Defensive Neurophysiological Response:
Exploring the Neural and Autonomic Correlates of Social Behavior

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ABSTRACT

Current literature suggests neurological (i.e., insula, amygdala) and autonomic (i.e., respiratory sinus arrhythmia; RSA) markers of language, social, and behavioral challenges in autism spectrum disorders (ASD; Bal et al., 2010; DiMartino, Ross, et al., 2009; Lorenzi, Patriquin, & Scarpa, 2011; Patriquin, Scarpa, Friedman, & Porges, 2011), that hypothetically reflect a defensive neurophysiological circuit (i.e., hyper-arousal within the central and autonomic nervous systems). It is unknown how this neurophysiological state contributes to difficulties in ASD. Therefore, the current study quantified peripheral and central nervous system activity and investigated how this neurophysiological circuit may be related to different social and behavioral patterns that characterize ASD. Participants with (n = 16) and without (n = 30) ASD listened to classical music while brain (via functional magnetic resonance imaging) and autonomic (via pulse oximeter and plethysmogram) data were collected. Results indicated that decreased insula and amygdala activity during physiological hyper-aroused states predicted symptoms associated with ASD, and predicted higher levels of comorbid anxiety, stress, and depression. Contrary to hypotheses, no baseline RSA or amygdala differences were noted between ASD and controls groups, suggesting that adults with ASD may have developed effective coping strategies for reducing physiological threat responses. It will be important for future studies to continue to explore and clarify the neural connections of peripheral nervous system activation in individuals with and without ASD, including extending this research to children.

Dedication

I dedicate my dissertation to my grandmother, Mémère. Her unwavering love, encouragement, and support inspires me to always, “keep on going.”

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Introduction

Prevalence estimates of autism spectrum disorder (ASD) indicate an urgent social and behavioral health concern as ASD is currently the most common developmental disorder, affecting 1 in 88 children (Centers for Disease Control and Prevention, 2012), and is associated with lifelong impairment (Fombonne, 2009). ASD directly impacts an individual's developmental trajectory in multiple domains, including language, social relationships, and adaptive behavior (American Psychiatric Association, 2000). In addition to the personal and familial impact conferred by ASD, fiscal consequences associated with ASD have been estimated to be at least 3.9 million dollars per person per year, or a total societal cost of $40 billion per year for lifetime direct medical, non-medical, and lost productivity to individuals with ASD and their immediate caretakers (Ganz, 2006). Despite the personal, societal, and fiscal consequences of ASD, comprehensive treatments require multiple hours of therapy per day, and even focused treatments do not alleviate this burden – they require several months of daily teaching or weekly caregiver support (Odom, Boyd, Hall, & Hume, 2010). Treatment inefficiencies as well as the imprecise understanding of the etiological pathways leading to the autistic phenotype are the motivations behind the current study.

Specifically, the current study examines the neurophysiological processes underlying neurophysiological states (i.e., respiratory sinus arrhythmia [RSA], amygdala and insula response) in typically developing adults (control group) and adults with high-functioning ASD. Differences in neurophysiological responding between the two groups are compared. In prior studies, neural (amygdala) and autonomic (RSA) defensive response tendencies (e.g., over-activation of the amygdala, lower RSA) have been correlated to social difficulties in populations with ASD (Bal et al., 2010; Dalton et al., 2005; Patriquin et al., 2011). As such, the current study

also examines the relationship between neurophysiological state and reactivity and behaviors characteristic of ASD, including social behavior.

Unlike prior studies, which assess neural and autonomic patterns independently, the present study utilizes both measures simultaneously. Although only a few studies have combined human functional magnetic resonance imaging (fMRI) with autonomic measures, including the use of psychophysiological recording with fMRI can enrich the investigation of the mind-body relationship (Gray et al., 2009). Notably, a better understanding of the basic underlying neurophysiological mechanisms associated with effective social behavior in typically developing individuals and difficulties with social behavior in individuals with ASD could lead to more efficient, targeted treatments for ASD through the identification of neurophysiological response patterns that could be targeted (e.g., through neurofeedback).

Autonomic Correlates of Defensive Biological States and Social Behavior

Psychophysiological measures, especially heart rate variability (HRV), have been used for over 50 years to understand how physiological mechanisms may relate to psychological outcomes. More recently, psychophysiology has focused on a measure of HRV, RSA, as an index of the vagal modulation of heart rate (Demeersman & Stein, 2007). RSA provides theoretical insight into effective/ineffective social behavior due to its measurement of the vagus nerve, a cranial nerve within the Social Engagement System (Porges, 2007). Measurement of the vagus nerve (e.g., with RSA) grants researchers an indirect but objective measure of cranial nerve and neural functioning even though the specific neural mechanisms have not been elucidated. One theoretical model of RSA and social behavior provides testable hypotheses regarding defensive autonomic states (i.e., lower RSA), neural functioning, and social behavior: the Polyvagal Theory.

Autonomic activity: Typically developing. The Polyvagal Theory (Porges, 1995, 1998, 2001, 2003b, 2007, 2009; Porges & Lewis, 2009) is a conceptual framework for understanding the link between neurophysiological functioning and effective social behavior. The Polyvagal Theory describes a social communication circuit comprised of autonomic and somatomotor components. The autonomic component focuses on a myelinated branch of the vagus (measured by RSA) with a source nucleus located in the nucleus ambiguus. The somatomotor component involves the neural regulation of the striated muscles of the face and head via special visceral efferent pathways traveling through five cranial nerves (i.e., V, VII, IX, X, XI). The myelinated vagus provides efferent control over the heart by regulating the sinoatrial node (i.e., the "pacemaker" of the heart). RSA allows for the quantification of myelinated vagus control of the heart by measuring the fluctuations in heart rate (HR) during spontaneous breathing (Porges, 1995).

To promote effective social communication in typically developing individuals, the myelinated vagus actively slows the intrinsic rate of the heart (69-128 beats per minute; Jose & Collison, 1970). Higher RSA reflects greater myelinated vagus control of the heart, or a soothed autonomic state, that is theorized to promote social communication by coordinating cranial nerves associated with social behavior (e.g., facial nerve, facial expression). Conversely, lower RSA demonstrates less influence of the myelinated vagus on the heart (leading to cardiac arousal), which may interfere with the ability to regulate behavioral state and to spontaneously socially engage (Porges, 1995, 1998, 2001, 2003b, 2007, 2009; Porges & Lewis, 2009). As such, RSA gives a non-invasive index of a neurophysiological state that may be related to social behavior.

Due to communication in the brainstem between the neural circuits that control the heart and the face (see Porges, 2009), RSA provides insight into the functional features of the neural circuits that regulate the striated muscles of the face and head (i.e., cranial nerves V, VII, IX, X, and XI). These cranial nerves are involved in functions related to social behavior, including facial expression (i.e., cranial nerves V and VII), ingestion (cranial nerve V), listening (cranial nerves V and VII), vocalizations (cranial nerves IX and X), and head gestures (cranial nerve XI). As such, the centralized origin of these cranial nerves in the brainstem provides a neuroanatomical face-heart connection that functions as an integrated social engagement system (Social Engagement System; Porges, 2001, 2003a, 2007; Porges et al., 2008; Porges & Lewis, 2009). (Note: cranial nerve V also innervates the abdomen, but this is not a focus of the current study.) RSA provides a broad index of the functioning of the Social Engagement System cranial nerves and thus may provide insight to neural pathways associated with ASD and other psychiatric disorders where effective social behavior is compromised.

Autonomic activity: ASD. A pattern of defensive cardiac responding emerges across contexts for individuals with ASD (see Table 1). Defensive cardiac responding is defined herein as lower baseline heart period (HP) and lower RSA. Specifically, individuals with ASD show defensive cardiac states (i.e., lower baseline HP, higher heart rate [HR], lower RSA) when compared to healthy controls (Bal et al., 2010; Denver, 2004; Goodwin et al., 2006; Ming, Julu, Brimacombe, Connor, & Daniels, 2005). In particular, individuals with ASD show mean HR responses approximately 20 beats per minute higher than age- and sex-matched individuals during baseline and stressful situations (Goodwin et al., 2006).

HR and HP, however, provide a non-specific index of cardiac activation because both are influenced with both parasympathetic and sympathetic nervous system activity, whereas RSA

provides specific measurement of the vagus nerve that reflects only parasympathetic nervous system activity. In line with the conceptualization of the Polyvagal Theory, RSA provides insight to cranial nerves and brainstem functioning that promotes effective social engagement. Importantly, the diagnostic criteria outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) specifically note behaviors that are controlled by the Social Engagement System outlined by the Polyvagal Theory: (1) marked impairment in the use of nonverbal behaviors, including eye-to-eye gaze, facial expression, body postures [cranial nerves VII, XI]; (2) lack of spontaneous seeking to share enjoyment, interests, or achievements [cranial nerves VII, IX, X, XI]; (3) delay in or total lack of the development of spoken language or marked impairment in the ability to initiate or sustain a conversation with others [cranial nerves X, IX].

Studies have also found evidence that RSA is correlated with positive social functioning in ASD. Children and adolescents (aged 7-17 years old) with Autistic Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) who had higher amplitude RSA at baseline recognized emotions better than individuals with Autistic Disorder or PDD-NOS with lower amplitude RSA at baseline (Bal et al., 2010). Similarly, children with ASD (aged 8-12 years old) with higher baseline RSA had better social skills and fewer behavior problems as reported by parents (Van Hecke et al., 2009). When social behavior is measured experimentally by independent observers, children with ASD who have higher baseline RSA demonstrate more joint attention and conventional gestures than children with lower baseline RSA (Patriquin et al., 2011). Thus, RSA seems related to social behavior in ASD, which provides strong motivation to continue exploring the relation between RSA and social behavior in ASD and typically developing individuals.

Despite correlations between RSA and social functioning in individuals with and without ASD, the brain areas associated with RSA have not been explored. This study examines RSA and HP and their neurological correlates by collecting HP and fMRI data simultaneously. This study assessed neurophysiological response patterns in both control and ASD groups in order to understand the neurophysiological circuits associated with neurophysiological defensive responding that may predict high energy (e.g., arousal) states. Physiologically, high energy is defined as decreased RSA, and amygdala and insula activation.

Neural Correlates of Cardiac Defensiveness and Social Behavior

One potential neural structure linking cardiac defensiveness (i.e., low RSA) and social behavior is the amygdala. In typically developing individuals, dysregulation of the amygdala (as well as other limbic structures) is associated with greater sympathetic activation as indexed by higher HR and lower HRV (Mujica Parodi et al., 2009) – the same autonomic pattern evident in ASD at baseline and when completing tasks. Unlike the present study, which examines cardiac and neural functioning continuously, Mujica Parodi and colleagues assessed cardiac variables and functional brain activation during separate sessions. It is hypothesized that individuals with ASD may show a chronically defensive autonomic state relative to their typically developing peers. This defensive state in ASD may also be evident in amygdala activation, as reflected in studies showing amygdala hyper-activation in ASD relative to typically developing controls (Critchley et al., 2000; Dalton et al., 2005; Grelotti et al., 2005). Other studies, however, have found amygdala hypoactivity in individuals with ASD relative to controls (e.g., Baron-Cohen et al., 1999; DiMartino, Ross, et al., 2009). Given that including psychophysiological measurement enriches neural data (Gray et al., 2009), the mixed findings of amygdala response in ASD may

be better understood by examining RSA patterns and other neural structures (e.g., insula) that are involved with autonomic responding.

Amygdala: Typically developing. Amygdala activation is demonstrated in typically developing individuals when responding to threat/fear (Lang, Davis, & Öhman, 2000; Öhman & Mineka, 2001; Schultz et al., 2000; Williams et al., 2005). The amygdala shows stimulus specificity to threat (Breiter et al., 1996; Williams et al., 2005) and negative information (Cunningham, Van Bavel, & Johnsen, 2008), but it also may show general reactivity in anticipation of unpredictable stimuli (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Herry et al., 2007). Amygdala activation, however, does show the ability to discriminate between social stimuli. For example, the amygdala has shown reactivity across multiple facial emotion expressions: fear, disgust, anger, sadness, happiness, and neutral (Fitzgerald et al., 2006). Yet, amygdala reactivity in some studies is preferentially activated to fearful and happy faces versus neutral faces, suggesting that the amygdala may activate to any emotionally-valenced faces (Breiter et al., 1996); although, others have found that the amygdala reacts more to negative information than positive information (Cunningham et al., 2008). Interestingly, when autonomic measures are included with fMRI, neurophysiological profiles emerge that differentiate between fear, anger, and disgust (Williams et al., 2005): (1) fear is characterized by increased EDA (i.e., electrodermal activity: rise time, amplitude) with amygdala activity; (2) anger is characterized by rapid onset and slow recovery of EDA with anterior cingulate activity; and (3) disgust is characterized by insula and basal ganglia activity. Thus, autonomic measurement provided insight to the psychophysiological states associated with neural and emotional responses.

Taken together, these studies suggest that the amygdala plays a general role in detecting unpredictability (Herry et al., 2007), that it specifically activates to salient facial expressions

(Breiter et al., 1996; Fitzgerald et al., 2006), and that it is more reactive to negative information compared to positive information (Cunningham et al., 2008). Moreover, amygdala and autonomic reactivity patterns correlated to fear (Williams et al., 2005). Within the typically developing literature, the amygdala appears connected to defensive neurophysiology. Since the amygdala is responsive under multiple contexts (e.g., unpredictability, salient facial expressions, negative information), the amygdala serves multiple functions. Although it is acknowledged that the amygdala is multifaceted, fear responses (or defensive responding to threat) are one apparent function of the amygdala (Öhman, 2005; Williams et al., 2005).

Amygdala: ASD. In ASD, the findings of amygdala activation are also mixed. A recent meta-analysis of 39 studies that used social (e.g., faces) and nonsocial (e.g., objects) stimuli revealed general amygdala hypoactivation across studies (DiMartino, Ross, et al., 2009). For example, in an fMRI study that used a face perception task, typically developing adults showed activation in the amygdala while the autism group showed a lack of positive activation (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001). Similarly, other studies demonstrated that participants with autism do not show amygdala activation during face perception, face expression, or face familiarity tasks (Baron-Cohen et al., 1999; Hall et al., 2010; Pierce, 2004; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004).

Di Martino et al. (2009) also stressed, however, that recent studies are finding the opposite pattern – amygdala hyperactivation – in ASD. Specifically, when judging facial expressions, adults with ASD demonstrated significant activation of the amygdalohippocampal junction compared to typically developing adults (Critchley et al., 2000). Amygdala activation was shown during facial discrimination tasks in adolescents with high-functioning autism – the autism group showed significant amygdala activation to facial photographs compared to control

participants (Dalton et al., 2005). Lastly, activation of the amygdala may not be specific to social stimuli and may instead become activated to stimuli with significant reward value in ASD (Grelotti et al., 2005).

Even though researchers have targeted the amygdala as a structure central to challenges in ASD (Bachevalier & Loveland, 2006; Baron-Cohen et al., 2000), a consistent pattern of results is not evident. In studies examining reactivity to social stimuli in ASD versus control groups, for example, some show similar amygdala activation in both groups (Hall et al., 2010; Pierce, 2004), others show more amygdala activation in individuals with ASD (Critchley et al., 2000; Dalton et al., 2005; Grelotti et al., 2005), and still others show less amygdala activation in individuals with ASD (Baron-Cohen et al., 1999; Pierce et al., 2001; Wang et al., 2004).

The insula: Autonomic perception. The anterior insula, which has efferent projections to the amygdala, is central in the perception of one's bodily state (e.g., HR perception) and the experience of emotion (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Current research suggests that the right anterior insula is a neglected structure in the ASD neuroimaging literature (DiMartino, Ross, et al., 2009). The meta-analysis DiMartino and colleagues (2009) found hypoactivation of the insula across ASD studies, suggesting that individuals with ASD have difficulty perceiving their autonomic state, which may then impact their ability to experience emotion. Dysregulation of the insula, therefore, may contribute to difficulties that individuals with ASD have in deriving emotional experience from their autonomic states. In accordance with the conceptualization of neurophysiological defensiveness (i.e., low RSA, amygdala over-activation) affecting social behavior, it may be that neurophysiological defensiveness, as processed by the anterior insula, is not accurately perceived in individuals with ASD. This error in autonomic perception may inhibit the ability to consciously or unconsciously regulate arousal

(i.e., low RSA, low HP) and may lead to the chronic defensive autonomic state seen in ASD across contexts (Goodwin et al., 2006). In addition, decreased awareness of physiological cues of emotion can contribute to decreased understanding of emotions.

Music: Evoking Continuous Neurophysiological Activation

The present study uses classical music, without vocalizations, to evoke continuous neurophysiological response throughout time. Currently, the simultaneous assessment of central and peripheral measures have not been used to characterize hyper-arousal states found in individuals with ASD (e.g., Bal et al., 2010; Goodwin et al., 2006; Van Hecke et al., 2009). Further, it is not understood how these neurophysiological responses are associated with subjective ratings of arousal in people with and without ASD.

Importantly, classical music is a stimulus that can elicit dynamic changes in neurophysiological and subjective states associated with arousal (Dean, Bailes, & Schubert, 2011). It is also a stimulus that has existed in popular culture for decades (e.g., Pachelbel's Canon in D Major, 1919), and therefore, provides a well-accepted and continuous assay of neurophysiological responsivity. Musical stimuli allow subjects to rate their subjective experience of neurophysiological changes continuously. As such, the music pieces, subjective ratings, neural patterns, and autonomic responses are temporally linked and dynamic changes can be examined. This provides critical improvements over current methodologies, which include examining continuous neurophysiological responses to subjective, still stimuli (e.g., pictures; Bal et al., 2010; Dalton et al., 2005).

For the pilot study, seven well-known classical music pieces were randomly presented in the scanner to 19 typically developing adults: Palladio, Gayane: Sabre Dance, Toreador's Song from 'Carmen', Canon in D Major, On the Beautiful Blue Danube, Op. 314, Ein Kleine

Nachtmusick, K. 525: I. Allegro-Allegro, and 5th Symphony. Participants continuously rated the music pieces during an fMRI scan while they listened to the music pieces. Following the completion of the pilot study, individual energy (red) and preference (blue) ratings were plotted for each song to ensure the music pieces elicited variation in subjective ratings. After plotting the ratings, it was qualitatively apparent that the music pieces evoked intra-individual variation on the energy scale. In addition to plotting participant energy and preference ratings, the classical music pieces were spectrally decomposed to qualitatively examine the association between subjective ratings and music frequencies. Frequencies within the subjective auditory range (20Hz-20,000kHz) were extracted. Qualitative examination of subjective ratings and spectral decomposition of the classical music pieces indicated a close association between frequency changes in the music pieces and subjective ratings. As such, these songs were considered adequate in not only evoking rating variability, but in evoking ratings that corresponded to the quantitative decomposition of the music pieces.

As these seven music pieces were found to generate adequate variability in subjective ratings of energy that corresponded to the spectral decomposition of the music pieces and due to the correlations between music and physiology (Dean et al., 2011), these pieces were considered appropriate to include to examine neurophysiological response. All seven music pieces were included in the present study. Variation in the music pieces was critical in determining the link between social behavior and neurophysiological response in the present study. In particular, hypotheses regarding neurophysiology and behavior indicate that chronically hyper-aroused neurophysiological states (e.g., as seen in ASD) contribute to more social communication difficulties and more vagal control/soothed neurophysiological states contribute to improved engagement in the social context (e.g., Porges, 2007). Importantly, it is hypothesized that

neurophysiological flexibility may contribute to quicker adaptive responding to environmental stimuli or emotional stimuli (Feldman & Eidelman, 2009). As such, more effective and adaptive social behavior should be associated with greater neurophysiological flexibility/responsivity during the music-listening task. Yet, some individuals may not develop the physiological organization necessary to promote effective social engagement and cognitive skills (e.g., individuals with ASD). Individuals with ASD can be characterized by both social-cognitive difficulties and differences in RSA.

Confounding Variables

Since individuals with ASD are more likely to have significant comorbid psychopathologies, including anxiety (White, Oswald, Ollendick, & Scahill, 2009) and depression (Ghaziuddin, Ghaziuddin, & Greden, 2002), these variables were examined in the analyses presented below. Individuals with ASD may, due to comorbid psychopathology, demonstrate more neural and peripheral nervous system activation (e.g., heightened amygdala response) congruent with individuals experiencing anxiety. Additionally, due to difficulties with change, adults with ASD may experience more anxiety when placed in the scanner compared to the control group. As such, both ASD and control groups rated their Subjective Units of Distress regarding their distress prior to entering the scanner, their experience during the scan, and how they felt after the scanning session was completed. These variables were used to determine if distress, anxiety, or depression would affect neurophysiological variables differentially between ASD and control groups.

Hypotheses

The current study simultanously recorded inter-beat interval (IBI) data and functional brain activity while participants continously rated their perceived arousal (i.e., high energy vs.

low energy) and preference (i.e., like a lot to do not like) to seven classical songs containing no vocalizations. This study only used energy ratings to examine perceptual differences in arousal (i.e., energy), due to hypotheses regarding hyper-arousal in ASD. Although a second, non-rated scanning session was conducted, these data are not included. In the future, these data could be used to control for motor cortex activation produced by button presses during the rated scanning session. Herein, the rated music-listening session will be called the "task."

In order to examine differences across the amygdala and insula in arousal that was *autonomically* and *perceptually* defined, amygdala and insula regions of interest (ROI) were extracted that corresponded to a participant's lowest values of RSA or highest ratings of energy, respectively. For all variables, the onset times of the rating or lowest RSA are considered the "event." ROI data were extracted 4s prior to an event, 20s after an event, and during this event. The 4s of data prior to the event were averaged and subtracted from the ROI signal during and 20s after the event (each functional image is taken every 2s, $n = 11$ total ROI time points). Subtracting the 4s period prior to the event controlled for "baseline" ROI signal in the hemodynamic response during and after the event.

For the autonomically-defined baseline amygdala and insula ROI signal, the lowest three values of RSA were identified and the onset times of RSA were used to extract the corresponding baseline amygdala and insula ROI signal. These three epochs were averaged to form the *autonomically-defined baseline* amygdala and insula ROI variables. In order to examine the autonomically-defined amygdala and insula ROI signal across the task, the lowest ten values of RSA and their corresponding onset times during the task were identified. These ten onset times were used to extract ten epochs of the amygdala and insula ROI signal and were averaged to form the *autonomically-defined task* amygdala and insula ROI variables. To extract the

amygdala and insula ROI signal that corresponded to the perception of hyper-arousal, ten of the highest energy ratings (during task) and their corresponding onset times were identified. The amygdala and insula epochs for task were averaged, after accounting for the pre-event activation (i.e., subtracting average of activation 4s prior to the event), in order to form the *perceptually-defined task* amygdala and insula ROI variables. (Note: perceptually-defined amygdala and insula signal can only be examined during task because ROI data are extracted based on energy ratings).

Regarding the autonomically-defined amygdala and insula ROI during baseline and task, it was hypothesized that the ASD group would demonstrate greater amygdala activation, suggesting a more threatened/hyper-aroused state relative to the control group. In addition, it was hypothesized that the ASD group would demonstrate lower autonomically-defined insula activation compared to the control group due to difficulties perceiving a hyper-aroused physiological state.

Regarding the perceptually-defined amygdala and insula ROI during task, it was hypothesized that the ASD group would demonstrate lower perceptually-defined insula activation because of difficulties for ASD participants to perceive their autonomic state. Due to hypothesized difficulties in perception of autonomic state in the ASD group, no specific direction was hypothesized (i.e., more/less) for the activation of the amygdala compared to the control group. From prior brain and peripheral nervous system literature (e.g., Bal et al., 2010; Dalton et al., 2005), it was hypothesized that participants with ASD would have greater/chronic neurophysiological activation compared to their typically developing counterparts, but it is unclear whether individuals with ASD will be able to percieve these hightened levels of arousal.

Thus, no directional hypothesis were made regarding the perceptually-defined amygdala activation between groups.

In accordance with the literature reviewed above, it was also hypothesized that the ASD group would demonstrate lower baseline and task RSA compared to their typically developing peers. Prior findings of lower RSA in ASD groups compared to control groups are found in children and adolescents (e.g., Bal et al., 2010; Van Hecke et al., 2009), not adults.

Lastly, it was predicted that autonomically-defined baseline amygdala and insula ROIs would predict social behavior related to ASD or symptoms of ASD (i.e., on the Social Responsiveness Scale [SRS], Autism Spectrum Quotient [AQ]) across the ASD and control groups. Within the ASD group, it was predicted that autonomically-defined baseline amygdala and insula ROIs would predict subscale and total scores on the Autism Diagnostic Observation Scheduled (ADOS), a gold-standard assessment measure of ASD, such that higher baseline amygdala and less insula activation would predict higher ADOS scores. Further, it was predicted that baseline RSA would predict SRS-A, SRS-A-SR and AQ scores across the ASD and control groups, and ADOS subscale and total scores in the ASD group, such that lower baseline RSA would predict more social difficulty and scores more symptomatic of ASD.

Method

Participants

Forty-six adults ($n_{\text{male}} = 24$, $n_{\text{female}} = 22$) aged 18-35 ($M = 22.150$, $SD = 4.361$) were recruited from Southwest Virginia using flyers, email, and a participant database established by the Human Neuroimaging Laboratory at the Virginia Tech Carilion Research Institute (VTCRI). Individuals were screened through online questionnaires and an in-person screening session to determine group (i.e., control or ASD) membership. All participants had a composite IQ above

70 and between 87-137 (M = 105.3478, SD = 11.022) on the Kaufman Brief Intelligence Test, second edition (KBIT-2). Individuals with a history of neurological disorders (e.g., epilepsy or head injury), or bearing shrapnel or metal/electronic implants were excluded due to the use of MRI.

The control group consisted of thirty typically developing adults (n_{male} = 14, n_{female} = 16) aged 18-31 (M = 21.630, SD = 3.855). Control participants were screened to exclude individuals with current psychiatric illnesses (i.e., schizophrenia, affective disorders, anxiety disorders, and personality or behavioral disorders) using the Structured Clinical Interview for the DSM-IV Axis I (SCID-I; First, Spitzer, Gibbon, & Williams, 1997) and Axis II (SCID-II; First, Gibbon, Spitzer, & Williams, 1997). Additionally, if any control participants scored 32 or greater on the Autism-Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) they were excluded**;** however, no control participants reached this score (maximum AQ score for control group = 27). Ten control participants were on medications (e.g., birth control, multivitamin), including one participant who was on Adderall but did not meet criteria for a DSM-IV disorder.

Sixteen adults (n_{male} = 10, n_{female} = 6) previously diagnosed with an ASD aged 18-35 years old (M = 23.130, SD = 5.175) also participated. ASD diagnosis was based on the following: score of ≥ 32 on the AQ, prior diagnosis by a community professional, meeting criteria on the DSM-IV-TR checklist (Appendix A) or meeting criteria for autism or an autism spectrum disorder on the Autism Diagnostic Observation Schedule - Generic (Lord et al., 2000) as determined by a research-reliable doctoral-level graduate student clinician. ASD and control groups did not significantly differ by IQ, $t(44) = .598$, $p = .889$., or gender, $c^2(1, N = 46) = 1.048$, $p = .306$. Mean IQ scores were in the average range for both groups (ASD: M = 106.688,

SD = 11.848; control: *M* = 104.633, *SD* = 10.695). Eleven ASD participants were on medications (e.g., anti-depressants, anti-anxiety).

Behavioral Measures

The following measures were used to obtain demographic/background information, fMRI safety screening information, and assess intelligence, ASD symptoms, social symptoms associated with ASD, general anxiety, social anxiety, depression, stress, psychiatric conditions, autonomic response, and neural patterns.

Demographics Form (Appendix B). This measure was used to check for past/current medications, general health, and any treatment or special help that the participant has received in the past for learning or emotional problems, as well as past psychiatric diagnoses the participant had received or for which there is a family history. This measure also collected basic demographic information such as race, age, and education.

FMRI Safety Screener (Appendix C). This measure was used to screen for a history of neurological disorders (e.g., epilepsy or head injury), and the presence of shrapnel or metal/electronic implants.

DSM-IV-TR Checklist for ASD (Appendix A). An adapted version of the DSM-IV-TR checklist, which has been previously used in adults with ASD (Brooks & Benson, 2011), assessed for the presence of symptoms associated with ASD across social interaction, communication, and repetitive and stereotyped behaviors/interests/activities domains. A doctoral-level graduate clinician completed the questionnaire based on clinical judgment following the in-person session with the individuals with ASD.

Kaufman Brief Intelligence Test, second edition (KBIT-2; Kaufman & Kaufman, 2004). The KBIT-2 is a standardized, norm-referenced test used to measure verbal and nonverbal

abilities. The test is individually administered for approximately 20 minutes and is used for assessing the intellectual ability of children, adolescents, and adults aged 4-90. The KBIT-2 assesses cognitive abilities through two scales: crystallized (verbal) and fluid (nonverbal) scales. An IQ composite is derived from the two scales. Scores are provided on a scale where the mean = 100 and standard deviation = 15. All participants had a composite IQ > 70.

Autism Diagnostic Observation Schedule - Generic (ADOS; Lord et al., 2000). To confirm an ASD diagnosis, participants with a prior ASD diagnosis were administered the ADOS. The ADOS is a 45-60 minute observation and diagnostic test to assess deficits associated with Autism Spectrum Disorders in various domains, including Communication, Reciprocal Social Interaction, Stereotyped Behaviors and Restricted Interests domains, and Creativity and Imagination domain. The ADOS provides scores to distinguish between Autism, Autism Spectrum, and non-spectrum categories. ADOS scores were determined by a research-reliable, doctoral-level graduate clinician in clinical psychology.

Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001). This 50-item questionnaire required participants to respond that they "definitely agree," "slightly agree," "slightly disagree," and "definitely disagree" in order to determine traits associated with autism in adults with average intelligence. For dichotomous scoring, items were rated as a '0' or '1' and summed to create an overall score. A score of 32 or greater indicated that the participant has clinically significant levels of traits associated with autism and was used in the control group to screen for symptoms of autism. The AQ has been validated in typically developing adults and in adults with Asperger's Disorder and high-functioning autism (Baron-Cohen et al., 2001). In the present study, continuous scoring was also used. Continuous scoring was used that recoded items from 1-4, such that a high score (i.e., 4) corresponds to more autistic-like behavior, for the

following five areas: social skill, attention switching, attention to detail, communication, and imagination (Austin, 2005). For the present study, internal consistencies were as follows: dichotomous total AQ score (Cronbach's α = .93), social skill (Cronbach's α = .92), attention switching (Cronbach's α = .87), attention to detail (Cronbach's α = .77), communication (Cronbach's α = .89), and imagination (Cronbach's α = .62).

Social Responsiveness Scale, Second Edition (SRS-2; Constantino & Gruber, 2012) . The Social Responsiveness Scale for Adults (SRS-A, other-report) and Social Responsiveness Scale Self-report for Adults (SRS-A-SR, self-report) were used from the SRS-2. The SRS-A is a 65-item questionnaire that is completed by an individual who knows the participant in a naturalistic social setting. The SRS-A and SRS-A-SR assess social-communicative skills and stereotypical restricted behaviors/interests that are often associated with autism. For both measures, an overall score is obtained from items to form a single score of autistic social impairment. Scores range from 0 (high social competence) to 195 (significant social impairment). The SRS-A has been used in prior studies with typically developing individuals (Constantino & Todd, 2005) and neuroimaging studies with individuals with ASD (DiMartino, Shehzad, et al., 2009). It has also been demonstrated to be a reliable and valid measure of the presence and severity of social impairment within the autism spectrum (Constantino & Gruber, 2012). In the present study, the SRS-A and SRS-A-SR had excellent internal consistencies of α = .91 and α = .95, respectively. Of note, the SRS-A and SRS-A-SR only had complete data for 19 participants across both group due to experimenter error; thus, analyses involving these questionnaires are likely underpowered.

Liebowitz Social Anxiety Scale (LSAS; Heimberg et al., 1999). The LSAS assessed social phobia in the past week. Participants rated their fear and avoidance during the past week

on a Likert scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe (Fear/Anxiety); 0 = never (0%), 1 = occasionally (1-33%), 2 = often (33-67%), 3 = usually (67-100%) (Avoidance). As the calculation of a total score is a common method of scoring (Heimberg et al., 1999), a total score was calculated by summing the total fear and total avoidance scores. The LSAS has been used successfully to assess social phobia individuals with ASD (Cath, Ran, Smit, van Balkom, & Comijs, 2008) and in the current study had excellent internal consistency (Cronbach's α = .96).

Depression Anxiety Stress Scales, 21-item (DASS-21; Antony, Bieling, Cox, Enns, & Swinson, 1998). The DASS measures depression, anxiety, and stress symptoms that have been present in the past week. Participants rated their symptoms on a likert scale: 0 = did not apply to me at all, 1 = applied to me to some degree or some of the time, 2 = applied to me a considerable degree or a good part of time, 3 = applied to me very much or most of the time. Scores were summed to create depression (Cronbach's α = .93), anxiety (Cronbach's α = .82), and stress (Cronbach's α = .92) total scores.

Structured Clinical Interview for DSM Disorders, Axis I (SCID-I; First, Spitzer, et al., 1997) and Axis II (SCID-II; First, Gibbon, et al., 1997). The SCID-I and SCID-II were used to screen individuals in the control group for current Axis I and Axis II disorders. To shorten the administration of the SCID-II, the SCID-II Personality Questionnaire was administered (approx. 30 minutes) to participants. Only disorders that screened positive on the SCID-II Personality Questionnaire were followed-up on the SCID-II administration. Full SCID administration took approximately 2 hours. The SCID-I shows substantial reliability, with Kappa ranging between 0.61 to 0.83 and having a mean of 0.71 (Lobbestael, Leurgans, & Arntz, 2010). The SCID-II also shows good reliability, with Kappa ranging between 0.78-0.94 (Lobbestael et al., 2010).

Debriefing questionnaire (Appendix D). The examiner asked participants to rate their subjective units of distress (SUDS) from 0 (not anxious) to 10 (extremely anxious) before and after completing the music task in the scanner. After completing music listening in the scanner, the participant completed questions regarding their focus on the task, how well they understood the directions, how frequently they listened to music, their familiarity with the songs, and if the songs evoked positive or negative memories. A total SUDS score was calculated by summing all SUDS ratings from the rated music-listening scanning session.

Neurophysiological measurement. Functional brain images were captured with a Siemens 3.0T MRI. While in the scanner, the participant was in constant voice-communication with a MRI technician or investigator via an intercom. Participants were helped into the scanner by the experimenter and given another opportunity to ask any questions about the fMRI scanning process. Participants were instructed that they could squeeze a bulb at any time to alert the experimenter to any problem that would necessitate stopping the experiment.

HP data were collected on an MRI-compatible MP150 data acquisition system from BIOPAC Systems, Inc. (Goleta, CA, USA) using OXY100E and PPG00C-MRI amplifiers. Both amplifiers collect HP data, however, the OXY100E would often “flat-line” at points during data collection (e.g., when the scanner began a functional scan). As such, the PPG100C-MRI was purchased due to its improved, robust signal acquisition. Due to these technical difficulties, some participants do not have HP data for baseline (n = 4) and/or task (n = 8).

The MP150 was located in the MRI control room. The amplifier was connected to a signal filter (MRIRFIF-2; BIOPAC Systems, Inc., Goleta, CA, USA). In the scanner room, the OXY100E/PPG100-C cable connected from the signal filter to the subject’s right hand. MRI image and HP acquisition was synchronized using an isolated digital interface (STP100C;

BIOPAC Systems, Inc., Goleta, CA, USA). Specifically, the scanner sent a Transistor-Transistor Logic (TTL) signal to the MP150 at the beginning of image collection, which was received by the STP100C amplifier and started the MP150 data acquisition.

Music Stimuli

Prior to data collection, a pilot study (*N* = 19) was conducted to determine familiar music pieces that elicited variability in the subjective report of energy. Pilot participants continuously rated the music pieces in the scanner, using the same rating scale as the participants included in the current study, i.e., high energy vs. low energy (Figure 1). Each music piece was spectrally decomposed in order to qualitatively determine the pieces that elicited the most variability within individuals and between groups. Spectral decomposition was conducted MATLAB 7.11 (Mathworks, Natick, Massachusetts). The music pieces selected were: Palladio, Gayane: Sabre Dance, Toreador's Song from 'Carmen', Canon in D Major, On the Beautiful Blue Danube, Op. 314, Ein Kleine Nachtmusick, K. 525: I. Allegro-Allegro, and 5th Symphony (See Table 1 for song information). These songs were selected for high variability of subjective rating of energy within the single music piece and that the variability in responses correlated, qualitatively, with subjective ratings and differentiated between TD and ASD groups. Participants in the current study indicated that the songs evoked a positive memory (76.1%), they were familiar (45.7%) or very familiar (37.0%) with the songs, and that they often (43.5%) or always (50.0%) listen to music.

Procedure

Control and ASD groups completed three study phases: online screening, in-person screening, and fMRI session. Separate informed consents were obtained at each phase. ASD and

control participants were compensated at a rate of $20 per hour for their participation in the in-person screening and fMRI sessions.

Online screening: Control and ASD groups. To determine eligibility of control and ASD participants, individuals completed online questionnaires on LimeSurvey (http://www.limesurvey.org/). Participants completed the demographic/background questionnaire, fMRI safety questionnaire, AQ, SRS-A, SRS-A-SR, LSAS, and DASS. The online screening questionnaires took approximately 45 minutes to complete. Eligible participants did not have a history of neurological disorders, or have the presence of shrapnel or metal/electronic implants. Controls participants did not have an AQ score ≥ 32. Eligible participants were scheduled via email for the in-person screening.

In-person screening: Control group. Once eligibility had been confirmed through online screening, control participants were invited to the Virginia Tech Autism Clinic or Virginia Tech Carilion Research Institute (VTCRI) for the in-person screening. During the in-person screening, the following measures were administered (approximately 2-3 hour session): KBIT-2 to assess intelligence level and the SCID-I and SCID-II to assess for current Axis I and Axis II psychiatric disorders. If participants had an IQ > 70 and did not meet criteria for any psychiatric disorder, they were scheduled for the fMRI session. Three participants being screened for the control group met criteria on the SCID I for a DSM-IV-TR Axis I disorder and were excluded from the study.

In-person screening: ASD. After completing the online screening questionnaires, the experimenter contacted the participants with ASD and they were scheduled for an in-person screening at the Virginia Tech Autism Clinic or VTCRI. Participants with ASD were administered the KBIT-2, ADOS, SCID-I, and SCID-II (approximately 3 hour session). Eligible

participants had a score of ≥ 32 on the AQ, prior diagnosis by a community professional, met criteria on the DSM-IV-TR checklist or met criteria for autism or an autism spectrum disorder on the ADOS as determined by a research-reliable doctoral-level graduate student clinician. If ASD participants met criteria for scanning, their fMRI session was scheduled during the in-person session.

Experimental fMRI session: Control and ASD groups. Upon arrival to the Human Neuroimaging Laboratory at VTCRI or the Corporate Research Center, participants received detailed instructions about the music task and were given the opportunity to ask questions (Appendix E). At the end of the session, the majority of participants indicated that they understood (41.3%) or completely understood (52.2%) the directions. After receiving the task instructions, the participant was given a safety talk about the scanners by the experimenter or MRI technician. Participants were helped into place in the scanner by the experimenter and given another opportunity to ask any questions about the fMRI scanning process. Time (approximately 5 minutes) was allowed for both controls and ASD participants to become acclimated to the scanner before collecting data. Participants were instructed that they could squeeze a squeeze bulb at any time to alert the experimenter to any problem that would necessitate stopping the experiment.

After the participant became acclimated to the scanner, a structural scan lasting 5 minutes was performed. At this time, participants were instructed to sit quietly and relax. After the structural scan, a resting functional scan and pulse data were collected for 5 minutes as the participant viewed a fixation cross. The task began following the resting scan. The participant was in the scanner for approximately 45 minutes. Participants completed two scanning sessions

(rated and non-rated); however, only data during the rated session are presented in the current study. Sessions were counterbalanced between participants.

During the rated music-listening task, participants were asked to continuously rate their subjective experience of classical music pieces on arousal (i.e., high energy vs. low energy) and preference (i.e., like a lot vs. do not like) dimensions (see Figure 1 for scale). Participants were instructed to press buttons on a subject response box in order to rate the music. In the non-rating session, participants were not given a button box and were asked to only listen to the music. After they completed the functional scan, participants were helped from the scanner and answered the debriefing questions (Appendix D).

Psychophysiological Data Reduction

Inter-beat intervals (IBI) were edited using CardioEdit (Brain-Body Center, University of Illinois at Chicago) by manually detecting and adjusting outliers. Outliers, caused by missed pulse-wave identification (e.g., IBI too long = 2 seconds), faulty identification of a pulse-wave (e.g., inter-beat interval too short = 0.1 second), or ventricular arrhythmias, were identified and edited via integer arithmetic (i.e., adding short periods together or dividing long period).

After outliers were edited, data were analyzed using CardioBatch (Brain-Body Center, University of Illinois at Chicago). CardioBatch incorporates algorithms that extract the heart rate variance within the frequencies of spontaneous breathing to operationally define RSA amplitude (Porges, 1985; Porges & Bohrer, 1990). Based on these algorithms, sequential heart periods were re-sampled every 250 ms to generate a time series of values at equal intervals. To assess RSA in adults, a frequency band of 0.15- 0.40 Hz was used. RSA and HP data generated were averaged across 30s epochs for baseline (5 minute) and task (27.5 minutes) RSA. In order to align RSA

with brain image acquisition (TR = 2s), RSA time series data were re-sampled every 2 seconds in MATLAB 7.11 (Mathworks, Natick, Massachusetts).

FMRI Data Reduction

Preprocessing steps were completed with MATLAB with SPM8 toolbox (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/): 1) realignment, 2) coregistriation, 3) segmentation, 4) normalization, and 5) smoothing. Anatomically defined regions of interest (ROI) for the amygdala and insula signal were extracted using REX (The Gabrieli Lab, Massachusetts Institute of Technology; http://gablab.mit.edu/).

Data Analysis

Prior to conducting any data analysis, autonomically-defined and perceptually-defined amygdala and insula ROI variables were calculated as described in the hypothesis section. Briefly, autonomically-defined amygdala and insula ROI variables were calculated by averaging three (baseline) or 10 (task) epochs of amygdala or insula ROI signals that began at the onset time of the lowest values of RSA, taking into account the 4s prior to the onset of the lowest RSA values. The perceptually-defined amygdala and insula ROI variables were calculated by averaging the 10 (task) epochs of amygdala or insula ROI signal that began at the onset of the 10 (task) highest ratings of energy. ROI data were calculated for both right and left amygdala and insula in order to detect any differential activation between hemispheres.

After ROI data were calculated, descriptives (i.e., mean, standard deviation, range) were conducted on all demographic and primary study variables. Next, correlations were run between all continuous variables of interest in order to determine any confounding variables. No variables were consistently correlated with variables across the study (e.g., questionnaires, amygdala/insula ROI, and RSA). As such, no covariates were used in the regression analyses.

In order to test the between group hypotheses, independent samples t-tests were conducted to examine between group differences. Regression analyses were then used to predict behavioral measures associated with social behavior related to ASD (AQ social total, SRS-A, SRS-A-SR) across ASD and controls, and ADOS scores within the ASD group, from perceptually- and autonomically-defined neural (i.e., amygdala, insula) and RSA variables. Results are presented below and summarized in Tables 19-21.

Results

Descriptives

To characterize the sample, descriptives were conducted on all demographic variables (i.e., age, minority status, education level) and the primary study variables (i.e., ADOS score, IQ composite, verbal IQ, nonverbal IQ, AQ, SRS-A, SRS-A-SR, DASS-21, LSAS, RSA, right/left autonomically-defined baseline amygdala ROI, right/left autonomically-defined task amygdala ROI, right/left perceptually-defined task amygdala ROI, right/left autonomically-defined baseline insula ROI, right/left autonomically-defined task insula ROI, right/left perceptually-defined task insula ROI. See Tables 3-5 for demographics and primary study variables by group.

Correlations

See Table 6 for correlations between all continuous variables of interest. Notable correlations existed for total social anxiety scores as measured through the LSAS. In particular, total social anxiety was significantly positively correlated with ADOS total score, ADOS social score, ADOS communication score, AQ total score, AQ attention switching, AQ communication, AQ imagination, AQ social score, DASS depression, DASS anxiety, DASS stress, SRS-A total sore, SRS-A-SR total score, and SUDS total score, such that more anxiety was associated with more impairment across each questionnaire. Total social anxiety, however, was not significantly

correlated with left and right physiologically- or perceptually-defined amygdala or insula activation during baseline or task.

During the task, right autonomically-defined amygdala activation and left autonomically-defined insula activation were significantly negatively correlated with the ADOS total score, ADOS social score, ADOS communication score, and DASS depression. Right autonomically-defined insula activation during the task was significantly negatively correlated with ADOS total score, ADOS social score, DASS depression, and was marginally correlated with the ADOS communication score. Further, right autonomically-defined task insula activation was also significantly negatively correlated with DASS anxiety, DASS stress, and AQ communication score. All findings suggested that lower autonomically-defined amygdala and insula activation during the task was associated with greater social and communication impairments related to ASD, as measured by the ADOS, and with more comorbid anxiety, stress, and depression.

Regarding perceptually-defined amygdala and insula activation, lower activation in the right amygdala, left insula, and right insula was associated with significantly more depression (via DASS depression score) and other-reported social symptoms associated with ASD (via the SRS-A score). In addition, less activation in the perceptually-defined right amygdala and insula ROIs were significantly correlated with more stress and anxiety as measured by the DASS.

Additional significant positive correlations emerged between nonverbal IQ and the DASS anxiety, and age (in years) and the SUDS total. Age and IQ were not significantly correlated with any other variables of interest; thus, were not controlled for in the regression analyses presented below. Further, because other variables (e.g., DASS, LSAS) were not significantly correlated across the questionnaire, symptom, and neurophysiological variables, they were not controlled for in the analyses presented below.

T-tests

Independent samples t-tests were conducted to assesses for group differences between all continuous variables of interest. Significant group differences emerged, such that the ASD group reported greater stress, anxiety, depression, and symptoms associated with ASD. Specifically, the ASD group demonstrated significantly higher scores on most subscales of the AQ, with the exception of attention to detail: total score ($t(44) = 8.638$, $p < .001$), switching attention ($t(44) = 6.533$, $p < .001$), attention to detail ($t(44) = 1.467$, $p = .150$), communication ($t(44) = 8.845$, $p < .001$), imagination ($t(44) = 4.564$, $p < .001$), and social skill ($t(44) = 10.344$, $p < .001$). The ASD group demonstrated significantly higher scores (more self-reported impairment) regarding: social anxiety ($t(43) = 5.946$, $p < .001$), depression ($t(40) = 3.363$, $p = .002$), general anxiety ($t(40) = 3.251$, $p = .002$), and stress ($t(40) = 4.274$, $p < .001$).

Significant group differences emerged regarding neurophysiological variables. Specifically, right autonomically-defined task amygdala activation was significantly greater for the control group when compared to the ASD group, $t(44) = 2.087$, $p = .043$. A trend was found for left autonomically-defined insula activation, such that the control group demonstrated more activation relative to the ASD group, $t(44) = 1.664$, $p = .061$. There were no significant group differences for the perceptually-defined ROIs. A significant difference was found for the total SUDS score such that the ASD group demonstrated greater SUDS throughout the task relative to the control group, $t(44) = 2.460$, $p = .018$.

Behavioral Correlates

Perceptually-defined. To examine the social correlates of perceived hyper-arousal in both the ASD and control group, regression analyses were used with amygdala and insula ROI and baseline RSA data to predict AQ social total, SRS-A, and SRS-A-SR. Additionally, in the

ASD group, neurophysiological data were used to predict ASD symptom severity (measured by ADOS total, communication, and social scores). For the entire sample, AQ social total, SRS-A, SRS-A-SR were regressed on perceptually-defined amygdala, insula, and baseline RSA variables. For the ASD group only, ADOS scores were regressed on perceptually-defined amygdala, insula, and baseline RSA. See Tables 7-12 for complete regression results.

For the AQ social total and SRS-A total score, none of the predictor variables were significant: left/right perceptually-defined amygdala, left/right perceptually-defined insula, or perceptually-defined RSA. For the SRS-A-SR (self-report), less left perceptually-defined insula activation predicted higher scores on the SRS-A-SR across control and ASD participants, $b = -1.669$, $t(19) = 2.154$, $p = .044$. The left/right perceptually-defined amygdala ROI, right perceptually-defined insula ROI, and perceptually-defined RSA did not predict SRS-A-SR scores.

Within the ASD group, there was a trend for the prediction of the ADOS social score from the left perceptually-defined insula activation, $b = -1.093$, $t(11) = 1.881$, $p = .067$, such that lower activation of the left insula predicted higher ADOS social scores. The left perceptually-defined insula activation significantly predicted ADOS communication, $b = -1.265$, $t(11) = 2.209$, $p = .032$, in the same direction: less insula activation associated with higher ADOS communication scores. No other predictors were significant for the ADOS total, social, and communication scores.

Autonomically-defined. Using the right/left autonomically-defined baseline and task amygdala and insula data, in addition to autonomically-defined baseline RSA data (i.e., averaging the three lowest epochs of RSA data), regression analyses were used to predict AQ

social total, SRS-A, SRS-A-SR across both groups, and only ADOS scores in the ASD group. See Tables 13-18 for complete regression results.

For the ASD group, there was a trend for autonomically-defined left insula positively predicting ADOS total score, $b = .953$, $t(11) = 1.883$, $p = .068$, the ADOS social score, $b = .949$, $t(11) = 1.852$, $p = .072$, and the ADOS communication score, $b = .869$, $t(11) = 1.814$, $p = .078$. Additionally, the autonomically-defined right amygdala during task negatively predicted the SRS-A-SR, $b = -3.236$, $t(6) = -2.208$, $p = .047$. These results indicated that greater left autonomically-defined insula activation at baseline was associated with greater scores on the ADOS. Conversely, lower right amygdala activation during task was associated with higher scores on the SRS-A-SR. No other questionnaires/behavioral measures were significantly predicted by the autonomically-defined neurophysiological variables across both groups.

Discussion

In this study, fMRI and HP data (used to measure RSA) were continuously collected, along with subjective reports of energy/arousal, while participants with and without ASD listened to classical music. Three continuous streams of data were collected: 1) functional brain images, 2) peripheral nervous system data (via RSA), and 3) perception (i.e., self-reports) of arousal. The relationship between neurophysiological data (i.e., RSA, amygdala, and insula) and measures of social behavior and characteristics of ASD were examined. See Tables 19-21 for summaries of significant findings.

It was hypothesized that the ASD group would demonstrate significantly greater autonomically-defined amygdala activation at baseline, suggesting a threatened/hyper-aroused state compared to the control group. It was also hypothesized that the ASD group would demonstrate significantly lower autonomically-defined baseline insula activation relative to the

control group due to potential difficulties in the perception of physiological state. Contrary to these hypotheses, independent samples t-tests revealed no significant group differences between left/right amygdala and insula ROI signals at baseline. Findings did indicate, however, that right amygdala and right insula, corresponding to the lowest RSA values (i.e., greatest hyper-arousal), were significantly different between the ASD and control groups. As predicted, the ASD group demonstrated lower right insula activation compared to the control group, suggesting that when individuals experienced heighted levels of peripheral nervous system arousal they did not recruit similar structures (i.e., the insula) in order to accurately perceive their physiological state. Yet, contrary to the hypotheses, the ASD group also demonstrated significantly lower right amygdala activation when more autonomically activated. Therefore, contrary to the notion of simultaneous autonomic and amygdala activation reflecting a defensive neurophysiological state, these results instead suggest that when adults with ASD experience an autonomically heighted state, they may experience less amygdala activation then their typically developing peers. Further, this lower right amygdala activation significantly predicted self-reported social behavior associated with ASD (via the SRS-A-SR). Thus, lower right amygdala activation during an autonomically heightened state may be associated with social difficulties related to ASD.

Similar to hypotheses regarding threat responses in the brain, it was also hypothesized that adults with ASD would demonstrate significantly lower RSA than the control group. This was not found: no significant between group differences were found for baseline RSA. Notably, prior findings of lower RSA in ASD groups relative to control groups were found in children and adolescents (e.g., Bal et al., 2010; Van Hecke et al., 2009), not in adults.

In addition to amygdala and insula signal that corresponded to the most heightened physiological state, amygdala and insula ROIs were extracted that corresponded to participant's

highest self-reported arousal (i.e., highest rated “energy”). It was hypothesized that the ASD group would demonstrate lower insula activation, due to difficulties in their perception of their autonomic state. Specific hypotheses were not made regarding amygdala activation. Although overall it was hypothesized that participants with ASD would have greater/chronic neurophysiological activation compared to their typically developing counterparts based on prior literature (e.g., Bal et al., 2010; Dalton et al., 2005), it was unclear whether individuals with ASD would percieve these hightened levels of arousal. In fact, the results indicated that there were no significant between group differences for amygdala or insula activation that corresponded to subjective reports of energy during the task, which suggests that the amygdala and insula activation corresponding to highest subjective reports of arousal are similar between adults with and without ASD.

It was predicted that autonomically-defined baseline amygdala and insula would predict social behavior related to ASD or symptoms of ASD (i.e., on the Social Responsiveness Scale [SRS], Autism Spectrum Quotient [AQ]) across the ASD and control groups, such that greater amygdala activation (indicative of a threat response) and less insula activation (difficulties with perception of autonomic state) would be associated with more impairment. It was predicted that autonomically-defined baseline amygdala and insula ROIs would predict subscale and total scores on the Autism Diagnostic Observation Scheduled (ADOS), a gold-standard assessment measure of ASD: greater amygdala activation and less insula activation associated with higher scores on the ADOS. It was also predicted that baseline RSA would predict SRS and AQ scores across the ASD and control groups, and ADOS subscale and total scores in the ASD group, with lower baseline RSA predicting more social difficulty and scores more symptomatic of ASD. Opposite of the hypotheses, results indicated a trend for greater left autonomically-defined insula

activation predicting higher ADOS total score, ADOS social score, and ADOS communication. Social symptoms on the AQ, SRS-A, or SRS-A-SR, were not predicted by any neurophysiological variables.

Regarding perceptually-defined ROI signal, the perceptually-defined left insula significantly predicted ADOS total score, ADOS social score, and ADOS communication, such that lower insula activity was associated with greater impairment on the ADOS. Additionally, lower perceptualy-defined left insula activity significantly predicted higher scores on the SRS-A-SR. Further, perceptually-defined RSA significantly predicted SRS-A-SR scores, such that lower perceptually-defined RSA was associated with more social difficulties related to ASD.

Overall, these results demonstrate that left insula activity is decreased in adults with ASD compared to the control group. In particular, perceptually-defined left insula activity significantly predicted ADOS scores, such that lower perceptually-defined left insula activity is related to greater ADOS total scores, ADOS social scores, and ADOS communication scores. Lower perceptually-defined left insula is also associated with more impairments in social behavior related to ASD. These results suggest that greater insula activity and the more accurate perception of physiological state is associated with lower scores on the ADOS and fewer social behavior symptoms related to ASD. As such, the perception of one's physiological state may play an important role in social behavior and symptoms related to ASD in ASD and control groups. These results may also point towards more sensitivity of individuals with ASD to their autonomic state – that neural activation of the insula is less in the ASD group because it does not need to be recruited as heavily in order for individuals with ASD to perceive their autonomic state. A second, alternative explanation may be that the perceptually-defined insula activations may be related to participants with ASD dectecting deviations from the norm (Montague &

Lohrenz, 2007). Instead of being more sensitive to their autonomic state, individuals with ASD may be more sensitive to deviations from the norm (e.g., to their autonomic state, changes in the music); thus, may contribute to the findings that insula patterns defined by subjective report predict ADOS scores. Further, it is well known that rigidity and routine are characteristic of ASD (American Psychiatric Association, 2000) and therefore the experience of change (e.g., in autonomic state, in the music) may elicit a stronger subjective response/interpretation. Lastly, due to the significantly higher levels anxiety self-reported in the ASD group, insula activation could potentially be related to anxiety levels. For example, anxiety-prone individuals demonstrate significantly greater bilateral insula activation to emotionally-salient stimuli compared to a control group (Stein, Simmons, Feinstein, & Paulus, 2007). Notably, anxiety was not controlled for in the current study because it was not significantly related to the neurophysiological variables. In future analyses, the relationship between the insula, anxiety, and continuous changes in neurophysiology could be explored.

Unlike predictions regarding the insula, baseline RSA and amygdala responses in the present study did not indicate a chronically mobilized or threatened state, as is demonstrated in studies including children and adolescents (e.g., Bal et al., 2010; Patriquin et al., 2011) and is posited in the Polyvagal Theory (Porges, 2007) and was hypothesized in this study. Instead, findings indicated decreased perceptually-defined amygdala activation predicted more self-reported social behavior symptoms related to ASD. Importantly, the current study was conducted in adults with and without ASD. Unlike children, these adults have the social experience, social exposure, and in some cases, therapeutic interventions that may have altered their neurophysiological baseline states and reactivity. The participants in this study had IQ scores ≥ 70 and as such, were high functioning individuals with ASD. Lower functioning

individuals with ASD typically demonstrate a more chronically activated autonomic nervous system (Goodwin et al., 2006) than their higher functioning peers with ASD who demonstrate more flexibility to stimuli (Bal et al., 2010). Interestingly, this inflexibility of autonomic reactivity may be specific to ASD rather than to intellectual disability. Prior studies have found that children with intellectual disabilities demonstrate psychophysiological reactivity (e.g., heart rate) to stimuli, such as light and sound (Ronca, Tuber, Berntson, & Boysen, 1991).

Limitations to the present study should also be noted. Due to experimenter error, the SRS-A and SRS-A-SR only had complete data for 19 participants across both group; thus, analyses involving these questionnaires were underpowered. There were also no group differences between baseline or rating RSA, which differs from prior studies that found group differences in RSA between ASD and typically developing groups (e.g., Bal et al., 2010). Unlike prior studies that find autonomic differences between ASD and control groups, however, this study was conducted in high functioning adults. Other studies have found significant differences in HRV indices in child and adolescent populations (Bal et al., 2010; Van Hecke et al., 2009) or lower functioning adults with ASD (Goodwin et al., 2006).

Although the simultaneous use of fMRI and psychophysiology provided a rich, unique dataset, consistent data acquisition was initially difficult due to unreliable equipment. As such, data were not acquired for four participants during baseline and eight during the rated music-listening task. These missing data were caused by the original BIOPAC amplifier (OXY100E), which would often flat-line when functional scans were commenced. Because of the unreliable data acquisition, a new amplifier was purchased (PPG100C-MRI), which yielded a reliable and robust pulse signal. Additionally, the neural correlates of low autonomic (i.e., high RSA) and energy (i.e., low energy ratings) were not examined. Future research should examine the neural

correlates of low autonomic/energy states in order to compare brain responses for low/high states and reactivity. ROI data were averaged over a time series (i.e., averaged over 0-20s); therefore, informative hemodynamic response patterns following the "events" (i.e., low RSA or high energy rating) were lost. Future research should also analyze these ROI data as a time series in order to retain the hemodynamic response patterns that may be related to symptoms of ASD, including symptoms related to social behavior. In addition, future research should include greater ASD group sample size in order to improve power for multiple regressions. Due to missing data and a small ASD group, the power of the regressions presented herein are underpowered. A greater sample size in both groups will also improve analyses that incorporate group matching. Due to similar brain areas associated with anxiety and ASD (e.g., insula, amygdala; Stein et al., 2007), future studies should also include an additional group of participants (e.g., social anxiety) in order to identify regions and activation patterns unique to ASD. Lastly, these data will need to be replicated in order to provide meaningful conclusions in understanding the neurophysiological responses that underlie social behavior across control and ASD groups.

This study provides encouraging data to pursue future research in the relationship between peripheral and central nervous system responses during actual and perceived hyper-arousal. Importantly, the insula demonstrated the ability to significantly predict ADOS scores. As the ADOS is a gold-standard diagnostic measure for ASD, this supports the notion of examining psychopathology, including ASD, from a biologically-based perspective in order to improve current psychiatric nosology (Montague, Dolan, Friston, & Dayan, 2012). Clinically, the insula may also be a structure that would show changes pre- and post-intervention; therefore, acting as an objective measure of treatment outcomes. Direct treatments (e.g., via neurofeedback) could target structures such as the insula in order to gauge an individual's ability

to perceive their physiological state. Since the perception of bodily state are associated with symptoms related to ASD this may be one brain area to target for outcomes of an intervention.

In the future, the relationship between autonomic measures, particularly those that are hypothesized to have specific neural connections (e.g., RSA), and brain activity need to be clarified. This is the first study to connect peripheral and central nervous system activity in ASD, despite the large bodies of literature within psychophysiology and neuroimaging that examine these biological processes separately. As both peripheral nervous and central nervous system differences exist across individuals with and without ASD, it will become increasingly important to understand the parallels (or lack thereof) between central and autonomic nervous systems, and how their relationship may be related to symptoms associated with ASD.

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Table 1

Studies of Autonomic Experience in Children, Adolescents, and Adults with ASD

Author (year)	N[a]	Sample characteristics[b]	Cardiovascular Measure(s)[c]	Control Group [d]	Primary findings [e]
Althaus et al. (1999)	36	PDD-NOS. Age range: 7-12 (*M*: 9.8); WISC-R *M*: 106.6	HR, MF HRV	Age, IQ-matched (18). Age: 7-12 (*M*: 9.8); WISC-R *M*: 108	↔ HR baseline PDD-NOS vs. control ↔ MF HRV in PDD-NOS vs. control for attention-demanding task
Bal et al. (2010)	33	AD or PDD-NOS. Age range: 7-17 (*M*: 10.3); K-BIT *M*: 104.13	RSA, HR	Age, IQ-matched (36). Age: 7-17 (*M*: 11.16); K-BIT *M*: 105.66	↓ RSA in ASD vs. control; ↑ HR in ASD vs. control
Bernal et al. (1971)	20	S-A. Age range: 3-13 (*M*: 6.5)	HR	No physical, mental, or emotional disability (20). Age range: 2-11.5 (*M*: 6.10)	↔ HR for tones and lights for S-A vs. control
Cohen et al. (1977)	10	AD. Age range: 5-20 (*M*: 11.3)	HR	Non-ASD (10). Age range: 7-15 (*M*: 10.3)	HR ranged 60-110 bpm for control during task and rest; HR ranged 70-110 bpm for AD (4) during task and rest; HR ranged 110-150 bpm for AD (6) during task and rest
Denver (2004)	20	AD. Age *M*: 15.9; Mental age *M*: 10.1	RSA, HP	Non-ASD (20). Age *M*: 16.5; No mental age reported	↓ RSA in AD vs. control at rest; ↓ HP in AD vs. control at rest
Graveling et al. (1978)	5	AD. Age *M*: 7.6; IQ *M*: 36.4	HP, MSSD, Variance, SeD	Age, sex, education-matched (5). Age *M*: 8.10; IQ *M*: 42.8	↔ HR AD vs. control at rest; ↑ MSSD, Variance, SeD AD vs. control at rest
Goodwin et al. (2006)	5	AD. Age range: 8-18 (*M*: 13.8); CARS *M*: 39	HR	Age, sex-matched (5). Age range: 8-18 (*M*: 13.8)	↑ Baseline HR in AD vs. control; Higher HR (~ > 20 bpm) in AD vs. control for stressors (loud noise, unstructured time)
Hutt et al. (1975)	9	AD. Age range: 4-12 (*M*: 8.9)	HR, Variance	Age-matched group (6). Age range: 4.8-11 (*M*: 7.5)	↑ Variance during stereotypy in AD; ↔ HR across conditions AD vs. control
Lake et al. (1977)	11	AD. Age range: 8-35 (*M*: 15)	HR	Age-matched (12). Age range: 10-20 (*M*: 15)	↔ Baseline or standing HR in AD vs. control
MacCulloch et al. (1971)	19	AD. Age range: 1.3-14.5 (*M*: 8.8)	HR, Variance	Non-AD (10). Age range: 3.8-9.6 (*M*: 6.4)	↑ Variance in AD vs. both control groups; HR ranged 86.1-141.7 for AD during rest; HR ranged 98.4-121.2 for Non-AD, subnormal during rest; HR ranged 90-136.9 for Non-AD
Miller et al. (1971)	20	AD. Age range: 3.75-13 (*M*: 7)	HR	TD (20). Age range: 3.8-11.4 (*M*: 7)	↔ HR in AD vs. control; ↑ HR in control to tone and light, not in AD
Ming et al. (2005)	19	AD symp. (15). Age *M*: 9.4 AD asymp. (14). Age *M*: 9.3	CVT, HR	Asymp., no chronic illness or developmental disorder (17). Age *M*: 8.3	↓ CVT in AD symp., AD asymp. vs. control; ↑ HR in AD symp., AD asymp. vs. control; ↓ CVT in AD symp. vs. AD asymp.
Palkovitz et al. (1980)	10	AD. Age range: 5.8-10 (*M*: 7.6); IQ: mildly-severely deficient	HR	Age-matched (10). Age *M*: 7.7	↔ HR in AD vs. control for all stimuli and baseline; ↑ HR in control to tone, not in AD; ↓ HR in control to meaningful speech, not in AD
Patriquin et al. (2011)	23	AD (12); AS (10); PDD-NOS (1). Age range: 4-7 (*M*: 5.72); PPVT *M*: 88.70	RSA	None	↑ RSA, ↑ PPVT; ↑ RSA, ↑ sharing behaviors; ↑ RSA, ↑ conventional gestures
Sigman et al. (2003)	22	AD. Age *M*: 4.28; Bayley *M*: 2 years	HP	Mental, language age-matched (22). Downs (11); MR (11) Age *M*: 3.95; Bayley *M*: 2 years	↔ HP baseline AD vs. control; ↔ HP in AD vs. control for stressors (stranger, separation from mother)
Toichi et al. (2003)	20	AD. Age *M*: 19.0; VIQ *M*: 83.4	HP, CVI	Age, sex, years education, non-verbal reasoning-matched (20). Age *M*: 20.5; VIQ *M*: 79.8	↔ HP, CVI baseline AD vs. control; ↓ HP in control vs. ↔ AD for mental tasks; ↓ CVI in control vs. slight increase AD for mental arithmetic
Van Hecke et al. (2009)	19	AD or PDD-NOS. Age range: 8-12 (*M*: 9.95); K-BIT *M*: 102.42	RSA	Age, IQ-matched (14). Age range: 8-12 (*M*: 9.93); K-BIT *M*: 103.86	↓ RSA overall in ASD vs. control; ↓ RSA in ASD vs. control for an unfamiliar person; ↑ RSA related to ↑ social skills and ↓ behavior problems
Zahn et al. (1987)	13	AD. Age range: 18-39 (*M*: 27.8); IQ (8) ≥ 80; IQ (3) ~ average	HR, HRV	TD (19). Age range: 20-38 (*M*: 27.5)	↔ HR for AD vs. control at rest; ↓ HRV for AD vs. control at rest; ↓ HR for control groups to reaction time task, not in AD

[a]Size of ASD sample.

[b]Diagnosis (number of participants with specific diagnoses). AD = Autistic Disorder, AS = Asperger's Syndrome, PDD-NOS = Pervasive Developmental Disorder-Not Otherwise Specified, symp. = symptoms of autonomic dysfunction, asymp. = no symptoms of autonomic dysfunction, S-A = schizophrenia of the autistic type, K-BIT = Kaufman Brief Intelligence Test, Bayley = Bayley Scale of Infant Development, VIQ = verbal IQ, PIQ = performance IQ, PPVT = Peabody Picture Vocabulary Test 3rd edition, WISC-R = Wechsler Intelligence Scale for Children-Revised.

[c]HR = heart rate, CVT = cardiac vagal tone, RSA = respiratory sinus arrhythmia, HP = heart period, CVI = cardiac vagal index, MF HRV = mid frequency band heart rate variability (0.07-0.14 Hz), bpm = beats per minute, MSSD = mean square successive difference, HRV = heart rate variability, SeD = second differential.

[d]Downs = Down's syndrome, MR = mental retardation, TD = typically developing.

[e] ↑ = significantly higher or significant increase, ↓ = significantly lower or significant decrease, ↔ = no significant difference or change.

Table 2

Classical Music Songs used in the Current Study and Pilot Study

Song Name	Composer	Performer(s)
Palladio	Karl Jenkins	Karl Jenkins & The Smith Quartet
Gayane: Sabre Dance	Aram Khachaturian	Royal Philharmonic Orchestra & Yuri Simonov
Toreador's Song from 'Carmen'	Georges Bizet	Royal Philharmonic Orchestra
Canon in D Major	Johann Pachelbel	London Philharmonic Orchestra & David Parry
On the Beautiful Blue Danube, Op. 314	Johann Strauss II	London Philharmonic Orchestra & David Parry
Eine Kleine Nachtmusick, K. 525: I. Allegro-Allegro	Wolfgang Amadeus Mozart	Royal Philharmonic Orchestra & Yuri Simonov
5th Symphony	Ludwig Van Beethoven	Philharmonia Orchestra

Table 3

Descriptive Statistics for Continuous Sample Characterization Variables for ASD (n = 16) and control (n = 30) groups

Variable	ASD Mean (*SD*)	ASD Range	TD Mean (*SD*)	TD Range
Age	23.13 (5.18)	18.00-35.00	21.63 (3.86)	18.00-31.00
KBIT total standard score	106.69 (11.85	93.00-137.00	104.63 (10.69)	87.00-125.00
KBIT verbal standard score	105.63 (15.75)	85.00-145.00	102.60 (10.79)	75.00-126.00
KBIT nonverbal standard score	105.38 (12.67)	86.00-130.00	104.77 (12.51)	85.00-132.00
ADOS total score	9.75 (4.25)	2.00-18.00	-	-
ADOS social interaction total	7.25 (2.96)	2.00-12.00	-	-
ADOS communication total	2.50 (1.90)	0.00-6.00	-	-
AQ total score (binary scoring)	19.511 (10.57)	2.00-42.00	18.95 (6.13)	8.00-27.00
AQ total score (continuous scoring)**	137.88 (14.76)	115.00-166.00	96.07 (16.07)	55.00-124.00
AQ switch**	31.38 (3.91)	24.00-37.00	22.03 (4.944)	12.00-30.00
AQ detail	28.44 (3.41)	22.00-34.00	26.00 (6.14)	12.00-38.00
AQ communication**	26.81 (4.85)	20.00-34.00	15.10 (3.95)	10.00-25.00
AQ imagination**	22.75 (4.63)	16.00-30.00	17.27 (3.43)	11.00-24.00
AQ social**	28.50 (4.50)	21.00-38.00	15.67 (3.73)	10.00-26.00
LSAS total**	58.93 (21.60)	17.00-106.00	25.77 (15.37)	1.00-60.00
DASS depression**	6.00 (5.02)	0.00-20.00	1.90 (2.88)	0.00-14.00
DASS anxiety**	5.08 (4.57)	0.00-14.00	1.59 (2.41)	0.00-12.00
DASS stress**	8.69 (5.92)	0.00-20.00	3.00 (2.78)	0.00-13.00
SRS-A	97.80 (32.44)	44.00-151.00	24.41 (21.87)	3.00-93.00
SRS-A-SR	93.60 (30.78)	45.00-139.00	25.94 (17.25)	2.00-70.00
SUDS total	8.13 (5.91)	0.00-21.00	4.33 (4.42)	0.00-14.00

Note: KBIT = Kaufman Brief Intelligence Test, ADOS = Autism Diagnostic Observation Schedule, AQ = Autism Quotient, LSAS = Leibowitz Social Anxiety Scale, DASS = Depression, Anxiety, and Stress Scales, SRS-A = Social Responsiveness Scale Adult Version Other-Report, SRS-A-SR = Social Responsiveness Scale Adult Version Self-Report, SUDS total = total score for Subjective Units of Distress, significant group differences = * $p < .05$, ** $p < .01$.

Table 4

Descriptive Statistics for Neurophysiological Variables (N =46)

Variable	ASD Mean (*SD*)	ASD Range	TD Mean (*SD*)	TD Range
Baseline Amygdala Left[1]	-.29 (1.80)	-4.62-2.18	-.72 (2.10)	-6.58-1.92
Baseline Amygdala Right[1]	-.13 (1.24)	-2.31-1.76	-.45 (1.73))	-4.78-2.24
Baseline Insula Left[1]	-.01 (1.21)	-2.04-2.30	-.30 (1.35)	-3.44-3.19
Baseline Insula Right[1]	-.13 (1.51)	-1.90-3.31	-.36 (1.69)	-4.13-4.44
Task Amygdala Left[1]	-.48 (1.36)	-4.13-1.41	-.20 (1.18)	-4.55-1.90
Task Amygdala Right[1]	-84 (1.84)	-5.41-1.16	.00 (.90)	-2.33-1.38
Task Insula Left[1]*	-.61 (1.50)	-3.86-.71	-.03 (.89)	-2.82-2.22
Task Insula Right[1]**	-.84 (2.14)	-7.10-.80	.00 (.83)	-2.41-1.75
Energy Amygdala Left[2]	.50 (1.55)	-2.28 (4.97)	.25 (1.65)	-4.93-2.94
Energy Amygdala Right[2]	.96 (2.59)	-.54-10.19	-.26 (3.05)	-13.89-3.89
Energy Insula Left[2]	.51 (2.56)	-3.13-9.04	-.24 (2.35)	-9.66-2.41
Energy Insula Right[2]	1.10 (3.95)	-1.48-15.14	-.30 (2.76)	-11.29-3.02
Baseline RSA (ln(ms)^2)	7.43 (1.53)	5.67-10.90	7.35 (1.34)	4.98-10.93
Task RSA (ln(ms)^2)	7.47 (1.60)	5.30-10.28	7.39 (1.14)	5.32-9.77
Perceptually-defined RSA (ln(ms)^2)	7.27 (1.76)	5.08-10.40	7.28 (1.39)	5.32-10.00

Note. 1 = autonomically-defined ROI, 2 = perceptually-defined ROI, RSA = respiratory sinus arrhythmia, significant group differences = * $p < .05$, ** $p < .01$.

Table 5

Descriptive Statistics for Categorical Variables of Interest (N = 46)

Variable	Percentage (*n*)
ASD Gender	
Men	62.52 (10)
Women	37.5 (6)
TD Gender	
Men	46.7 (14)
Women	53.3 (16)
Race/Ethnicity	
Caucasian	78.3 (36)
African American/Black/ African Origin	6.5 (3)
Hispanic/Latino/Latina	6.5 (3)
Asian American/Asian Origin/Pacific Islander	4.3 (2)
Other	4.3 (2)
Highest Level of Education	
Graduated high school	34.8 (16)
Attended college/specialized training	52.2 (24)
Graduated from college	10.9 (5)
Completed grad school	2.2 (1)

Table 6

Pearson Moment Correlations Among All Continuous Variables of Interest (N =46)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.	31.	32.	33.	34.	35.
1. Age	1																																		
2. ADOS total	.18	1																																	
3. ADOS social	.16	.98***	1																																
4. ADOS comm	.20	.91***	.82***	1																															
5. AQ total	.09	.64***	.65***	.51***	1																														
6. AQ switch	.01	.60***	.60***	.51***	.92***	1																													
7. AQ detail	.09	.11	.12	.05	.45***	.27	1																												
8. AQ comm	.11	.65***	.67***	.52***	.94***	.84***	.26	1																											
9. AQ imagine	.14	.42**	.46**	.27	.84***	.70***	.33*	.77***	1																										
10. AQ social total	.04	.70***	.71***	.61***	.89***	.84***	.12	.87***	.67***	1																									
11. LSAS total	.06	.57***	.55***	.56***	.74***	.81***	.15	.72***	.48***	.72***	1																								
12. DASS depress	.09	.43***	.41***	.45***	.54***	.57***	.23	.56***	.41***	.41***	.47***	1																							
13. DASS anx	.04	.34*	.35*	.29	.46***	.50***	.15	.49***	.36*	.35*	.48***	.81***	1																						
14. DASS stress	.03	.42**	.42**	.39*	.58***	.65***	.17	.60***	.45***	.47***	.61***	.75***	.86***	1																					
15. KBIT verb	-.19	.17	.19	.11	.20	.30*	.03	.15	.10	.18	.27	.25	.15	.03	1																				
16. KBIT nonverb	.08	-.06	-.06	-.06	.17	.19	.14	.13	.20	.08	.13	.27	.32*	.27	.15	1																			
17. KBIT total	-.08	.07	.08	.03	.24	.32*	.12	.19	.19	.17	.25	.32*	.29	.20	.76***	.76***	1																		
18. SRS-A	.13	.61***	.66***	.52***	.78***	.71***	.22	.80***	.56***	.72***	.67***	.72***	.68***	.69***	.06	.34	.26	1																	
19. SRS-A-SR	.21	.76***	.73***	.67***	.87***	.84***	.35	.89***	.52***	.79***	.79***	.72***	.79***	.69***	.22	.27	.33	.85***	1																
20. SUDS	.32*	.21	.20	.21	.37*	.28	.12	.36*	.38**	.28	.34*	.41**	.39*	.39*	-.26	.02	-.16	.45*	.34	1															
21. Base_amygL	.01	.03	.06	-.03	.05	.04	-.07	.13	-.08	.13	.00	.13	.08	.11	-.14	.30	.10	.23	.16	.21	1														
22. Base_amygR	.07	.09	.09	.09	.07	.03	-.09	.15	.00	.15	.02	.19	.10	.06	-.12	.26	.09	.29	.28	.11	.87***	1													
23. Base_insL	.17	.22	.19	.29	.06	-.02	.13	.08	-.01	.06	-.02	.27	.16	.11	-.08	.16	.06	.37	.39	.07	.52***	.71***	1												
24. Base_insR	.19	.14	.10	.23	.05	-.02	.17	.04	-.03	.03	-.02	.30	.21	.17	-.09	.14	.03	.35	.32	.08	.48***	.68***	.95***	1											
25. Rate_amygL	.08	-.08	-.11	.00	-.13	-.08	-.08	-.17	-.16	-.06	.09	-.16	-.09	-.06	.05	.16	.15	.07	.00	-.03	.09	.19	.13	.24	1										
26. Rate_amygR	-.02	-.30*	-.33*	-.19	-.24	-.17	-.11	-.32*	-.21	-.16	-.02	-.34*	-.22	-.23	.02	.22	.17	-.27	-.25	-.18	-.06	.02	-.14	-.04	.84***	1									
27. Rate_insL	-.03	-.35*	-.34*	-.31*	-.18	-.12	-.10	-.24	-.17	-.12	-.05	-.38*	-.23	-.18	-.07	.05	.00	-.24	-.30	.00	.10	.04	-.21	-.10	.73***	.84***	1								
28. Rate_insR	-.10	-.32*	-.32*	-.27	-.23	-.15	-.14	-.31*	-.21	-.14	-.06	-.51***	-.34*	-.31*	.03	.07	.08	-.32	-.34	-.19	-.03	-.05	-.27	-.19	.71***	.91***	.92***	1							
29. Energy_amygL	.22	.02	.01	.06	.00	-.03	.18	.01	-.14	-.01	.01	.24	.09	.14	-.10	.05	-.04	.28	.12	.08	.01	.01	.25	.25	.02	-.24	-.23	-.34*	1						
30. Energy_amygR	.25	.13	.13	.12	.06	-.01	-.07	.22	-.08	.10	.03	.44**	.33*	.31*	-.25	-.03	-.19	.42*	.33	.29	.06	.03	.17	.16	-.21	-.43***	-.38*	-.50***	.56***	1					
31. Energy_insL	.28	.03	.03	.03	.05	.00	-.08	.19	-.09	.10	.05	.37*	.23	.27	-.28	.04	-.17	.41*	.26	.31*	.11	.07	.15	.18	-.12	-.35*	-.25	-.42**	.65***	.93***	1				
32. Energy_insR	.29	.11	.10	.11	.13	.08	.02	.26	-.01	.14	.11	.51***	.36*	.37*	-.25	.05	-.14	.46*	.35	.35*	.09	.06	.19	.20	-.26	-.50***	-.43***	-.60***	.65***	.93***	.96***	1			
33. Base_RSA	-.26	.00	.00	-.01	.01	.11	.03	-.02	-.09	.02	.05	.18	.24	.08	.11	.10	.13	.17	.17	.11	.27	.18	.19	.16	.06	.02	.07	-.01	.12	.06	.00	.06	1		
34. Rate_RSA	-.05	-.10	-.11	-.07	.16	.13	.24	.11	.15	.06	-.01	.17	.28	.12	-.12	.21	.04	.28	.24	.28	.20	.18	.21	.18	-.08	-.08	-.04	-.17	.06	.17	.05	.15	.71**	1	
35. Energy_RSA	-.04	-.16	-.15	-.18	.06	.04	.16	.02	.07	-.01	-.02	.18	.23	.14	-.21	.31	.07	.26	.14	.31	.39*	.31	.31	.26	-.08	-.09	-.01	-.16	.02	.13	.06	.13	.81***	.82***	1

Note. ADOS = Autism Diagnostic Observation Schedule, ADOS total = ADOS total score, ADOS social = ADOS social interaction subtotal, ADOS comm = ADOS communication subtotal, AQ = Autism Quotient, AQ total = AQ total score, AQ switch = AQ switching attention, AQ detail = AQ paying attention to details, AQ comm = AQ communication, AQ imagine = AQ imagination, AQ social = AQ social behavior, LSAS = Liebowitch Social Anxiety Scale, DASS = Depression, Anxiety, and Stress Scales, DASS depress = DASS depression subscale, DASS anx = DASS anxiety subscale, DASS stress subscale, KBIT = Kaufman Brief Intelligence Test, KBIT verb = KBIT verbal standard score, KBIT nonverb = KBIT nonverbal standard score, SRS-A = Social Responsiveness Scale Adult Other-report, SRS-A-SR = Social Responsiveness Scale Adult Self-report, SUDS = Subjective Units of Distress Scale total score, Base_amygL = autonomically-defined baseline left amygdala ROI, Base_amygR = autonomically-defined baseline right amygdala ROI, Base_insL = autonomically-defined baseline left insula ROI, Base_insR = autonomically-defined baseline right insula ROI, Task_amygL = autonomically-defined task left amygdala ROI, Task_amygR = autonomically-defined task right amygdala ROI, Task_insL = autonomically-defined task left insula ROI, Task_insR = autonomically-defined task right insula ROI, Energy_amygL = perceptually-defined left amygdala ROI, Energy_amygR = perceptually-defined right amygdala ROI, Energy_insL = perceptually-defined left insula ROI, Energy_insR = perceptually-defined right insula ROI, Base_RSA = baseline RSA (averaged 3 minutes), Rate_RSA = task RSA (averaged 10 minutes), Energy_RSA = perceptually-defined RSA, * $p < .05$, ** $p < .01$.

Table 7

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting AQ Social Score (N = 46)

Variable	*B*	*SE*	β	
Outcome: AQ Social Score				
Step 1				
Amygdala Left	-.43	.79	-.10	
Amygdala Right	.36	.44	.15	$F(2, 42) = .347$, $p = .709$, $R^2 = .02$
Step 2				
Amygdala Left	-.82	.91	-.19	
Amygdala Right	-.60	1.11	-.25	
Insula Left	-.67	1.69	-.24	
Insula Right	1.55	1.31	.72	$F(4, 40) = .568$, $p = .687$, $\Delta R^2 = .04$
Step 3				
Amygdala Left	-.87	.92	-.20	
Amygdala Right	-.53	1.13	-.23	
Insula Left	-.73	1.72	-.25	
Insula Right	1.56	1.32	.73	
Energy RSA	-.12	.33	-.06	$F(5, 39) = .473$, $p = .794$, $\Delta R^2 = .00$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 8

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting SRS-A (N = 25)

Variable	*B*	*SE*	β	
Outcome: SRS-A				
Step 1				
Amygdala Left	1.95	5.18	.08	
Amygdala Right	4.59	2.69	.38	$F(2, 23) = 2.556$, $p = .099$, $R^2 = .10$
Step 2				
Amygdala Left	-.64	6.62	-.03	
Amygdala Right	-.04	8.72	-.00	
Insula Left	-7.00	11.78	-.48	
Insula Right	10.12	9.18	.94	$F(4, 21) = 1.539$, $p = .227$, $\Delta R^2 = .55$
Step 3				
Amygdala Left	-.81	6.55	-.03	
Amygdala Right	3.07	9.00	.25	
Insula Left	-9.40	11.82	-.64	
Insula Right	10.05	9.08	.93	
Energy RSA	-3.23	2.67	-.25	$F(5, 20) = 1.551$, $p = .219$, $\Delta R^2 = .24$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 9

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting SRS-A-SR (N = 24)

Variable	*B*	*SE*	β	
Outcome: SRS-A-SR				
Step 1				
Amygdala Left	-1.18	4.79	-.06	
Amygdala Right	3.73	2.39	.36	$F(2, 22) = 1.408$, $p = .266$, $R^2 = .11$
Step 2				
Amygdala Left	-2.68	5.66	-.12	
Amygdala Right	3.00	7.00	.29	
Insula Left	-17.21	10.21	-1.37	
Insula Right	13.49	8.14	1.48	$F(4, 20) = 1.622$, $p = .208$, $\Delta R^2 = .13$
Step 3				
Amygdala Left	-2.24	5.30	-.11	
Amygdala Right	8.19	7.07	.79	
Insula Left*	-21.01	9.75	-1.67	
Insula Right	12.63	7.64	1.383	
Energy RSA	-4.11	2.11	-.40	$F(5, 19) = 2.242$, $p = .092$, $\Delta R^2 = .13$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 10

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting ADOS Total (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Total				
Step 1				
Amygdala Left	-.23	.60	-.70	
Amygdala Right	.30	.33	.17	$F(2, 14) = .424$, $p = .657$, $R^2 = .02$
Step 2				
Amygdala Left	.05	.66	.02	
Amygdala Right	.93	.81	.53	
Insula Left	-2.40	1.24	-1.12	
Insula Right	1.09	.96	.68	$F(4, 12) = 1.164$, $p = .341$, $\Delta R^2 = .08$
Step 3				
Amygdala Left	-.05	.67	-.02	
Amygdala Right	1.07	.82	.60	
Insula Left*	-2.52	1.24	-1.17	
Insula Right	1.13	.96	.70	
Energy RSA	-.27	.24	-.18	$F(5, 11) = 1.199$, $p = .327$, $\Delta R^2 = .03$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 11

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting ADOS Social (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Social				
Step 1				
Amygdala Left	-.22	.45	-.09	
Amygdala Right	.24	.25	.18	$F(2, 14) = .464$, $p = .632$, $R^2 = .02$
Step 2				
Amygdala Left	-.01	.50	-.00	
Amygdala Right	.71	.61	.53	
Insula Left	-1.68	.93	-1.05	
Insula Right	.73	.72	.61	$F(4, 12) = 1.057$, $p = .390$, $\Delta R^2 = .07$
Step 3				
Amygdala Left	-.08	.50	-.03	
Amygdala Right	.80	.62	.60	
Insula Left	-1.76	.94	-1.09	
Insula Right	.76	.72	.63	
Energy RSA	-.18	.18	-.16	$F(5, 11) = 1.052$, $p = .401$, $\Delta R^2 = .02$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 12

Hierarchical Linear Regressions: Perceptually-Defined Amygdala, Insula, and RSA predicting ADOS Communication (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Communication				
Step 1				
Amygdala Left	-.01	.17	-.01	
Amygdala Right	.06	.09	.13	$F(2, 14) = .295$, $p = .746$, $R^2 = .01$
Step 2				
Amygdala Left	.06	.18	.07	
Amygdala Right	.22	.23	.45	
Insula Left*	-.72	.34	-1.20	
Insula Right	.36	.27	.80	$F(4, 12) = 1.253$, $p = .304$, $\Delta R^2 = .10$
Step 3				
Amygdala Left	.03	.18	.03	
Amygdala Right	.27	.23	.54	
Insula Left*	-.76	.34	-1.27	
Insula Right	.37	.26	.83	
Energy RSA	-.09	.07	-.21	$F(5, 11) = 1.394$, $p = .248$, $\Delta R^2 = .04$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 13

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting AQ Social Score (N = 40)

Variable	*B*	*SE*	β	
Outcome: AQ Social Score				
Step 1				
Amygdala Left	-.04	1.15	-.01	
Amygdala Right	.74	1.45	.16	$F(2, 38) = .467$, $p = .630$, $R^2 = .02$
Step 2				
Amygdala Left	-.33	1.23	-.09	
Amygdala Right	1.49	1.88	.33	
Insula Left	.91	2.82	.17	
Insula Right	-1.38	2.22	-3.12	$F(4, 36) = .381$, $p = .821$, $\Delta R^2 = .02$
Step 3				
Amygdala Left	-.26	1.29	-.08	
Amygdala Right	1.42	1.94	.32	
Insula Left	.99	2.89	.18	
Insula Right	-1.39	2.26	-.32	
Baseline RSA	-.12	.60	-.04	$F(5, 35) = .304$, $p = .907$, $\Delta R^2 = .00$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 14

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting SRS-A (N = 23)

Variable	*B*	*SE*	β	
Outcome: SRS-A				
Step 1				
Amygdala Left	-1.88	8.84	-.09	
Amygdala Right	9.19	10.19	.36	$F(2, 21) = .990$, $p = .388$, $R^2 = .09$
Step 2				
Amygdala Left	.35	9.18	.02	
Amygdala Right	-.51	13.97	-.02	
Insula Left	21.27	28.36	.73	
Insula Right	-8.24	22.65	-.36	$F(4, 19) = .818$, $p = .529$, $\Delta R^2 = .06$
Step 3				
Amygdala Left	2.39	9.83	.11	
Amygdala Right	-2.43	14.49	-.10	
Insula Left	25.10	29.39	.86	
Insula Right	-10.17	23.19	-.45	
Baseline RSA	-2.65	4.07	-.16	$F(5, 18) = .720$, $p = .617$, $\Delta R^2 = .02$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 15

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting SRS-A-SR (N = 21)

Variable	*B*	*SE*	β	
Outcome: SRS-A-SR				
Step 1				
Amygdala Left	-6.89	7.56	-.42	
Amygdala Right	12.30	8.70	.65	$F(2, 19) = 1.27$, $p = .305$, $R^2 = .12$
Step 2				
Amygdala Left	.06	8.62	.00	
Amygdala Right	-1.17	13.08	-.06	
Insula Left	42.85	27.51	1.89	
Insula Right	-26.14	19.88	-1.50	$F(4, 17) = 1.32$, $p = .301$, $\Delta R^2 = .12$
Step 3				
Amygdala Left	.48	9.67	.03	
Amygdala Right	-1.72	14.34	-.09	
Insula Left	43.89	29.85	1.94	
Insula Right	-26.67	21.04	-1.52	
Baseline RSA	-.36	3.23	-.03	$F(5, 16) = 1.00$, $p = .449$, $\Delta R^2 = .00$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 16

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting ADOS Total (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Total				
Step 1				
Amygdala Left	-.50	.87	-.19	
Amygdala Right	.86	1.10	.25	$F(2, 14) = .326$, $p = .724$, $R^2 = .02$
Step 2				
Amygdala Left	-.42	.90	-.16	
Amygdala Right	.16	1.38	.05	
Insula Left	3.67	2.07	.89	
Insula Right	-2.18	1.63	-.66	$F(4, 12) = 1.024$, $p = .408$, $\Delta R^2 = .09$
Step 3				
Amygdala Left	-.20	.93	-.08	
Amygdala Right	-.08	1.40	-.02	
Insula Left	3.93	2.09	.95	
Insula Right	-2.21	1.63	-.67	
Baseline RSA	-.40	.43	-.16	$F(5, 11) = .989$, $p = .439$, $\Delta R^2 = .02$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 17

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting ADOS Social (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Social				
Step 1				
Amygdala Left	-.17	.65	-.08	
Amygdala Right	.41	.83	.16	$F(2, 14) = .183$, $p = .833$, $R^2 = .01$
Step 2				
Amygdala Left	-.16	.68	-.08	
Amygdala Right	.04	1.03	.02	
Insula Left	2.80	1.55	.91	
Insula Right	-1.81	1.22	-.73	$F(4, 12) = .927$, $p = .459$, $\Delta R^2 = .08$
Step 3				
Amygdala Left	-.06	.71	-.03	
Amygdala Right	-.08	1.06	-.03	
Insula Left	2.92	1.58	.95	
Insula Right	-1.82	1.23	-.74	
Baseline RSA	-.19	.33	-.10	$F(5, 11) = .798$, $p = .559$, $\Delta R^2 = .01$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 18

Hierarchical Linear Regressions: Autonomically-Defined Amygdala, Insula, and Baseline RSA predicting ADOS Communication (N = 16)

Variable	*B*	*SE*	β	
Outcome: ADOS Communication				
Step 1				
Amygdala Left	-.33	.24	-.44	
Amygdala Right	.45	.31	.47	$F(2, 14) = 1.105$, $p = .342$, $R^2 = .06$
Step 2				
Amygdala Left	-.26	.25	-.34	
Amygdala Right	.13	.38	.13	
Insula Left	.87	.57	.75	
Insula Right	-.38	.45	-.40	$F(4, 12) = 1.483$, $p = .228$, $\Delta R^2 = .09$
Step 3				
Amygdala Left	-.14	.25	-.19	
Amygdala Right	.00	.37	.00	
Insula Left	1.01	.56	.87	
Insula Right	-.39	.44	-.42	
Baseline RSA	-.21	.12	-.30	$F(5, 11) = 1.922$, $p = .116$, $\Delta R^2 = .07$

Note. RSA = respiratory sinus arrhythmia; * $p < .05$, ** $p < .01$.

Table 19

Summary of Significant Correlations

Variable	Correlated	Direction
LSAS	ADOS Total, ADOS Social, ADOS Communication, AQ Total, AQ Attention Switching, AQ Communication, AQ Imagination, AQ Social, DASS Depression, DASS Anxiety, DASS Stress, SRS-A, SRS-A-SR, SUDS	+
Right autonomically-defined task amygdala	ADOS Total, ADOS Social, ADOS Communication, DASS Depression	-
Left autonomically-defined task insula	ADOS Total, ADOS Social, ADOS Communication, DASS Depression	-
Right autonomically-defined task insula	ADOS Total, ADOS Social, ADOS Communication*, DASS Depression	-
Right perceptually-defined amygdala	DASS Depression, SRS-A	-
Left perceptually-defined insula	DASS Depression, SRS-A	-
Right perceptually-defined insula	DASS Depression, SRS-A	-
Nonverbal IQ	DASS Anxiety	+
Age (years)	SUDS total	+

Note. ADOS = Autism Diagnostic Observation Schedule, AQ = Autism Spectrum Quotient, DASS = Depression Anxiety Stress Scale, SRS-A = Social Responsiveness Scale, Other-Report, SRS-A-SR = Social Responsiveness Scale, Self-Report, SUDS = Subjective Units of Distress total score, * p = .08-.051.

Table 20

Summary of Significant Between Group (ASD vs. TD) Differences

Variable
↑ASD ↓TD
AQ Total
AQ Switching Attention
AQ Attention to Detail
AQ Communication
AQ Imagination
AQ Social Skill
LSAS
DASS Depression
DASS Anxiety
DASS Stress
SUDS
↓ASD ↑TD
Right autonomically-defined task amygdala
Left autonomically-defined task insula*

Note. AQ = Autism Spectrum Quotient, LSAS = Liebowitz Social Anxiety Scale, DASS = Depression Anxiety Stress Scale, SUDS = Subjective Units of Distress total score, * p = .08-.051.

Table 21

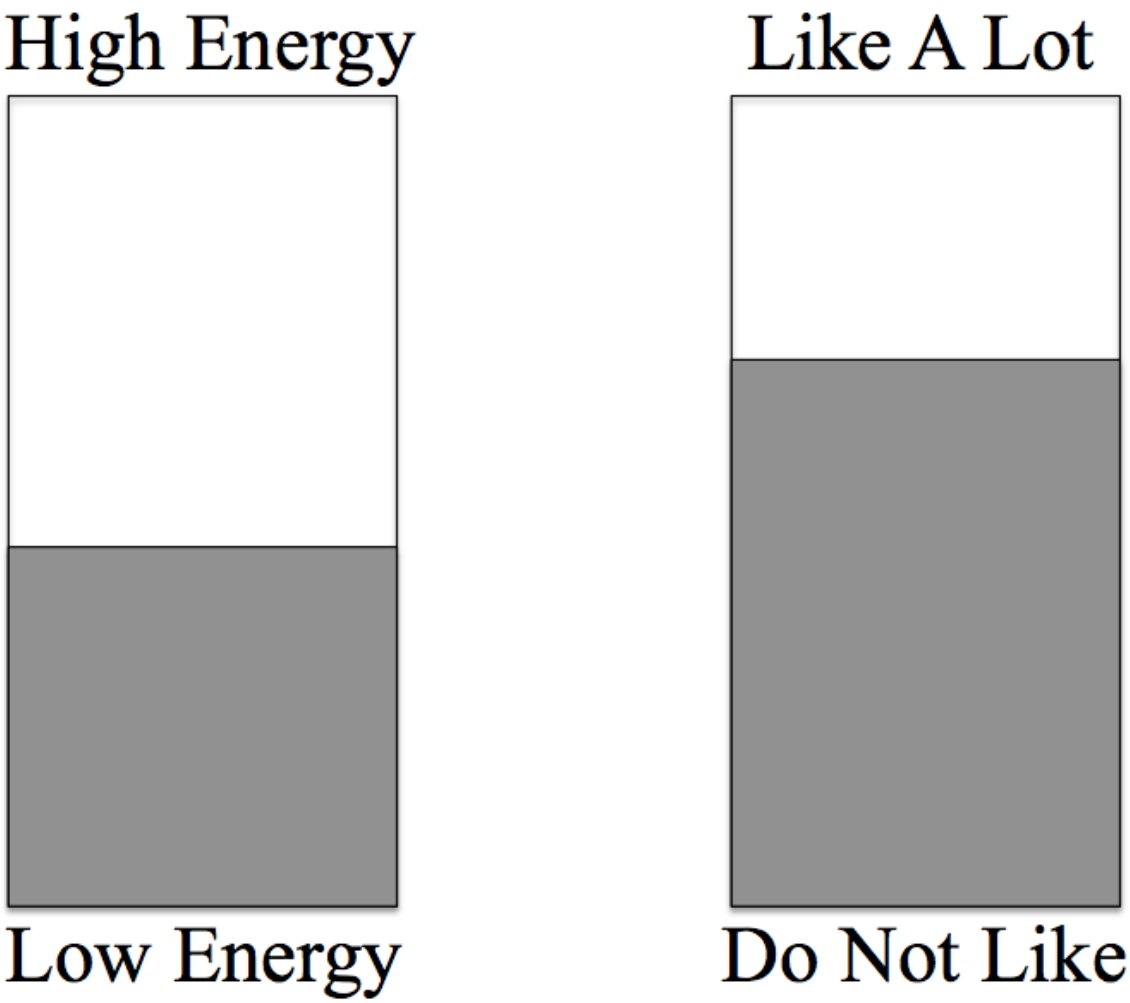
Summary of Significant Predictors from Hierarchical Regressions

Predictor	Outcome Variable	Direction
Left perceptually-defined insula	SRS-A-SR	-
Left perceptually-defined insula	ADOS Social	-
Left perceptually-defined insula	ADOS Communication	-
Right autonomically-defined task amygdala	SRS-A-SR	-
Left autonomically-defined baseline insula	ADOS Total	+
Left autonomically-defined baseline insula	ADOS Social	+
Left autonomically-defined baseline insula	ADOS Communication	+

Note. ADOS = Autism Diagnostic Observation Schedule, SRS-A-SR = Social Responsiveness Scale, Self-Report, * p = .08-.051.

Figure Captions

Figure 1. Visual representation of arousal and preference rating scale projected inside the MRI scanner.


High Energy
Low Energy
Like A Lot
Do Not Like

Appendix A
DSM-IV-TR Symptom Checklist

Subject ID #: _____
Date: _____

A. Complete the following items concerning characteristics observed. Circle "Yes," "No," or "Unknown" to each of the following questions.

Social Interaction

1) Does the individual use non-verbal cues, facial expression, body posture, and gestures when communicating with others?

Yes No Unknown

2) Does the individual have friendships comparable to other individuals the same age?

Yes No Unknown

3) Does the individual show enjoyment of interests or achievements with other people by showing or pointing out objects?

Yes No Unknown

4) Does the individual ask how other people are feeling or show concern when another person is hurt or upset?

Yes No Unknown

Communication

5) Does the individual lack spoken language?

Yes No Unknown

6) If the individual does lack spoken language, does he or she attempt to communication through gestures or sign language?

Yes No Unknown

7) Does the individual show the ability to initiate or continue conversations with other people, if able to speak?

Yes No Unknown

8) Does the individual exhibit repetitive or odd use of language, such as making up words or using words in the wrong context?

Yes No Unknown

9) Does the individual show spontaneous imaginative or social play appropriate to developmental level (if applicable)?

Yes No Unknown

Repetitive, Stereotyped Patterns of Behavior, Interests and Activities

10) Does the individual exhibit preoccupation with abnormal interests (e.g. collecting silverware) or normal interests with extreme intensity (e.g. consistently interrupting daily activities in order to engage in preferred interests)?

Yes No Unknown

11) Does the individual engage in apparently inflexible, non-functional routines?

Yes No Unknown

12) Does the individual show stereotyped and repetitive motor movements (e.g., hand or finger flapping or twisting, or whole-body movements, such as rocking back and forth)?

Yes No Unknown

13) Does the individual seem to be preoccupied with parts of objects?

Yes No Unknown

Appendix B
Demographic Questionnaire

Date of Birth: _____ Age: _____ Gender: M_____ F_____

Race: Asian: _____ Black: _____ Hispanic: _____ White: _____ Other: _____

May we contact you about opportunities for participation in future research projects we conduct through the clinic? We would contact you simply to inform you about new studies; you would be under no obligation to participate.

_____ Yes, you may contact me about future studies.
_____ No, please do not contact me about research.

EDUCATION & EMPLOYMENT HISTORY

Are you currently attending school or an educational program? Yes: _____ No: _____

If yes,
School Name: _____ Grade: _____

Have you ever been retained in school? Yes: ____ No: ____ If so, what grade(s)? _____

What kinds of grades do you make? _____

How do you feel about school and about your teachers? _____

If you have ever been evaluated psychoeducationally by a school or private consultant, please indicate below:

Date: Evaluated by: Outcome:

_____

_____

_____

Please check any special programs in which you are currently enrolled in school:

A. None

B. Counseling

Name: _____

C. Learning disabled (LD) or resource

Areas: _____ Number of hrs/day _____

D. Seriously emotionally disturbed (SED)

E. Chapter 1 Reading

F. Chapter 1 Math

G. Other Health Impaired (OHI)

H. Developmentally Delayed

I. Other: _____

Please indicate the highest grade that you have completed:

___ less than 7th grade

___ partial high school education (9th, 10th or 11th grade)

___ graduated from high school

___ graduated from trade school or business school

___ attended college or specialized training program

___ graduated from college: BA___, BS___, Engineering___, Architecture ___, Other_____

___completed graduate school in: _____

Are you employed outside the home? Yes: _____ No: _____

If yes, what is your company's name?

_____

What is your job title?

_____

What is your estimated gross income?

_____

FAMILY INFORMATION

Please list all individuals in your immediate family and their relationship to you:

Name:	Relationship:	Age:	Gender

HEALTH/MEDICAL HISTORY

What is your current height: _____ Current Weight: _____

Are you: R-handed: ____ L-handed: ____ Mixed handedness: _____

Have there been any major changes for you in the past year? (e.g., moved, new job, new school, new baby, death in family, etc.) Yes____ No____
Please explain:

_____

Have you ever been in an accident resulting in serious injury? Yes___ No___
Please explain:

_____

Medical Conditions: Please indicate whether you have ever had any of the following:

Meningitis	Encephalitis	Asthma	Diabetes
Heart Disease	Heart murmur	Hydrocephalus	Cerebral palsy
Seizures	Leukemia	Anemia	Arthritis
Bone disease	Muscle disease	Kidney problems	Tuberculosis
Cancer	Measles	Mumps	Chicken pox

Hospitalizations: Have you ever had any medical hospitalizations: Yes___ No___

Age: Length of stay: Reason for hospitalization:

Medications: Are you currently taking any medications, including the following? Yes____ No__

ADHD medications Dosage Time of Day
Name of medication

Anti-Depressant medications Dosage Time of Day
Name of medication

Anti-Anxiety medications Dosage Time of Day
Name of medication

Anti-Seizure medications Dosage Time of Day
Name of medication

Allergy/Asthma medications Dosage Time of Day
Name of medication

Other medications Dosage Time of Day
Name of medication

Other medications Dosage Time of Day
Name of medication

Medications: In the past, have you taken any medications, including the following? Yes__ No__

ADHD medications Dosage Time of Day
Name of medication

Anti-Depressant medications Dosage Time of Day
Name of medication

Anti-Anxiety medications Dosage Time of Day
Name of medication

Anti-Seizure medications Dosage Time of Day
Name of medication

Allergy/Asthma medications Dosage Time of Day
Name of medication

Other medications Dosage Time of Day
Name of medication

Other medications Dosage Time of Day
Name of medication

Developmental History: In the following section, please report to the best of your ability information you know, otherwise, please leave blank.

Your birth weight: _____ Length: _____

Please specify the type of delivery:
_____ Vaginal _____ Normal _____ Induced _____ Forceps _____Caesarian

If labor or delivery was abnormal in any way, please explain:

_____

What language(s) is/are spoken in your home?
_____

Do you hear adequately?
_____

Family Medical History:

Do any members of your family have a medical or psychological problem? Yes: _____ No:_____

If yes, list this person's name and describe briefly:

Name: _____ Concern: _____

Name: _____ Concern: _____

Name: _____ Concern: _____

PSYCHIATRIC/EMOTIONAL HISTORY

If you have ever been treated or received special help for learning or emotional problems outside not listed elsewhere on this form, please describe. Please also indicate any past diagnosis you have received.

Date: Evaluated by: Outcome:

_____

_____

_____

_____

Appendix C
FMRI Safety Screener

Prior to receiving an fMRI scan, we require the information in the form below. If you are eligible for the study, this information will ensure that your time in the scanner is safe and comfortable, so please provide accurate and complete answers. The answers you provide will remain confidential.

For these experiments, you must be in good health. Since the MRI machine is a large magnet, people with permanent metal in their body will not be able to participate in our fMRI studies (most orthodontia is okay). You should not participate if there is any possibility that you are currently pregnant.

If you have any questions regarding this form or the experiment itself, please call **Michelle Patriquin at (540) 998-3414**.

Name:_____
Native Language:_____

Date of Birth: __/__/____
Age:_____

Gender: M/F
Height:_____
Weight:_____

Phone: Home-_____

Mobile-_____

Email: _____

Preferred contact method and time:_____

Are you right handed, left handed, or ambidextrous? R/L/A

Do you currently have a drug/alcohol abuse problem? Y/N

Have you had a drug/alcohol abuse problem in the past? Y/N
Date of last treatment:_____

If you answer 'yes' to any of the questions on this page, please explain in the column to the right.

Have you had an MRI before?	Y/N	
Do you have any metal in your body (accidental or implanted)?	Y/N	
Is there any possibility that you are currently pregnant?	Y/N	
Are you at all claustrophobic?	Y/N	
Do you have sinus problems?	Y/N	
Have you recently experienced dizziness, loss of balance, or loss of consciousness?	Y/N	
Do you currently have braces or other unremovable orthodontia?	Y/N	

Have you ever worked with metals (e.g. welding, grinding, etc)?	Y/N	

Please indicate if you currently have, or have ever had, any of the following:

Heart surgery/ heart valve/ pacemaker/ defibrillator	Y/N	
Neurostimulator/ Biostimulator	Y/N	
Brain tumor/ brain surgery/ shunt	Y/N	
Aneurysm/ aneurysm clips	Y/N	
Ear surgery/cochlear implants/ hearing aids/ hearing loss	Y/N	
Gunshot wounds/ shrapnel/ BBs	Y/N	
Shunts/ stents/ intravascular coil/ filters	Y/N	
Internal electrodes or wires/ IV access port	Y/N	
Prostheses of any kind	Y/N	
Infusion pump/ implanted drug pump	Y/N	
Joint replacement	Y/N	
Spinal fixation device/ Spinal fusion procedure	Y/N	
Any type of implant held in place by a magnet	Y/N	
Seizures	Y/N	
Neurological diseases or disorders (eg. Stroke, Parkinson's etc)	Y/N	
Meniere's disease	Y/N	
Head injury	Y/N	
Metal implants (pins, staples, rods, plates, clips, screws, etc)	Y/N	
Surgery of any kind (please describe and include date)	Y/N	

Please indicate if you currently have, or have ever had, any of the following:

Permanent eyeliner or tattoos with metal in the ink	Y/N	
Body piercings or other jewelry that cannot be removed	Y/N	
Nitro patch (unremovable) or Nicotine Patch	Y/N	
IUD (copper-7)	Y/N	
Hairpiece/ wig/ toupee	Y/N	
Colored contact lenses	Y/N	

Do you require eyeglasses to see a computer screen while you sit at a desk? Y/N

By clicking the "I accept" button below you confirm that the above information is correct to the best of your knowledge and have had the opportunity to ask questions related to this form and the study.

Appendix D
Debriefing Questions

Subject ID#: _____

1. **Prior to scan: On a scale from 0-10 can you rate how anxious you feel about getting into the scanner today? With 0 meaning feeling not anxious and 10 feeling extremely anxious.**
   _____

2. **After scan: On a scale from 0-10 can you rate how anxious you feel right now about the scanner? With 0 meaning feeling not anxious and 10 feeling extremely anxious. _____**

3. **After scan: On a scale from 0-10 can you rate how anxious you felt in the scanner today? With 0 meaning feeling not anxious and 10 feeling extremely anxious. _____**

4. How well did you feel you focused on the rating-music task?
   a. Did not focus on task
   b. Focused moderately on task
   c. Focused on task
   d. Very focused on task

5. How well did you feel you understood the directions for the rating-music task?
   a. Did not understand the directions
   b. Moderately understood the directions
   c. Understood the directions
   d. Completely understood the directions

6. How frequently do you listen to music?
   a. Never listen to music
   b. Sometimes listen to music
   c. Often listen to music
   d. Always listen to music

8. How familiar were you with the songs played?
   e. Not familiar
   f. Moderately familiar
   g. Familiar
   h. Very Familiar

7. Did the songs played evoke positive or negative memories?
   a. Positive
   b. Negative
   c. None

If the songs evoked a positive or negative memory, please describe the memory here:

Appendix E
Music Task Instructions

For this study, you will rate your experience of listening to music on two rating scales (*point to Nemo computer*) using button boxes in the scanner. We would like you to continuously adjust the scales *(point to scales)* to tell us …

1) How much you like what you are hearing? And…
2) How energetic does what you are hearing make you feel?

You are to rate how much you like what you are hearing and how much energy you feel throughout the entire experiment. Please change the rating bars whenever you feel a change in your preference or energy. Just so you are clear, you will hear two types of noises: 1) the sounds of the scanner (e.g., loud banging, car alarm) and 2) the music playing through the headphones.

Any questions?