed above, FMRP has a broad impact on neural pathways that influence cognitive and emotional development and deficiency in this protein is associated with social withdrawal, anxiety/depression, social adaptive impairment, and language delay in FXS (Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Hessl et al., 2001). Understanding the impact of FMRP deficiency (and more generally, the impact of the *FMR1* mutation) on physiological arousal could help map *FMR1*-related molecular effects to broader autonomic nervous system functioning, thereby informing links between genetic etiology, mediating biological processes, and eventual behavioral endpoints. While it is unclear what neural mechanisms regulate cardiac vagal tone, involvement of several cortical regions has been suggested, including the amygdala, prefrontal cortex, and hypothalamus (see Thayer et al., 2012). Some of these regions, such as the amygdala, have also been implicated in FXS (Gothelf et al.,

2008; Hazlett et al., 2009), which might suggest a link between FMRP's role as a critical protein involved in brain development and physiological dysregulation. Given the limited empirical evidence in this area, it remains unclear whether FMRP contributes to cardiac regulation. Two studies (Hall et al., 2009 and Roberts et al., 2001) did not detect associations between arousal and FMRP levels in boys with FXS (although neither study employed quantitative measurement of actual FMRP levels, instead relying on earlier assays that count the number of cells producing FMRP). The range of FMRP was also restricted in both the Hall et al. and Roberts et al. samples, which may have limited statistical power. When examining females with FXS, who show a wider range of FMRP owing to their second unaffected X chromosome, Hall et al. (2009) found that higher (i.e., more normal) FMRP levels predicted heart rate variability patterns that were the most similar to that of controls. It is also possible that physiological dysregulation in FXS is related to *FMR1*-associated molecular variants other than the direct expression of FMRP, such as activation ratio, mRNA, or CGG repeat length. Such associations could be fruitfully explored through basic science approaches capable of more directly addressing how autonomic function may be affected by *FMR1* gene dysfunction.

Cardiac Autonomic Functioning in Other Neurodevelopmental Disorders Associated with Autism

Delineating mechanistic overlap across genetic disorders may increase power to identify symptoms of common pathophysiological origin and develop targeted treatments for those symptoms (Levy & Ebstein, 2009). The study of autonomic regulation in other neurodevelopmental disorders is a promising avenue for future study, as delineating the effects of specific genetic disorders on autonomic functioning may lend insight into genetic and brain bases of physiological arousal systems. Relatively little research has been conducted on cardiac regulation in neurodevelopmental disorders other than autism and FXS, with most existing research focused on the role of cardiac activity in syndrome-specific physical health issues, such as sudden cardiac death in Rett syndrome or obesity in Prader-Willi syndrome. This research is nonetheless informative in considering future directions in the field. Below, we consider cardiac functioning in other genetically-based neurodevelopmental disorders associated with increased risk for autism: Williams syndrome, Down syndrome, Prader-Willi syndrome, and Rett syndrome.

Cardiac Activity in Williams Syndrome

Williams syndrome is a neurodevelopmental disability affecting approximately 1 in 20,000, caused by deletions on chromosome 7 (Donnai & Karmiloff-Smith, 2000). Williams syndrome is of particular relevance in this review because, in contrast to autism, individuals with Williams syndrome show a distinctive profile of increased social drive. However, despite their hypersociability, children with Williams syndrome struggle with social interaction and about 50% meet diagnostic criteria for autism spectrum disorder (Klein-Tasman, Mervis, Lord, & Phillips, 2007). Although only two investigations have examined cardiac functioning in Williams syndrome, these reports nonetheless provide insights into the coupling of cardiac orienting responses and distinctive social phenotypes. Considering the increased social appetitive in Williams syndrome, Plesa Skwerer et al. (2009) tested the

hypothesis that heightened social interest in Williams syndrome would be reflected in heightened cardiac orienting responses to emotional faces. In line with this hypothesis, findings revealed greater cardiac deceleration in response to emotional faces in Williams syndrome (reflecting increased attentional engagement), compared to groups of age matched typically developing individuals and age, IQ, and language matched individuals with developmental disabilities. Interestingly, the heightened physiological responses of the individuals with Williams syndrome were not accompanied by improved social-cognitive performance; despite physiological evidence of augmented attention to the emotional faces, the individuals with Williams syndrome did not demonstrate improved emotional recognition. Jarvinen et al. (2012) also examined cardiac responses to emotionally valenced social and nonsocial stimuli in Williams syndrome (n = 22) and typical development. In contrast with the findings of Plesa Skwerer and colleagues, results indicated that the individuals with Williams syndrome *increased* heart rate in response to faces whereas the controls showed cardiac deceleration consistent with attentional orienting. However, it is notable that the stimuli were presented for five seconds, with heart activity measured at a latency of seven seconds following each presentation. Given that cardiac reactivity is immediate, with less than a one second lapse between stimulus and response, these findings are questionable and suggest that the cardiac index reflected response to the inter-trial-interval as opposed to reactivity to the social stimuli themselves, thus accounting for the discrepant findings.

Evidence from Williams syndrome provides further evidence of potential disassociations between implicit measures of autonomic social processing and corresponding social-cognitive phenotypes. However, neither of the existing Williams studies included autism or autism symptoms as variables, limiting study comparisons. However, like the Plesa Skwerer et al. (2008) study, findings from autism have shown that attentional engagement to social information, as indexed by cardiac orienting, may not precisely map onto social-cognitive behaviors. As reviewed above, atypical cardiac orienting to social stimuli has generally not been detected in autism, despite the hypothesis that individuals with autism demonstrate decreased social interest (e.g., Louwerse et al., 2013; Mathersul et al., 2013a, 2013b). Given the potential disconnect between complex autonomic and behavioral indices, psychophysiological methods may provide unique insights into neural substrates underlying behavioral output, illuminating patterns of biobehavioral organization.

Cardiac Activity in Down Syndrome

Down syndrome is present 1 in 971 live births (Shin et al., 2009) and is most commonly caused by an extra copy of chromosome 21 (Trisomy 21). Down syndrome is the leading genetic form of intellectual disability and the prevalence of autism within Down syndrome is substantially higher than in the general population; about 18% of individuals with Down syndrome meet criteria for autism spectrum disorder (DiGuiseppi et al., 2010). Cardiac activity in Down syndrome has been examined fairly extensively from a medical perspective, with the bulk of this research focusing on autonomic dysfunction as a potential cause of elevated cardiovascular morbidity and mortality in this population (e.g., Esbensen, Bishop, Seltzer, Greenberg, & Taylor, 2010). This work shows that individuals with Down syndrome have reduced vagal and heart rate reactivity in response to standard medical tests

designed to incite sympathetic activity, such as isometric hand group (Fernhall & Otterstetter, 2003; Figueroa et al., 2005), passive upright tilt (Agiovlasitis et al., 2010; Fernhall et al., 2005), and cold pressure testing (Fernhall & Otterstetter, 2003). Cardiorespiratory incompetence is also seen in Down syndrome, characterized by low peak heart rate during exercise (Baynard, Pitetti, Guerra, & Fernhall, 2004; Fernhall et al., 2001; Guerra, Llorens, & Fernhall, 2003) and delayed heart rate recovery following exercise (Figueroa et al., 2005; Mendonca & Pereira, 2010). While chronotropic incompetence (i.e., the failure to increase heart rate in a manner that is commensurate with increased physical activity) is a well-replicated feature of Down syndrome, the cause of this attenuated responsiveness is an area of active investigation. Because vagal control during the transition from rest to exercise is normal in Down syndrome, scientists have speculated that low peak heart rate during exercise cannot be accounted for by blunted vagal withdrawal alone (i.e., Baynard et al., 2004; Mendonca, Pereira, & Fernhall, 2011). Poor production of catecholamines (stress hormones produced by the adrenal system) has been suggested as a contributor of reduced heart rate responsiveness during exercise, consistent with direct evidence of reduced circulating catecholamines in individuals with Down syndrome during physical activity (Bricout et al., 2008; Fernhall et al., 2009). Therefore, it is possible that atypical cardiac responses in Down syndrome originate in the dysregulation of other interacting stress circuits rather than in dysfunction of the autonomic system itself. Given that cardiovascular risk is not elevated in autism or FXS, the quantification of cardiac activity during exercise has not been a research focus in these conditions. Nonetheless, findings from Down syndrome highlight the dynamic and complex biological systems involved in coordinated stress responses including affective, cognitive, and biological components (see *Beyond the Autonomic Nervous System: Integrating Evidence across Multiple Systems* for further discussion).

In contrast to exercise and other physical sympathoexcitatory tasks, there is inconsistent support for autonomic dysfunction in Down syndrome at rest. Evidence generally supports similar resting heart rate in Down syndrome compared to typical controls (Agiovlasitis et al., 2010; Iellamo et al., 2005; Mendonca et al., 2011) and individuals with other intellectual disabilities (Baynard et al., 2004). A number of reports have also documented normal baseline parasympathetic activity in Down syndrome using spectral analyses of high frequency power to index vagal tone (Agiovlasitis et al., 2010; Figueroa et al., 2005; Goulopoulou et al., 2006). Abnormally elevated resting vagal tone has been reported by Baynard et al. (2004), although differences did not persist when high frequency power was expressed in normalized units. When juxtaposing findings from Down syndrome to those in FXS, it is evident that the *profile* of autonomic dysregulation across neurodevelopmental disabilities is not universal-- FXS is characterized by chronically elevated arousal and diminished parasympathetic tone, whereas autonomic dysfunction in Down syndrome appears to be specific to blunted responsivity to physical sympathoexcitatory tasks, with limited evidence of persistent under- or overarousal. There have been no studies specifically investigating cardiac responsivity to cognitive or affective tasks in Down syndrome and no work examining the intersection of autism to autonomic responding.

Cardiac Activity in Prader-Willi Syndrome

Prader-Willi syndrome, a genetic condition caused by atypical gene expression of the q11-q13 region of chromosome 15, affects approximately 1 in 25,000 individuals (Smith et al., 2003). About 40% of individuals with Prader-Willi syndrome meet criteria for autism spectrum disorder (Veltman, Craig, & Bolton, 2005). Because Prader-Willi syndrome is the most common genetic form of obesity, it has been used as a model to explore autonomic contributions to weight and metabolic problems. For example, Purtell et al. (2013) examined cardiac activity before and after eating a meal to determine whether impaired autonomic responsiveness contributes to excessive appetite in Prader-Willi syndrome. The heart rate and vagal estimates of adults with Prader-Willi syndrome (n = 10) did not differ from those of obese and lean controls matched on age, gender, and BMI, although low frequency spectral power (an index of sympathetic activity) was reduced, possibly suggesting an impaired sympathetic meal response in Prader-Willi syndrome (Purtell et al., 2013). Others have examined cardiac responses to exercise as a potential contributor to obesity in the syndrome, with conflicting results. In a study of eight children with Prader-Willi syndrome, Castner, Pham, Judelson, and Rubin (2014) found slower heart rate recovery following exercise when compared with both lean and obese controls, possibly suggesting poorer cardiovascular fitness in children with Prader-Willi syndrome. However, in an investigation of 28 individuals with Prader-Willi syndrome and 26 control participants matched on age, gender and body mass index, Wade, De Meersman, Angulo, Lieberman, and Downey (2000) did not detect group differences in heart rate or vagal modulation across a number of physical conditions, which included supine resting, sitting, moderate exercise, and recovery.

Evidence regarding baseline autonomic activity in the disorder is similarly conflicting. While the findings of Wade et al. (2000) suggest normal resting vagal tone in Prader-Willi syndrome, a report by DiMario, Bauer, Volpe, and Cassidy (1996) found the resting vagal tone of 14 individuals with Prader-Willi syndrome to be lower than age and gender matched controls, even after controlling for BMI. Overall, existing research on Prader-Willi syndrome is difficult to interpret given limitations that are common to much developmental disabilities research; small samples, wide age ranges within those samples, and limited replication make it difficult to draw strong conclusions. Autonomic regulation in Prader-Willi syndrome has not yet been examined in relation to cognitive or affective domains, including autism features, which may be a fruitful avenue for future work.

Cardiac Activity in Rett syndrome

Rett syndrome is an X-linked neurodevelopmental condition most commonly caused by mutations in *Methyl-CpG-binding Protein 2* (*MECP2*). The syndrome is relatively rare, affecting approximately 1 in 10,000 females (Leonard, Bower, & English, 1996). Autistic features are a core part of the Rett syndrome phenotype. Life expectancy is reduced in Rett syndrome, with higher rates of sudden death that are thought to be related to cardiac instability (Guideri, Acampa, Hayek, Zappella, & Di Perri, 1999). Research on Rett syndrome fairly consistently points towards autonomic dysfunction. At rest, females with Rett syndrome show significantly lower vagal tone than healthy age matched females (Guideri, Acampa, DiPerri, Zappella, & Hayek, 2001; Guideri et al., 1999; Julu, Kerr, Hansen, Apartopoulos, & Jamal, 1996; Julu et al., 2001). Parasympathetic activity is also

atypically withdrawn at the height of sympathetic activity (such as during hyperventilation), which is consistent with sympathovagal imbalance and may increase risk for cardiac arrhythmia and sudden cardiac death (Julu et al., 1996). Some have also reported elevated heart rate in girls with Rett syndrome during daytime activities (Weese-Mayer et al., 2006), sleep (Weese-Mayer et al., 2008), and at rest (Guideri et al., 2001), although elevated heart rate has not been consistently detected (e.g., Julu et al., 2001).

Summary of Findings and Key Considerations for Future Research

Findings reviewed here suggest physiological dysfunction may be common to both autism and FXS. This is evidenced by overall patterns of hyperarousal (i.e., faster heart rate) and dampened parasympathetic vagal tone that are well documented in FXS and seen in at least a subset of individuals with autism. Across both disorders, there is emerging support for chronic autonomic imbalance that is consistent across both baseline and stressor conditions and are not task-dependent. Consistent with a large body of research supporting a link between autonomic regulation and social behaviors in typical development, this growing evidence indicates that a number of socially-mediated behaviors in autism and FXS are linked with physiological dysregulation, such as social communication, receptive and expressive language, gesture use, and general social ability. This evidence contributes to understanding of the process by which underlying biological processes contribute to complex behaviors in autism and FXS.

Importantly, evidence for overlapping autonomic profiles in autism and FXS is key to understanding how biological pathways may be common across etiologic subgroups of autism, and may be linked with behavioral and genetic variation associated with the *FMR1* gene. Evidence reviewed here is broadly suggestive of shared physiological mechanisms in FXS and autism (or at least in a subgroup of individuals with autism). To date, few cross-population studies have directly compared cardiac indicators of physiology in autism and FXS. In one recent report of this, Klusek et al. (2013) found no differences in the heart activity and vagal estimates of boys with autism and boys with FXS, suggesting that physiological mechanisms that are disrupted in FXS may also be common to idiopathic autism. Even if only evident in a subgroup of individuals with autism (who are perhaps more etiologically homogeneous), evidence of physiological overlap in autism and FXS will provide a clear roadmap for investigations of causes of autism and the dissection of heterogeneity within idiopathic autism. Autism, while constituting a single clinical disorder, is understood to have origins in a collection of common and rare variants with varying effect sizes that interact with each other and with environmental factors, such that the phenotypic presentation of autism may stem from an entirely different set of risk alleles across individuals (Geschwind, 2011). This significant etiologic heterogeneity hampers efforts to identify reliable and valid biological markers for autism (Bill & Geschwind, 2009). FXS, a disorder showing considerable overlap with autism that can be traced back to a mutation in a single gene (*FMR1*), can help reduce “genetic noise” in the study of autism and may assist in the identification of biological pathways that lead to common phenotypic endpoints. Specifically, the delineation of physiological profiles common to autism and FXS may lend insight into mechanistic underpinnings of behavior in both typical and atypical development, and how these features may be linked back to the neurobiological pathways associated with

FMR1. Evidence reviewed here suggests that autonomic dysregulation is an excellent candidate for such study, which may help uncover key systems that could be amenable to pharmaceutical or behavioral interventions.

Methodological Considerations

Critical evaluation of experimental conditions, the replicability of those conditions, and constructs being measured will be key to clarifying inconsistencies in the literature. First, cognitive versus social demands must be accurately characterized, as they may tax different neural systems. The use of standardized, replicable protocols that have been studied extensively in typical development, such as the Laboratory Temperament Assessment Battery (Goldsmith & Rothbart, 1996) or the Trier Social Stress Test (Kirschbaum et al., 1993) may help separate complex condition and cohort effects.

In the same vein, caution is warranted when applying biophysiological explanations that may be overly simplistic. While heart activity is sometimes cited as a more direct, "objective" measure, in reality, cardiac activity is as complex and multidimensional as are psychological constructs such as anxiety (Symons & Roberts, 2013). Careful consideration is needed when inferring the emotional significance of a given experimental condition, particularly given the idiosyncratic responses seen in individuals with autism. For example, it may be misguided to assume that physiological response to a particular stimulus reflects "anxiety" without confirming this assumption with behavioral indicators. It is evident from the unexpected responses detected by Jansen et al. (2003) and Toichi and Kamio (2003) that examiner identified "stressor" tasks may not, in fact, be stressful for individuals with neurodevelopmental disabilities. Underscoring this point, Groden et al. (2005) found that only one of ten individuals with autism increased arousal in response to the investigator-identified "unpleasant event" (the introduction of an unfamiliar staff person), whereas the "relaxing activity" (sitting alone with unstructured time) elicited significant increases in heart rate for 50% of the participants. Concurrent measurement of behavior and physiology can bolster confidence that a given stressor does, in fact, elicit the expected emotional or cognitive reaction. Moving forward, critical evaluation of what heart activity represents given the confines of the experimental context can only advance the translational use of this biomarker in psychological research.

Another critical methodological hurdle is the conceptual interpretation of the data. "Adaptive" cardiac responses are not universal, but depend on the properties of the task and the individual's physiological state prior to exposure. In this regard, the inclusion of a comparison group is critical to determine what is "normal" given the parameters of the experiment. Consideration of baseline arousal is also key, as adaptive response patterns may differ across individuals who are under-, over-, or optimally aroused at baseline. For example, Klusek, Martin, et al. (2013; reviewed in detail above) found that increased heart rate was associated with better social communication outcomes in boys with autism, whereas increased heart rate was maladaptive and linked with poorer performance among boys with FXS, who were hyperaroused at baseline. This finding illustrates the complexity of physiological responses and the expertise needed to infer what is "adaptive" for a particular individual within a given context.

Finally, consideration of the behavioral and biological impact of psychotropic medication use is needed, given its well-documented effect on cardiovascular activity (e.g., O'Brien & Oyebode, 2003; Rechlin, 1995; Silke et al., 2002). Group differences in baseline cardiac indices were not detected between medicated (n = 70) and unmedicated (n = 82) children with autism by Daluwatte et al. (2013). In an investigation of 50 boys and girls with FXS, Hall et al. (2009) also did not detect medication effects. Differences between those on and off medication have been reported by Mathewson et al. (2011), who found that only medicated children with autism demonstrated lower vagal tone than controls. However, this study was limited by small samples in the medicated (n = 8) and unmedicated (n = 7) subgroups, and was likely underpowered. Strong evidence concerning medication effects comes from Roberts et al. (2011), who conducted a treatment study of stimulant medication use in 10 boys with FXS. Physiological arousal was assessed at baseline and during academic testing on consecutive days, on and off stimulant medications. The mean heart rate and vagal tone of the boys did not differ across the days in either condition, although more significant arousal reactivity (the change in heart rate from baseline to the academic testing context) was observed when the boys were on medication. Behaviorally, the boys were more attentive while on medication and obtained higher scores on the academic assessment. This finding suggests that stimulant medication ameliorated blunted arousal regulation patterns that have been documented in FXS (e.g., Roberts et al. 2001), and was related to improved attention and academic performance.

Regardless of whether medication use has a meaningful impact on the cardiac activity of individuals with autism and FXS, the inconsistent handling of this confound across studies obscures findings and prevents replication. For example, excluding individuals who use medications (a common conservative approach) likely limits samples to only mildly affected individuals (i.e., those who do not need pharmaceutical intervention), who may show more typical autonomic responses. Additionally, this broad exclusionary criteria drastically reduces generalizability; approximately 55% of children with autism and 75% of individuals with FXS use psychotropic medications (Mandell et al., 2008; Morgan, Roy, & Chance, 2003; Valdovinos, Parsa, & Alexander, 2009). Furthermore, all patterns of physiological arousal, whether they are organic or pharmacologically induced, are likely to have functional effects on other systems and behaviors and therefore should be captured. The use of statistical techniques to control for medication use may improve external validity while controlling for this potential confound.

Developmental Considerations

Age effects—Thus far, most studies of physiological activity in autism and FXS have been limited to investigation of a single point in time, with little ability to infer developmental patterns or prospective features that might predict later impairment. Longitudinal studies are needed to fully understand autonomic profiles across development, a point that is underscored by recent evidence supporting developmental interactions in the relationship between vagal tone and the emergence of autism symptoms (with vagal activity not emerging as a correlate of autism until toddlerhood; Roberts, Tonnsen, et al., 2012). Further, two recent reports support the possibility of FXS-specific physiological trajectories. First, Heilman et al. (2011) found atypical patterns of age-related vagal decrease in a cross-

sectional sample of children and young adults with FXS (in typical development vagal tone increases with age; Alkon et al., 2003; Bar-Haim et al., 2000; Longin et al., 2006; Porges et al., 1994; Sahni et al., 2000). Second, Roberts et al. (2013) found that cardiac reactivity to auditory startle in young males with FXS (n = 27; age range 1–10 years) became more exaggerated with age, whereas age matched typical controls showed a nonsignificant trend for dampened reactivity over time. Further research is needed to determine how physiological regulation evolves over the lifespan and how the precise timing of physiological events may interact with other systems, such as behavioral, biological, environmental, cognitive, and affective processes. To date, no longitudinal studies of cardiac activity in autism have been conducted, and as a consequence the developmental emergence of physiological disturbance remains unspecified. Developmental effects may account for inconsistencies across findings, and would not be unexpected considering documented age effects on other biological substrates (e.g., brain volume; Aylward, Minshew, Field, Sparks, & Singh, 2002). Importantly, emerging evidence from longitudinal investigations of FXS supports a developmental shift in arousal that interacts with behavioral outcomes (e.g., Roberts, Hatton, et al., 2012; Roberts et al., 2013). Complementary longitudinal studies of autism are needed to evaluate possible divergences and similarities across development, within individuals, and across populations to further evaluate the significance of physiological regulation in the symptoms of these different disorders, including possible overlap.

Cognitive effects—While the relationship between cardiac activity and cognitive skills in autism and FXS has not been examined comprehensively, evidence from a number of reports does not support an unambiguous relationship between the two variables. For example, in a sample of 61 children with autism, Porges et al. (2013) did not find any association between IQ and heart rate but did detect a weak trend-level association between IQ and baseline vagal tone (r = .23, p = .074). Others have also failed to detect relationships between IQ and cardiac indices in smaller samples of children with autism (n's ranging from 18–30, Hollocks et al., 2014; Neuhaus et al., 2014; Van Hecke et al., 2009). Consistent with these findings, children with autism with high IQ (n = 78) and low IQ (n = 44) do not differ in heart rate or vagal tone estimates (Daluwatte et al., 2013). Only weak, nonsignificant correlations between mental age and heart activity (r = .10; Roberts, Tonnsen et al., 2012) and mental age and heart rate reactivity (r = .21; Roberts et al., 2013) have been reported in FXS.

Focused research is needed to more thoroughly examine the potential influence of cognition, however, it seems unlikely that autonomic dysfunction in autism and FXS presents solely as a consequence of intellectual impairment. First, autonomic imbalance is seen in high-functioning individuals with autism who have normal intelligence (Bal et al., 2010; Kushki et al., 2013; Neuhaus et al., 2014; Porges et al., 2013). Second, autonomic dysfunction is characteristic in a number of other disorders not traditionally associated with intellectual impairment, such as alcoholism (Ingjaldsson, Laberg, & Thayer, 2003) and depression (Kemp et al., 2010). Third, evidence does not support a universal *profile* of autonomic dysregulation across intellectual disabilities. For example, FXS is characterized by chronic patterns of hyperarousal and diminished parasympathetic tone, whereas autonomic

dysfunction in Down syndrome is most apparent in response to physical exercise, with limited evidence for persistent hyperarousal or diminished parasympathetic tone. Indeed, an abstract by Klusek, Losh et al. (2013) documented significantly *elevated* vagal tone and *reduced* heart rate at baseline in boys with Down syndrome in comparison to boys with FXS. This emerging evidence suggests that patterns of autonomic regulation may differ across genetic forms of intellectual impairment. Altogether, intellectual disability does not appear to be the driving factor in producing the autonomic profiles of autism or FXS, although more focused investigation of this relationship would be informative.

Comparison groups—Particularly in the study of physiology, the inclusion of a control group is essential in differentiating typical and atypical responses within a given experimental context. Comparison groups are of particular importance, and challenge, in the study of neurodevelopmental disabilities, where cognitive ability lags behind chronological-age-based expectations (e.g., Hodapp & Dykens, 2001). In the study of individuals with intellectual disabilities, chronological age matching with typically developing individuals results in a mismatch in other relevant developmental areas, such as intellectual level. Alternatively, the inclusion of younger, mental age matched typically developing controls may help avoid mismatch on relevant cognitive domains, although this approach introduces disparity in the age-related physical maturation of the groups (which is known to influence cardiac output). Mental and chronological age matching can be achieved together with the inclusion of intellectual disability comparison groups, although this approach is not without limitations as other genetic groups are often associated with their own unique phenotypic signatures. For instance, other neurodevelopmental groups, such as Down syndrome and Prader-Willi syndrome, may also be associated with a distinctive physiological profile (see discussion in *Cardiac Functioning in Other Neurodevelopmental Disorders*, above). Thus, conclusions for cross-syndrome comparisons must be tempered by profiles potentially unique to groups. The question of comparison group is a problem inherent to all research aimed at defining syndrome-specific profiles, as features may be unique to a given etiologic group, shared across several groups, or common across all neurodevelopmental disorders (Hodapp, 1997). The importance of a relevant reference group is more pronounced in psychophysiological research given the absence of standardized reference points available for many behavioral measures. Until the interface between intellectual level and autonomic dysfunction is better understood, a multiple comparison approach, incorporating both mental and chronological age-matches, is necessary to separate developmental influences from the specific effects of autism or FXS.

Accounting for Heterogeneity

Although atypical patterns of physiological arousal have been documented in some individuals with autism, findings are inconsistent, particularly with regard to static heart rate and vagal estimates. In some respects, this inconsistency is not surprising given the significant clinical and etiologic heterogeneity in autism (Betancur, 2011; Geschwind & Levitt, 2007). Considering the wide variation in the clinical presentation of the disorder, variable findings in autonomic response patterns in autism are not necessarily unexpected. Some studies have addressed heterogeneity through the investigation of clinically defined subgroups of autism, which might be more likely to share underlying physiological features.

For example, individuals with autism who show attention deficits (Althaus et al., 1999), and symptoms of general autonomic dysfunction (Ming et al., 2005) have greater impairment in parasympathetic vagal control than those who do not share these symptoms. The delineation of physiological profiles among clinical subgroups of autism may eventually inform which individuals might be most responsive to interventions targeted at strengthening the physiological system.

Given the significant variability in physiological response across individuals, it will be essential to look beyond group comparisons to explore individual response patterns and their relation with behavioral outcomes. For example, by grouping children with autism into physiological subgroups of “responders” and “nonresponders”, Sheinkopf et al. (2013) found that those children who “responded” (i.e., reduced vagal tone from baseline) had better adaptive socialization skills. Identifying physiological subgroups within a diagnostic group is a method for obtaining a more etiologically homogeneous group from which to better discern biobehavioral relationships. Rather than taking a dichotomous approach in analyzing response patterns, a number of studies have turned towards correlational statistics to inform within-group patterns. This approach may be flawed, however, as the use of correlational statistics assumes that arousal level is linearly related to behavior. In the study of arousal, an “inverted-U” hypothesis has been proposed, where arousal that is either too high *or* too low negatively impacts performance (Anshel, 2012; Yerkes & Dodson, 1908). Thus, responding to social stimuli with increased vagal tone may help an individual obtain an optimal arousal level to support performance. However, once optimal arousal is achieved, additional increases in vagal tone may be maladaptive, suppressing the sympathetic system to the point of causing under-arousal and reduced capacity to engage. Because correlations are unable to capture parabolic relationships, overreliance on this analytic strategy may limit our ability to capture complex associations between arousal and behavior.

Another approach for parsing apart heterogeneity is to define autism subgroups at the physiological level, treating physiological measures as endophenotypes (discussed more thoroughly, below), with the assumption that individuals who share physiological profiles may share some etiologic features. Indeed, common behavioral profiles may arise from distinct biological underpinnings, making it important to trace the origins of clinical-behavioral phenotypes. Such an approach may be useful for placing individuals into more homogeneous subgroups, which may increase power in molecular genetic and related studies of underlying neurobiology (Almasy, 2012; Persico & Sacco, 2014). This approach may also be useful for identifying common biological pathways shared across clinical (and non-clinical) populations. Cross-syndrome trait classification has been argued to facilitate the identification of endophenotypes common to different complex traits and disorders, as the validity of dichotomous cohort classification is challenged by issues related to within-syndrome heterogeneity, cross-syndrome overlap, and diagnostic comorbidities (e.g., Levy & Ebstein, 2009).

Cardiac Activity as a Candidate Endophenotype for Autism and FXS

As reviewed previously, cardiac indicators of arousal possess a number of properties that render them promising candidate endophenotypes for autism and FXS. Notably, heart rate

and vagal tone are highly heritable (Boomsma & Plomin, 1986; Ditto, 1993; Kupper et al., 2005), demonstrate good short and long-term test-retest reliability (Doussard-Roosevelt et al., 2003; Fracasso et al., 1994; Kleiger et al., 1991), and are stable within individuals across developmental stages (Calkins & Keane, 2004; El-Sheikh, 2005). Further, they are quantitative traits that can be assessed noninvasively, making them optimal for large-scale studies. Most critically, evidence reviewed here supports physiological differences that are of a large effect in FXS, and present in at least a subgroup of individuals with autism. Future research investigating the predictive validity of these features at the individual level may lend further support for their use as endophenotypes. It will also be important to examine autonomic markers in unaffected family members to further evaluate their utility as candidate endophenotypes (Almasy, 2012; Gottesman & Gould, 2003). However, caution is also warranted; given the methodological hurdles discussed above, thoughtful implementation and interpretation is necessary to avoid misrepresentation of these data.

Beyond the Autonomic Nervous System: Integrating Evidence across Multiple Systems

The autonomic nervous system is only one of many coordinated subsystems that contribute to the overall maintenance of an adaptive physiological state. For example, the neuroendocrine system (the hypothalamic-pituitary-adrenal axis) and the immune system (inflammation) are also involved in adaptive responsivity to changing conditions. Although the exact process by which different regulatory mechanisms work together is not completely understood, it is known that physiological regulation is achieved through the active interplay of the different regulatory subsystems. In certain situations, it may be most efficient for the body to respond with activation of one or several of these subsystems, as opposed to wide-spread activation of all regulatory mechanisms (McEwen, 1998). Therefore, narrow focus on the autonomic nervous system is likely to result in an incomplete understanding of biological factors contributing to adaptive responses; the immune, autonomic, and endocrine systems likely share neural regulatory circuits either directly or via feedback mechanisms. While some studies have adapted a broader approach through concurrent assessment of multiple regulatory subsystems, the results of these studies are not easily interpreted without a better understanding of the dynamic interaction between these subsystems. For example, Jansen et al. (2006) examined stress responses of individuals with autism using indices of cardiac activity as well as measures of the stress hormone cortisol, which is an index of hypothalamic-pituitary-adrenal axis functioning. Although decreased cardiac arousal in the individuals with autism was suggestive of atypical autonomic response, cortisol levels did not support dysfunction of the neuroendocrine system. Similarly, Kushki et al. (2013) detected increased heart rate in children with autism during a Stroop task, while electrodermal activity, a measure of sympathetic activation, was not increased as compared to typical controls. Smeekens et al. (2013) examined simple correlations between cardiac indices of arousal and cortisol levels in a sample of individuals with and without autism, and found no significant relationships between the measures. Further delineation of the interactions among regulatory subsystems is needed to provide a comprehensive account of physiological regulation as a mediator of behavior in autism and FXS.

Implications for Intervention

Although advances in basic science have allowed for the identification of a number of molecular treatment targets for FXS (which may also be applicable to cohorts with autism; Berry-Kravis, 2014), the lack of sensitive markers to assess response to treatment efficacy has slowed the translation of these targets to human therapies (Berry-Kravis et al., 2013). The delineation of reliable and valid biomarkers will facilitate the clinical translation of these drug targets by allowing for treatment responses to be measured not only behaviorally, but also by changes in underlying biology that may be more sensitive to change. Given the literature supporting autonomic dysfunction as a potential contributor to social dysfunction in autism and FXS, cardiac activity may prove useful as a potential outcome in pharmaceutical or behavioral interventions for autism and FXS. To date, no studies have examined the impact of pharmaceutical interventions on arousal in autism. Pharmaceutical trials of oxytocin and lithium did not have a measureable impact on cardiac vagal control in FXS, although much is still unknown regarding the requisite dosage and timing of pharmaceutical interventions (Hall, Lightbody, McCarthy, Parker, & Reiss, 2012; Heilman et al., 2011). One study did detect positive treatment effects on heart rate modulation following stimulant medication in a sample of boys with FXS (Roberts et al., 2011).

In terms of behavioral interventions to correct physiological targets, Porges et al. (2013) tested an auditory processing intervention designed to improve middle ear muscle function in autism, with the hypothesis that parallel improvements in vagal regulation would be seen, given that the vagus shares common brainstem regulatory mechanisms with the cranial nerves responsible for the middle ear muscles. Following the intervention, children with autism showed increased auditory processing abilities that were accompanied with increased vagal tone and patterns of vagal reactivity that were more similar to those seen in typically developing children. No other behavioral intervention studies to date have examined physiological treatment effects, although evidence from other populations suggests that behavioral interventions may be effective in treating vagal parasympathetic deficits. For example, at-risk infants who are treated with massage or skin-to-skin contact show elevated vagal tone and increased periods of alertness as compared to control infants (Feldman & Eidelman, 2003; Lee, 2005); individuals with Tourette syndrome show less sympathetic arousal and reduced frequency of tics following relaxation biofeedback (Nagai, Cavanna, & Critchley, 2009). Improved social and language skills following massage treatment have been documented in autism, although links with vagal regulation remain theoretical as effects of massage therapy on vagal activity in autism has not yet been directly evaluated (Silva, Schalock, Ayres, Bunse, & Budden, 2009). It appears that traditional behavioral interventions may also result in improvements in autonomic functioning; enhanced vagal regulation has been detected in toddlers following play-based therapy (Bagner et al., 2009; Graziano, Bagner, Sheinkopf, Vohr, & Lester, 2012). Studies of adults also support the potential for improving autonomic regulation with behavioral interventions, which have documented enhanced parasympathetic control following acupuncture and controlled relaxation interventions (Chambers & Allen, 2002; Miu, Heilman, & Miclea, 2009).

Physiological treatment research is promising and deserves further attention, although careful consideration of the multiple endogenous and exogenous influences on cardiac

output is needed to effectively incorporate physiological markers in intervention research. Context effects may limit the sensitivity of cardiac measures, or, if thoughtfully matched to outcomes of interest, may optimize their use. For instance, the measurement of cardiac output during social contexts may prove more sensitive to social-behavioral change than measurement at baseline or during cognitive stressors (e.g., Klusek, Martin, & Losh, 2013; Suess & Bornstein, 2000; Watson et al., 2010). Similarly, measures of reactivity may more sensitively tap autonomic flexibility than do baseline indices. The inclusion of a comparison group matched on relevant domains (age, gender, medication, and other confounds related to the outcome of interest) is also essential to making sense of the data.

Conclusion

Understanding the biological bases of autism is increasingly critical given the rising prevalence of the condition, the substantial economic burden it poses on society, and the serious impact of autism on the lives of individuals and families affected. Cross-syndrome approaches aimed at delineating biomarkers across genetic syndromes, such as that employed in the current paper, provide a promising method for elucidating biological origins of behavior, ultimately promoting better diagnosis, treatment, and characterization of autism and related neurodevelopmental disabilities. Evidence reviewed here suggests that physiological dysregulation is present in a subset of individuals with autism, with patterns of hyperarousal, dampened parasympathetic tone, and atypical reactivity that overlap with the well-documented physiological profile of FXS. Furthermore, evidence supports physiological health as a mediator of outcomes in autism and FXS, with documented associations with skills such as emotional identification, social-communication, and vocabulary. The identification of shared biological mechanisms in autism and FXS (a neurodevelopmental disability that can be traced to a single genetic mutation on the *FMR1* gene) provides a starting-point for determining how physiological regulatory mechanisms may interact with environmental and molecular-genetic factors to give rise to the behavioral end-points associated with autism (and highlights *FMR1* as a potential candidate gene). Cardiac indicators of arousal also possess a number of properties that render them promising candidate endophenotypes for autism and FXS, including high heritability, good short and long-term test-retest reliability, and non-invasive measurement. Despite the tremendous promise of incorporating biomarkers into the study of neurodevelopment, physiological indices are complex and must be utilized with caution, recognizing the multiple nuanced factors at play. A number of key methodological and conceptual considerations are discussed here, including factors related to comparison groups, context effects, individual differences, and the interplay between multiple bodily regulatory systems. Other future directions include focused investigation of autonomic regulation within other genetic syndromes associated with elevated risk for autism, which may inform the genetic and brain basis of physiological arousal systems, and, ultimately, the development of treatments. In sum, evidence reviewed here provides an exciting new perspective for understanding the process by which underlying physiological systems may contribute to complex behaviors associated with autism, informing biological mechanisms relevant to both atypical and typical development.

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Table 1

Cardiac Indices of Physiological Arousal

Cardiac index	Measurement	Relation to the autonomic nervous system	Behavioral correlate in autism or FXS
Heart rate	Inter-beat-interval	Reflects general arousal level, as influenced by both parasympathetic and sympathetic activity	• Autism symptom severity (Roberts, Tonnsen et al., 2012) • Communicative gesture use (Patriquin et al., 2013)
Heart rate reactivity	Change in inter-beat-interval from baseline	Adaption of general arousal level in response to a stressor	• Expressive language (Klusek, Martin, et al., 2013)
Vagal tone	RSA or descriptive measures of heart rate variability	Parasympathetic tone	• Sharing (Patriquin et al., 2013) • Receptive and expressive language (Patriquin et al., 2013; Watson et al., 2010) • Social-communication (Klusek, Martin, et al. 2013; Watson et al., 2010) • Social ability (Neuhaus et al., 2014; Van Hecke et al., 2009) • Emotional identification (Bal et al., 2010) • Autism symptom severity (Roberts, Tonnsen, et al., 2012)
Vagal reactivity	Change in RSA/heart rate variability from baseline	Adaption of parasympathetic tone in response to a stressor	• Receptive and expressive language (Klusek, Martin, et al. 2013)

Table 2

Summary of Group Comparisons on Heart Rate and Vagal Tone in Autism

Citation	Autism sample					Comparison sample (TD unless otherwise noted)				Sampling condition(s)	Findings[a]	
	n	Sex (M:F)	Age in years *M* (*SD*)	Level of Fxing	Psychotropic medication	*n*	Sex (M:F)	Age in years *M* (*SD*)	Matching		Heart rate	Vagal tone
Althaus et al. (1999)	36[b]	26:10	9.8 (1.6)	HF	NR	18	10:8	9.8 (1.6)	NR	Rest; Visual search task	Autism = TD (*d* unable to be computed)	Autism = TD (*d* unable to be computed)
Bal et al. (2010)	17	16:1	10.3 (2.2)	HF	7 taking meds	36	23:13	11.2 (2.9)	Age, IQ	Rest	Autism > TD (*d* = .69)	Autism < TD (*d* = .61)
Bink et al. (2013)	20	20:0	15.6 (2.6)	HF	11 taking meds	36 *ADHD	36:0	15.4 (6.6)	Age, gender, ADHD severity, stimulant medication use; IQ controlled statistically	Rest; Auditory oddball task	Autism = ADHD (*d's* across conditions = .14; .14)	Autism = ADHD (*d's* across conditions = .21; .30)
Corona et al. (1998)	22	20:2	4.3 (0.9)	LF	NR	22 *ID	14:8	3.9 (1.1)	Age, mental age, language age	Rest (toy play)	Autism = TD (*d* = .53)	
Daluwatte et al. (2013)	152	135:17	10.7 (3.4)	NR	70 taking meds; medication effects examined	116 *TD	79:28	10.9 (2.9	NR	Rest; Range of pupillary light reflex tasks; Recovery	Autism > TD (*d's* across conditions = .38; .46–.53; .48)	Autism = TD (*d's* across conditions = .16; .12–.21; .09)
						36 *ID	27:9	9.9 (3.0)	NR		Autism < ID (*d's* across conditions = .35; .20–.34; .38)	Autism = ID (*d's* across conditions = .29; .06–.27; .13)
Guy et al. (2014)	14	13:1	12.3 (3.0)	HF	NR	22	22:1	13.1 (3.0)	Age, IQ	Rest; Cognitive testing; Conversation	Autism > TD (*d's* across conditions = .99; 1.18; .86)	Autism < TD (*d's* across conditions = .86; .74; .63)
Hollocks et al. (2014)	52[e]	52:0	12.9 (2.0)	HF	Excluded	23	23:0	13.9 (1.9)	Gender; age and IQ controlled statistically	Baseline; Trier Social Stress Test	Autism w/o anxiety > TD (*d*'s unable to be computed)	Autism w/o anxiety = TD (*d*'s = .01; .07)[f]

Citation	Autism sample					Comparison sample (TD unless otherwise noted)				Sampling condition(s)	Findings[a]	
	n	Sex (M:F)	Age in years *M* (*SD*)	Level of Fxing	Psychotropic medication	*n*	Sex (M:F)	Age in years *M* (*SD*)	Matching		Heart rate	Vagal
											Autism vs. anxiety = TD (*d*'s unable to be computed)	Autism anxiety (*d*'s = 33
Klusek, Martin, & Losh (2013)	40	40:0	10.1 (3.0)	HF	12 taking meds	28	28:0	8.8 (2.4)	Gender, mental age; age controlled statistically	Rest (video watching); Conversation	Autism = TD (*d*'s across conditions = .20; .26)	Autism (*d*'s ac conditi 01; .
						39 *FXS	39:0	11.9 (2.5)	Gender; age controlled statistically		Autism = FXS (*d*'s across conditions = .44; .39)	Autism (*d*'s ac conditio 27; .
Kushki et al. (2013)	12	10:2	11.3 (2.3)	HF	Excluded	17	11:6	10.9 (2.3)	Gender, age; IQ controlled statistically	Rest (video watching); Color Stroop task	Autism > TD (*d*'s across conditions = 1.4; 1.6)	
Levine et al. (2012)	19	16:3	9.7 (1.4)	HF	Excluded	12[c]	7:4	9.6 (1.4)	Age, IQ, gender	Baseline; Trier Social Stress Test		Autism (*d* unal be com
Mathewson et al. (2011)	15	12:3	35.5 (7.6)	LF	8 taking meds; medication effects examined	16	12:4	35.7 (10.6)	Age, IQ, gender	Rest	Autism > TD (*d* = .99)	Autism (*d* = 1
Ming et al. (2005)	29[d]	24:5	9.4 (4.1)	NR	12 taking meds	17	11:6	8.3 (4.7)	NR	Rest	Symptomatic autism > TD (*d* = 1.33); Asymptomatic autism = TD (*d* = .72)	Sympto autism (*d* = 2 Asympt autism (*d* = 1
Neuhaus et al. (2014)	18	18:0	10.0 (1.1)	HF	NR	18	18:0	10.0 (9.3)	Age, IQ	Rest		Autism (*d* = .
Porges et al. (2012)	78	70:8	13.0 (3.9)	HF	Excluded	68	59:9	13.7 (4.3)	Age	Rest	Autism > TD (*d* = 1.32)	Autism (*d* = 1
Schaaf et al. (2013)	59	55:4	7.7 (1.1)	HF	Excluded	29	16:13	8.2 (1.3)	Age controlled statistically	Rest; Range of sensory stimuli		Autism (*d* unal be com

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Citation	Autism sample					Comparison sample (TD unless otherwise noted)				Sampling condition(s)	Findings[a]	
	n	Sex (M:F)	Age in years *M* (*SD*)	Level of Fxing	Psychotropic medication	*n*	Sex (M:F)	Age in years *M* (*SD*)	Matching		Heart rate	Vagal
Sheinkopf et al. (2013)	15	12:3	4.3 (1.2)	LF	NR	8*TD/I D	7:1	3.6 (1.0)	Age, IQ, gender	Rest (toy play); Distal stranger approach; Proximal stranger approach	Autism = TD/ID (*d*'s across conditions = .06; .11; .04)	Autis TD/ID acro conditio 01; .37
Sigman et al. (2003)	22	20:2	4.3 (0.9)	LF	NR	22 *ID	14:8	3.9 (0.1)	Age, mental age, language age	Interaction with mother; Interaction with stranger	Autism = ID (*d*'s unable to be computed)	
Toichi & Kamino (2003)	20	18:2	19.0 (4.9)	HF	Excluded	20 *ID/TD	18:2	20.5 (4.3)	Age, gender, IQ, education level	Rest; Mental arithmetic	Autism = TD/ID (*d*'s across conditions = .12; .45)	Autis TD/ID acro conditio 52; .
Van Hecke et al. (2009)	19	18:1	10.0 (1.6)	HF	6 taking meds	14	10:4	9.9 (2.0)	IQ	Rest; Range of social videos		Autism (*d*'s ac conditio 64; .50
Watson et al. (2012)	20	20:0	2.9 (4.3)	NR	Excluded	14	14:0	2.6 (0.5)	Age, gender	Nonsocial stimuli; Social stimuli	Autism > TD (*d*'s across conditions = .77; 1.14)	Autism (*d*'s ac conditio 20; .

Note:

[a] When not provided by the authors, absolute effect sizes were computed according to the formulas provided by Lipsey & Wilson (2001);

[b] Analyzed in subgroups of 18 based on the presence of hyperactivity.

[c] Five TD participants were siblings of children with autism.

[d] Analyzed in subgroups of 15 or 13 based on the presence of symptoms of autonomic dysfunction.

[e] Analyzed in subgroups of 32 and 20 based on the presence of comorbid anxiety disorders.

[f] IQ not controlled statistically in vagal tone comparisons. Functioning (Fxing) level was categorized as follows: Low Functioning (LF) = *M* IQ ≤ 75, High Functioning (HF) = *M* IQ ≥ 75. ADHD = attention deficit-hyperactivity disorder; ID = intellectual disability; TD = typically development; NR = not reported.

Table 3

Summary of Group Comparisons on Heart Rate and Vagal Tone in Fragile X Syndrome

Citation	FXS sample					Comparison sample ((TD unless otherwise noted)				Sampling condition(s)	Findings[a]	
	n	Sex (M:F)	Age in years *M* (*SD*)	Level of Fxing	Psychotropic medication	*n*	Sex (M:F)	Age in years *M* (*SD*)	Matching		Heart rate	Vagal tone
Hall et al. (2009)	26	26:0	14.6 (2.8)	LF	12 taking meds; medication effects examined	26	26:0	14.6 (3.8)	Age	Rest (video watching); Conversation with prompts to maintain eye contact	FXS > TD (*d*'s across conditions = 1.4; 1.3)[b]	FXS < TD (*d*'s across conditions = 1.5; 1.2)[b]
Heilman et al. (2011)	12	12:0	12.0 (4.8)	LF	Some participants taking meds (*n* NR)	21	21:0	12.0 (4.8)	Age	Rest; Word repetition	FXS > TD (*d*'s across conditions = 1.6; 1.5)[b]	FXS < TD (*d*'s across conditions = 1.6; 1.0)[b]
Klusek, Martin, et al. (2013)	39	39:0	11.9 (2.5)	LF	16 taking meds	28	28:0	8.8 (2.4)	Gender; age controlled statistically	Rest (video watching); Conversation	FXS > TD (*d*'s across conditions = .63; .63)	FXS = TD (*d*'s across conditions = .17; .23)
						40* Autism	40:0	10.1 (3.0)	Gender; age controlled statistically		FXS = Autism (*d*'s across conditions = .44; .39)	FXS = Autism (*d*'s across conditions = .27; .07)
Roberts et al. (2001)	29	29:0	4.1 (2.1)	NR	Excluded	31	31:0	5.0 (2.1)	Age, gender	Rest (video watching)	FXS > TD (*d* = .62)	FXS < TD (*d* = .89)
Roberts et al. (2006)	29	29:0	4.1 (2.1)	NR	Excluded	31	31:0	5.0 (2.1)	Age, gender	Rest (video watching)	FXS > TD	FXS < TD (*d* = .82) FXS < TD
Roberts, Tonnsen et al. (2012)	31	31:0	1.7 (0.9)	N/A	Excluded[c]	25	25:0	1.8 (0.9)	Age, gender	Rest (toy play); Arm restraint	(*d*'s unable to be computed)	(*d*'s unable to be computed)
Roberts, Hatton et al. (2012)	12	12:0	1.0 (NR)	N/A	Excluded[c]	10	12:0	1.0 (NR)	Age, gender	Toy play	FXS = TD (*d* = .29)	FXS < TD (*d* = 1.1)

Citation	FXS sample					Comparison sample ((TD unless otherwise noted)				Sampling condition(s)	Findings[a]	
	n	Sex (M:F)	Age in years *M* (*SD*)	Level of Fxing	Psychotropic medication	*n*	Sex (M:F)	Age in years *M* (*SD*)	Matching		Heart rate	Vagal tone
Tonnsen et al. (2013)	21	21:0	2.7 (1.0)	HF	Excluded[c]	19	19:0	2.8 (1.2)	Age, gender	Stranger approach	FXS = TD (*d* = .48)	FXS < TD (*d* = .86)

Note:

[a] When not provided by the authors, absolute effect sizes were computed according to the formulas provided by Lipsey & Wilson (2001);

[b] Unpublished data for computing effect size were provided by the authors.

[c] J. E. Roberts, personal communication. Functioning (Fxing) level was categorized as follows: Low Functioning (LF) = *M* IQ ≤ 75, High Functioning (HF) = *M* IQ ≥ 75. N/A = not applicable (i.e., participants too young for accurate IQ); TD = typically development; NR = not reported.