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Exploring the Relationship Between Anxiety Sensitivity and Heart Rate Variability

by

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Dissertation

Submitted to the Department of Psychology
Eastern Michigan University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY
in
Clinical Psychology

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June 19, 2019
Ypsilanti, Michigan

Acknowledgements

Completion of this project would have been impossible without the aid and support of many. I must first acknowledge my husband, co-parent, and partner in life, Nate Williams. I am endlessly thankful to you for your unwavering love and support during the many ups and downs of this project, and graduate school in general. We have made so many sacrifices to get to this point, and I can only hope that this epic demonstration of perseverance will benefit our children in the years to come. Thank you for always pushing me to do my best. Second, to my mom, Sue Gourley, my steadfast cheerleader—your efforts have gone above and beyond the call of duty. Because of you, I am a better parent, and will be a better parent to my children into their adulthood. Thank you for teaching me to TRUST in the process. With overwhelming gratitude, I dedicate this project to you both.

Among others, I must also acknowledge my wonderful research mentor and advisor, Dr. Koch—for her endless support, demonstrating flexibility and kindness along the way, particularly as I struggled to balance work alongside parenting young children. I am forever grateful to your insights and passion for my project, particularly during times when I was feeling drained. It has been an honor and inspiration to work with you. Further, to my committee members—Dr. Renee Lajiness-O'Neill, Dr. Thomas Waltz, and Dr. Jennifer Glass—I thank you for your guidance and support and for pushing me to think critically and carefully about the project. I have learned so much in this process and thank you all for your efforts and time.

Finally, to the research participants who made this project possible—thank you for your interest and investment in science, offering your time and energy to my project. I am so grateful to you all.

Abstract

Anxiety sensitivity (AS) is a multifaceted construct based on individual beliefs that anxiety symptoms and sensations will have harmful consequences. In general, literature demonstrates three underlying dimensions of AS: fear of cognitive dyscontrol (i.e., cognitive concerns), fear of physiological anxiety sensations (i.e., physical concerns), and fear of negative evaluation (i.e., social concerns). Elevated AS and underlying dimensions have been shown to underlie psychopathology, including anxiety and depression broadly, and are predictive of fear responding in the context of behavioral challenge paradigms whereby individuals with elevated AS demonstrate higher fear and sympathetic nervous system activation. To date, few studies have investigated AS alongside heart rate variability (HRV), a biomarker of autonomic activity. Like AS, HRV has been well studied in clinical samples. High-frequency heart rate variability (HF-HRV), which indexes parasympathetic activity, has been shown to be lower among clinical samples, relative to controls and during behavioral challenge paradigms designed to induce stress. Lower HF-HRV has shown associations with other traits thought to underlie psychopathology (e.g., worry, difficulty with thought suppression).

The present study sought to explore a plausible relationship between AS and HRV. Participants were recruited from the Eastern Michigan University campus community to take part in a brief online screening using the Anxiety Sensitivity Index-3 (ASI-3). Participants with normative (n = 60) and high (n = 60) levels of AS were invited to participate in an in-person study whereby HRV and participant-reported subjective distress were measured at baseline and during engagement in three behavioral challenge paradigms. Challenges were designed to

induce mild distress related to underlying AS dimensions (i.e., cognitive, physical, and social concerns).

Study findings revealed high AS participants to exhibit significantly greater increases in distress following each challenge, relative to baseline, than normative AS participants. After controlling for variance due to age, HF-HRV was significantly higher among normative AS participants at baseline and during the social challenge, compared with high AS participants. Unexpected findings also arose , whereby, after controlling for age, normative AS participants demonstrated significantly higher low-frequency HRV at baseline and during physical and social challenges, relative to high AS participants. .

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Exploring the Relationship Between Anxiety Sensitivity and Heart Rate Variability

Anxiety sensitivity (AS), the fear of anxiety-related sensations, has become an increasingly important construct in the field of psychology. Based on beliefs that anxiety symptoms and sensations will have harmful consequences (Reiss, 1991), AS is thought to underlie numerous psychological ailments, and in turn, a great deal of research has focused on the assessment of this construct, particularly for identifying those who may benefit from secondary prevention efforts.

Historical and Theoretical Foundations

Reiss and McNally formally coined the term AS in 1985, although many before them had contemplated the role of "sensitivity to stress" in anxiety psychopathology (McNally, 1999). Early psychodynamic theorists, for example, acknowledged a "fear of fear" frequently present in agoraphobic patients and, in particular, a "readiness" for these individuals to become easily frightened (Fenichel, 1945). Notably, rather than conceptualizing the "fear of anxiety" as a construct in and of itself, these theorists more generally regarded the phenomenon as a symptom of agoraphobia. Conceptualization of the role of fear in agoraphobia continued in this manner until 1979, when Goldstein and Chambless proposed a reanalysis of the disorder. Rather than focusing on fear of stimuli (e.g., open spaces) they emphasized the role of *fear of panic* as a maintaining characteristic of agoraphobia. In turn, they proposed that the anticipated consequences of agoraphobia (i.e., panic) were the result of Pavlovian interceptive conditioning: bodily sensations (i.e., conditioned stimuli) were seen to elicit panic (i.e., a conditioned response), causing an individual to become hyper-vigilant to bodily sensations and interpret future feelings of anxiety as signs of impending panic. Thus, rather than regarding fearfulness of

anxiety to be a facet of agoraphobia, Goldstein and Chambless (1979) saw fear of anxiety as important in understanding a wide range of psychopathology.

In 1986, Clark proposed an alternate theory of panic, underscoring the role of cognitive feedback loops in the development of fear of fear. He proposed that when an innocuous sensation (e.g., increased heart rate) is misinterpreted in a catastrophic way (e.g., being a sign of impending cardiac arrest), a positive feedback loop is initiated, worsening anxiety, intensifying symptoms further, until full-blown panic results. Clark specified that bodily sensations need not necessarily arise from anxiety, but also in addition to anxiety, and may also be associated with other emotional states such as anger, or increased physiological activity such as following caffeine consumption. Clark (1986) posited that regardless of the source of the sensation, panic will only follow if the sensation is interpreted as dangerous.

Expectancy theory. Drawing on these perspectives, Reiss and McNally (1985) introduced expectancy theory in order to explain individual differences in the tendency to develop fearfulness of anxiety. Embedded within this theory, the term AS was introduced as one of three fundamental fears or sensitivities which could be used to explain the development of "common fears," or specific fears such as fear of snakes or heights. These included fear of injury, fear of anxiety, and fear of negative evaluation. Like cognitive and learning perspectives, expectancy theory holds that both classical conditioning and misinterpretation of symptoms play a role in the development and maintenance of AS and anxiety symptoms. However, unlike Goldstein and Chambless (1979), who saw fear of fear as a result of panic attacks, expectancy theory holds that panic need not occur in order for a person to develop AS. Rather, the theory constitutes that AS may arise from other sources and in turn may itself constitute a risk factor for panic disorder/panic attacks (Reiss, 1991). It likewise posits that the experience of panic may

impact AS and possibly strengthen it by increasing one's catalogue of negative anxiety experiences (Reiss & McNally, 1985). Further, unlike cognitive theory, expectancy theory posits that although some high AS individuals may misconstrue consequences of anxiety sensations, this in and of itself is neither a necessary nor maintaining factor of anxiety or AS (Reiss, 1991). There is a small literature which provides support for expectancy theory (e.g., Ginsburg & Drake, 2002), although most research has focused on the role of AS specifically.

Emotion regulation theory. It is additionally worth noting that while research evaluating AS in the context of expectancy theory is lacking, there has been a burgeoning interest in the relationship of AS to emotion regulation. Emotion regulation refers to the conscious or unconscious attempts people make to modify their emotional responses (Gross & Thompson, 2007). Gratz and Roemer's (2004) model conceptualizes the construct as involving not just the modulation of emotional arousal, but also the awareness understanding, and acceptance of emotions, and the ability to act in desired ways regardless of emotional state. From this perspective, AS, or the fear of anxiety symptoms, may represent a form of emotional *dys*regulation. Indeed, there is evidence to suggest that individual differences in the regulation of anxiety may moderate the influence of AS (Olatunji, Forsyth, & Feldner, 2007). As such, it is possible that AS develops as a consequence of overarching difficulties in emotion regulation.

Anxiety Sensitivity

Although initially purported to be a unidimensional construct (Reiss & McNally, 1985), mounting evidence from factor analytic studies has provided evidence for at least three dimensions, including (a) fear of physiological anxiety sensations (i.e., AS physical concerns), (b) fear of cognitive dyscontrol (i.e., AS cognitive concerns), and (c) fear of negative evaluation

(i.e., AS social concerns; Stewart, Taylor, & Baker, 1997; Zinbarg, Barlow, & Brown, 1997; Taylor et al., 2007), which appear to nest under one overarching AS factor. Each of these factors appear to play a role in the development of psychopathology, and as such, assessment of sub-factors has been an important avenue whereby the AS literature has grown.

AS and risk for psychopathology. Over nearly three decades of research, AS has been implicated as a vulnerability factor in the pathogenesis of *DSM-IV* Axis I diagnoses (Schmidt, Zvolensky, & Maner, 2006) and emotional disorders broadly (Naragon-Gainey, 2010; Taylor, Koch, Woody, & McLean, 1996) and has shown strong associations with a variety of anxiety disorders (Olatunji & Wolitzky-Taylor, 2009), including generalized anxiety (Rector, Szacun-Shimizu & Leybman, 2007), obsessive compulsive (Cisler, Reardon, Williams, & Lohr, 2007; Blakey, Abramowitz, Reuman, Leonard, & Riemann, 2017), panic disorder (PD; Donnell & McNally, 1990; McNally, 2002; Schmidt et al., 2006; Durdu, Kayikcioğlu, Pirildar, & Köse, 2018), and acrophobia (Diemer, Lohkamp, Mühlberger, & Zwanzger; 2016). Although initially shown to be most strongly related with PD, recent work has shown equivalent levels of AS among PD and other anxiety disorder patients (e.g., Boswell et al., 2013; Naragon-Gainey, 2010).

Beyond anxiety disorders, AS has been linked with depression (e.g., Otto, Pollack, Fava, Uccello, & Rosenbaum, 1995), borderline personality disorder (Gratz, Tull, & Gunderson, 2008), eating pathology (e.g., Anestis, Selby, Fink, & Joiner, 2007; Fulton et al., 2012), and compulsive hoarding (e.g., Medley, Capron, Korte, & Schmidt, 2013). There is also a rather large literature linking AS to substance use disorders (Norton et al., 1997), including the use of alcohol (Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart, Peterson, & Pihl, 1995; Stewart, Zvolensky, & Eifert, 2002), heroine (Lejuez, Paulson, Daughters, Bornovalova, & Zvolensky,

2006), increased craving and drinking behaviors among heavy drinkers (McCaul, Hutton, Stephens, Xu, & Wand; 2017), and nicotine (Novak et al., 2003). Further, AS has been implicated as an important change variable in nicotine cessation, reducing withdrawal effects (Bakhshai et al., 2018) and mediating the effects of intervention on early abstinence (Zvolensky et al., 2018).

AS has additionally been studied in medical populations and has been linked with sleep difficulty and symptom severity in HIV-infected individuals (e.g., Leyro, Vujanovic, & Bonn-Miller, 2015), medication non-adherence in patients with uncontrolled hypertension (Alcántara, et al., 2014) and chronic pain (Ocañez, McHugh, & Otto, 2010).

Predictive utility. Other work has focused on AS more specifically as a predictor of future pathology (Berman, Wheaton, McGrath, & Abramowitz, 2010; Ehlers, 1995; Schmidt, Lerew, & Jackson, 1997). An early study by Maller and Reiss (1992), for example, found that individuals categorized with high AS in 1984 were five times more like to develop PD in 1987, as compared with those categorized as low AS. Findings from a larger, more recent study evidenced that after controlling for baseline trait anxiety, AS predicted the development of anxiety disorders (Schmidt et al., 2006). Although the association between AS and psychopathology development is not entirely clear, it appears that AS moderates the relationship between exposure to stressful life events and fear response whereby aversive life events, particularly when unexpected or uncued, may trigger anxious responding that high, but not low AS individuals respond to with anxiety and fear (Zvolensky, Kotov, Antipova, & Schmidt, 2005

Challenge paradigms. Behavioral challenge paradigms have also been used to establish an association between AS and fear response. A number of paradigms have been used, including, most commonly, hyperventilation (e.g., Brown et al., 2003; Carter, Suchday, & Gore,

2001; Donnell & McNally, 1990), or an inhalation of carbon dioxide and oxygen mixture (e.g., Beck, Shipherd, & Zebb, 1996; Eke & McNally, 1996; Feldner, Zvolensky, Stickle, Bonn-Miller, & Leen-Feldner, 2006) in order to induce fear responses. Physically oriented tasks such as caffeine (Telch, Silverman, & Schmidt, 1996), cold-pressor (Keogh & Mansoor, 2001), or mild electric shock (Conrod, 2006) paradigms have also been used. Other challenge tasks have been more specific in order to target social anxiety, such as through planning a self-disclosing speech (Conrod, 2006), or role-playing behavior of exposure to a personally relevant feared situation (Orsillo, Lilienfeld, & Heimberg, 1994). Others have attempted to trigger fear responses associated with cognitive distress, such as exposure to an aversive noise (Stewart & Pihl, 1994), mental arithmetic (Borden & Lister, 1994; Stewart et al., 2001), or use of a Stroop task (Orsillo et al., 1994).

AS and fear response. By and large, the literature has shown AS to predict subjective fear responses to such aforementioned paradigms. In CO2 challenge studies, for example, AS has been shown to predict panic symptoms (Eifert, Zvolensky, Sorrell, Hopko, & Lejuez, 1999; Eke & McNally, 1996; Gonzalez, Zvolensky, Hogan, McLeish, & Weibust, 2011) and self-reported anxiety (Forsyth, Lejuez, & Finlay, 2000; Gregor & Zvolensky, 2008) above and beyond other variables. Similar findings have been found in hyperventilation studies, whereby AS has been shown to predict anxious responding (Holloway & McNally, 1987; Rapee & Medoro, 1994).

Other evidence suggests that AS dimensions may differentially predict fear response to a behavioral challenge. For example, Brown et al. (2003) found that AS physical concerns predicted subjective fear during a two-minute hyperventilation challenge while AS social concerns predicted behavioral tolerance to the challenge. Zinbarg and colleagues (2001) found

that among anxiety disorder patients, AS physical concerns were associated with panic symptoms whereas AS cognitive concerns were associated with depressed mood. These authors additionally found AS physical concerns to account for variance associated with fear response following a CO2 challenge. Other evidence has underscored the utility of AS cognitive and social concerns as predictors of self-reported anxiety following a CO2 challenge of lower intensity than Zinbarg et al.'s 2001 investigation (Richey, Schmidt, Hofmann, & Timpano, 2010).

AS and physiological response. There is also a large body of work which has sought to better understand the role of AS in moderating physiological responses to stress, such that emotions, including anxiety, are associated with varying levels of physiological arousal (Levenson, 2003). A number of investigations have focused on indexing markers of the autonomic nervous system (ANS), a key system involved in generating physiological arousal associated with stress. The ANS is subdivided into two systems: an excitatory sympathetic nervous system (SNS) and an inhibitory parasympathetic nervous system (PNS). Frequently, these systems interact antagonistically producing varying degrees of physiological arousal. During times of physical or psychological stress, the SNS is activated to aid in adapting to challenges and physiological arousal arises, including increased heart rate (Appelhans & Luecken, 2006) and increased sudomotor activity (i.e., sweat gland stimulation; Bini, Hagbarth, Hynninen, and Wallin, 1980). During times of stability or relative safety, arousal is lower.

At present, most research into AS and autonomic arousal has been based on activation of the SNS, primarily through measuring galvanic skin response or skin conductance levels (SCL) as a measure of sudomotor activity (e.g., Beck et al., 1996; Forsyth, Eifert, & Canna, 2000; Feldner et al., 2006) and cardiac reactivity (e.g., Forsyth, Eifert, & Canna, 2000; Gregor &

Zvolensky, 2008). A number of challenge studies have also indexed respiration (e.g., Richey et al., 2010), as it is known to influence both cardiac and sudomotor activity (Lorig, 2007).

Studies indexing SCL have shown mixed support for a relationship with AS. The use of challenge paradigms intended to activate sympathetic activity (e.g., CO_2 inhalations, Gonzalez et al., 2011; social stress and mild electric shock, Conrod, 2006; observational fear, Kelly & Forsyth, 2009; and hyperventilation, Leen-Feldner, Feldner, Bernstein, McCormick, & Zvolensky, 2005) have yielded some support for an association between AS and SCL (Gregor & Zvolensky 2008; Stewart & Pihl, 1994), although most findings offer weak support or no support for such. For example, Beck and colleagues (1996) reported a non-significant trend for increased SCL in response to a CO_2 challenge paradigm, while still others have failed to link AS with SCL (Feldner et al., 2006; Kelly & Forsyth, 2009).

Studies evaluating the relationship between AS and cardiac reactivity have also yielded equivocal findings. In general, AS and its subfactors have not shown a relationship to heart rate change in response to CO_2 (Zvolensky, Feldner, Eifert, & Stewart, 2001), mental (Stewart, Buffett-Jerrott, & Kokaram, 2001), or aversive noise challenges (Stewart & Pihl, 1994). However, with regard to tracking heartbeats, it appears that high AS individuals are, however more accurate than low AS individuals in reporting the presence of cardiac arousal. That is, although studies investigating cardiac reactivity have not evidenced a relationship between AS and cardiac change in response to a challenge task, there is evidence that high AS individuals possess heightened interoceptive ability, or physiological awareness and acuity for reporting cardiac changes. Interestingly, these results have held up when individuals underwent exposure to a stressor such as a cognitively challenging task (Stewart et al., 2001; Sturges & Goetsch, 1996) but not following caffeine intake (Veltrum & Goetsch, 1991) or hyperventilation tasks

(Sturges, Goetsch, Ridly, & Whittal, 1998). One study has found high AS individuals estimate heart rate more accurately in the laboratory compared to low AS individuals regardless of having undergone exposure to a stressor or not (Stewart et al., 2001). Taken together, evidence suggests that *perception* of cardiac change, rather than actual physiological change, is dependent on AS, such that AS functions as an individual difference variable to increase self-focus and exaggeration of symptoms.

Heart Rate Variability

To date, there has been little work investigating a possible relationship between AS and heart rate variability (HRV), a physiological index which has come to be viewed as a transdiagnostic biomarker of psychopathology by and large. As summarized by Shaffer, McCraty, and Zerr (2014), HRV is based on the "understanding that healthy physiologic function is a result of continuous, dynamic interactions between multiple neural, hormonal, and mechanical control systems at both local and central levels" (p. 5). In terms of cardiac activity, such complex interactions result in highly irregular and variable heart rhythms in healthy organisms; HRV represents an index of such variability.

Cardiac anatomy. Anatomically, the heart is about the size of a closed fist and consists of two atria and two ventricles. As shown in Figure 1, the atria are upper receiving chambers for returning venous blood. Lying below the atria are the ventricles, which pump blood from the heart into the lungs and arteries. During the cardiac cycle, oxygenated blood enters the right atrium, flows into the right ventricle, and is pumped to the lungs via pulmonary arteries, where blood is re-oxygenated and wastes are removed. The re-oxygenated blood is then transported through the pulmonary veins to the left atrium and then enters the left ventricle. Blood is ejected

through the aorta to the arterial system when the left ventricle contracts. (Marieb & Hoehn, 2013).

A complete cardiac cycle consists of systole (ventricular contraction) and diastole (ventricular relaxation). During systole, the left ventricle ejects blood from the heart resulting in peak blood pressure. During diastole, the left ventricle relaxes, and blood pressure is at its lowest.

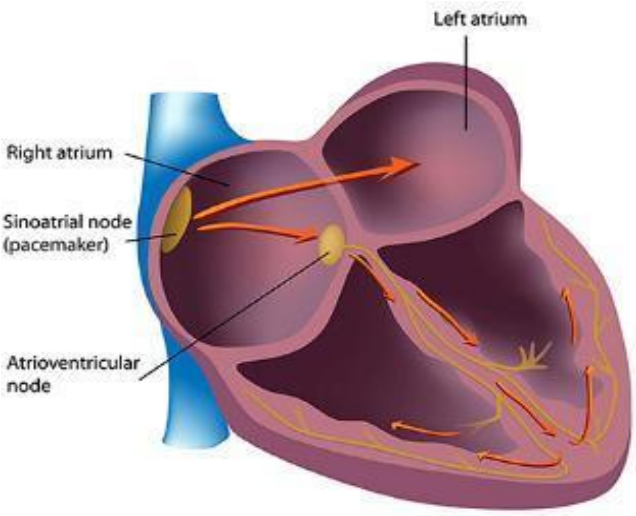

Figure 1. The heart. Reproduced from Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, *5*(1040), p. 2.

As shown in Figure 1, the heart consists of two internal pacemakers (i.e., the sinoatrial (SA) and atrioventricular (AV) nodes), which are responsible for initiating a heartbeat and thus a cardiac cycle. Use of an electrocardiogram (ECG) allows a graphic record of heart electrical activity to be produced. A typical ECG recording has three distinguishing waves or deflections: the P wave, the QRS complex, and the T wave (see Figure 2), each of which correspond with phases of the cardiac cycle (shown in Figure 3).

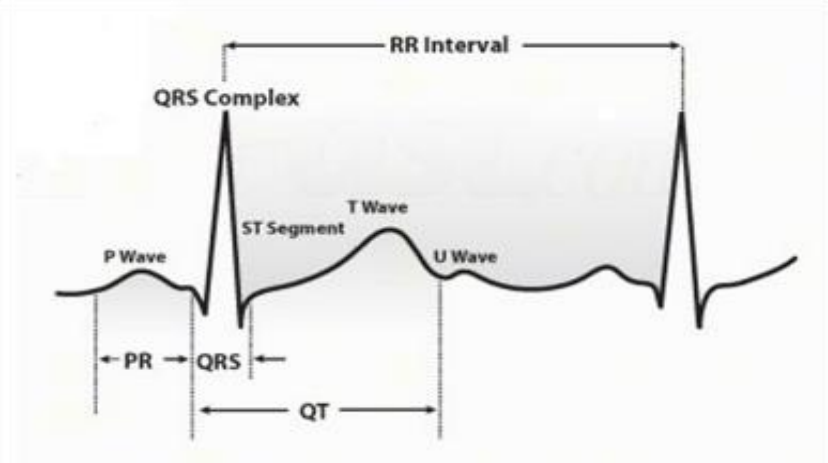

Figure 2. An example of an ECG recording, reproduced from CEUFast, Inc.

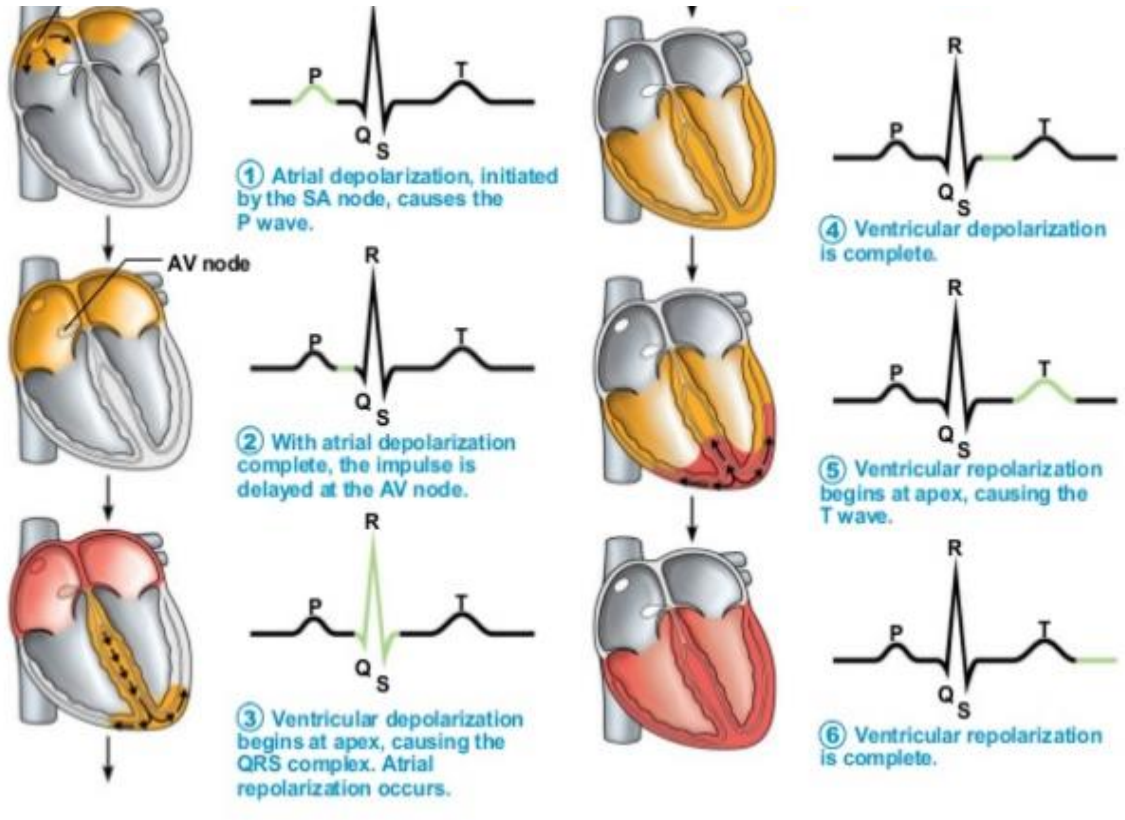

Figure 3. The cardiac cycle. Adapted from Marieb, E. N., and Hoehn, K. (2013). *Human Anatomy and Physiology*. San Francisco, CA: Pearson, p. 242

The sinoatrial node initiates the cardiac cycle by sending an electrical impulse through the atria to the AV node, resulting in depolarization. This generates an electrical impulse that

travels through the atria, causing the AV node to fire. As muscle cells in the atria depolarize, this results in contraction of the atria (i.e., atrial systole), thus producing the P wave of the ECG, which lasts about 0.08 seconds; see Figure 3). The signal is briefly delayed at the AV before depolarizing fibers in the ventricles, resulting in the QRS complex, which lasts approximately 0.08 seconds. The completion of ventricular depolarization results in the S-T segment. Ventricular repolarization then results in the T-wave. Completion of ventricular polarization marks the end of the cardiac cycle (Marieb & Hoehn, 2013). This is followed by atrial repolarization, characterized by the S-T segment. Repolarization of the ventricular myocardium generates the T wave, which typically lasts 0.16 seconds.

The time between R peaks, the highest amplitude value, shown in Figure 2, reflects an interbeat interval, or R-R interval. HRV represents the variability in time differences between R-R intervals. To provide perspective, the number of R waves occurring in a minute is used to calculate heart rate (HR) at beats per minute (bpm). An R-R interval measuring at 750 milliseconds, for example, would at one minute (i.e., 60,000 milliseconds) correspond with a heart rate of 80 beats bpm (i.e., 60,000/750=80) (Ahmed, Begum, & Islam, 2010). A complete cardiac cycle is completed in 0.8 seconds (Marieb & Hoehn, 2013; Shaffer et al., 2014); the human heart beats over 100,000 times a day.

The role of the ANS on HRV. The cardiac cycle and accompanying rhythms are regulated by a host of physiological and environmental factors. HRV represents the degree to which cardiac activity responds to situational demands (Appelhaus & Lueken, 2006). Two factors which are particularly important in understanding the role of HRV in psychophysiology are (a) the influence of the autonomic nervous system (ANS) on cardiac activity and (b) regulation of the ANS by the central autonomic network (CAN). With regards to the influence

of the ANS, the heart is dually innervated by the sympathetic and parasympathetic (vagal) branches of the ANS. These branches serve a regulatory role on heart rate by influencing the activity of the sinoatrial node, which serves as the hearts pacemaker. The sinoatrial node (SA) generates action potentials which travel through the cardiac tissue, causing the myocardium (i.e., heart muscle) to contract. Sympathetic fibers are activated in this process and exert an excitatory influence on the firing rate of the sinoatrial node, which results in increased heart rate. Alternatively, parasympathetic fibers exert inhibitory influence on the sinoatrial node, resulting in decreased heart rate. In other words, the sympathetic (SNS) and parasympathetic (PNS) regulate the time between consecutive heartbeats, or R-R intervals. More variability in the interval between heart beats is reflected as higher HRV, whereas lower HRV reflects less flexibility- heart beats which tend to occur at a steadier pace.

Qualitatively, a faster heart rate corresponds with shorter R-R intervals, whereas a slower heart rate corresponds with longer R-R intervals. Since cardiac activity is modulated by antagonistic interplay between the PNS and SNS, heart rate may be accelerated by either an increase in sympathetic activation or a decrease in parasympathetic inhibition (Berntson et al., 1997). PNS activity is predominant at rest, resulting in an average HR of 75 beats per minute, which is well below the intrinsic firing rate of the sinoatrial node (Applehans & Luecken, 2006; Shaffer et al., 2014) and has been shown to exert effects more rapidly (i.e., < 1 s) than SNS activity (i.e., > 5 s; Nunan, Sandercock, & Brodie, 2010). Such temporal effects are likely accounted for by the different signaling mechanisms employed by the SNS and PNS.

Neurotransmission of norepinephrine serves to mediate SNS activity, whereas neurotransmission of acetylcholine mediates PNS activity. Given the very short latency of acetylchine neurotransmission, parasympathetic activity rapidly modulates cardiac activity

whereas the sympathetic influence of norepinephrine results in much slower changes to heart rate. Given these differences in latency, parasympathetic activity is seen as a primary mediator of cardiac output and serves to inhibit sympathetic influence. That is, vagal activity has negative cardiac chronotropic and dromotropic effects that facilitate efficient cardiovascular functioning by restraining cardiac rate and electrical conduction speed (Thayer, 2006). Of note, when cardiac vagal and sympathetic inputs are blocked pharmacologically (e.g., with atropine plus propranolol, a "so-called double blockade"), intrinsic HR is higher than the normal resting HR (Jose & Collison, 1970), providing additional evidence that cardiac processes are primarily mediated by parasympathetic input (Thayer, Åhs, Fredrikson, Sollers & Wager, 2012). The interplay of these vagal and sympathetic influences is the basis for understanding HRV and the body's ability to flexibly respond to environmental demands (i.e., HRV; Applehans & Luecken, 2006).

The role of the central autonomic network (CAN). ANS influence on cardiac activity is regulated remotely by the CAN, which is comprised of the following structures: (a) the insular and medial prefrontal cortices, (b) the central nucleus of the amygdala and the bed nucleus of the stria terminalis, (c) the hypothalamus, (d) the periaqueductal gray matter in the mid brain, (e) the parabrachial Kölliker-Fuse region in the pons, (f) the nucleus of the tractus solitarius (NTS), and (g) the medullary intermediate reticular zone. The network represents an embedded component of an internal regulation system responsible through which visceromotor, neuroendocrine, and behavioral responses are controlled by the brain (Benarroch, 1993). CAN output is mediated by input from vagal and sympathetic neurons which dually innervate the heart. The interplay of these inputs to the sino-atrial node is the source of variability of heart rhythms and as such, the output of the CAN directly influences cardiac activity (Saul, 1990; Thayer & Lane, 2000). Thus,

HRV reflects the moment-to-moment output of the CAN in turn, an individual's capacity to generate regulated physiological responses in the context of emotional expression (Thayer & Lane, 2000; Thayer & Siegle, 2002).

Other influences on HRV. In addition to regulation by the ANS and the governing CAN, HRV is influenced by other physiological systems, including the respiratory system, endocrinological system, and immunological system, and the body's metabolic function in general. Most commonly discussed in the literature is the role of respiration on HRV, including respiratory sinus arrhythmia (RSA), which refers to the fluctuation of heart rate during the respiratory cycle. Respiration directly affects PNS function, whereby breathing air into the lungs temporarily inhibits vagal (i.e., parasympathetic) influence, and in turn increases heart rate. The exhalation of air alternatively reinstates parasympathetic activity and decreases heart rate (Beauchaine, 2015; Thayer, 2006). In other words, RSA is a naturally occurring variation in heart rate which occurs during respiration and is directly proportional to HRV. A wealth of literature has reported on RSA as an index of "vagal (i.e., parasympathetic) tone," or an index parasympathetically driven HRV (Berntson et al., 1997). Thus, lower RSA and lower vagally-mediated HRV are associated with lower tonic vagal (i.e., parasympathetic) modulation of heart rate. Quantitatively, RSA can be measured as high frequency heart rate variability (HF-HRV), typically observed at a frequency band of (i.e., > 0.15-.4 Hz; Draghici & Taylor, 2016), as it is characterized by R-R shortening with inhalation and lengthening with expiration.

It has been theorized that one of the functions of RSA is to influence blood pressure changes in response to changes in intrathoracic pressure changes during the respiratory cycle. During respiration, changes in intrathoracic pressure alter venous return to the heart, which impacts cardiac output and results in changes to arterial blood pressure (Draghici & Taylor,

2016). Relatedly, baroreflex sensitivity has also been shown to be a useful marker of vagal function (Thayer & Sternberg, 2006). The baroeflex represents a negative feedback loop of baroreceptors, stretch-sensitive receptors that detect rises in blood pressure (Shaffer et al., 2014). The baroreflex exerts inhibitory influence on sympathetic outflow and provides a source of excitatory drive to vagal motor neurons (Berntson et al., 1997). It is additionally relevant to the study of HRV, as the reflexes are able to phasically operate within the rapid time from of the highest of heart frequency rhythms.

In addition to the respiratory system, endocrinological and immunological systems have also been shown to have a role in regulating HRV. With regards to the endocrine system, key hormones appear to influence HRV. Work investigating ANS changes throughout the course of the menstrual cycle suggests that parasympathetic activity is influenced by estrogen, while the sympathetic activity is modulated by progesterone (Saeki, Atogami, Takahashi, & Yoshizawa, 1997). Further, the mammalian neuropeptide, oxytocin, which is strongly associated with human social behavior and cognition, has shown a positive association with HRV (Kemp, Quintana, Kuhnert, et al., 2012). From an immunological perspective, mounting evidence has demonstrated a negative relationship between HRV and inflammatory agents, including proinflammatory cytokines such as tumor necrosis factor, interleuken- 1 and -6, and C-reactive protein (i.e., Ernst, 2014; Gonzalez-Clemente et al., 2007; Thayer & Sternberg, 2006). Literature has also evidenced a negative correlation between cortisol levels and HRV in children (Michels et al., 2013) as well as adults (Rockliff, Gilbert, McEwan, Lightman, & Glover, 2008). Further, metabolic function appears to influence HRV, through the role of insulin. Reductions in HRV has been linked to glucose and insulin elevations (Meyer et al., 2016). HRV measurement is regularly used in the detection and diagnosis of diabetic neuropathy, even before the disease has

been diagnosed (Ernst, 2014). Likewise, low frequency heart rate variability (LF-HRV) has been shown to predict hypoglycemia (Cichosz, Frystyk, Tarnow, & Fleischer, 2017).

Finally, there is a substantial body of conflicting literature implicating age as a moderating factor of HRV. There is evidence that HRV increases in infancy and early childhood (Alkon et al., 2003) before stabilizing during early adolescence (e.g., Hinnant, Elmore-Staton, & El-Sheikh, 2011). Others have reported finding that HF-HRV increases with age, whereas LF-HRV decreases (Abhishekh et al., 2013) or that both HF-HRV and LF-HRV decrease with age (Antelmi et al., 2004). In general, further research is needed in order to clarify this the impact of age on HRV.

Theoretical perspectives. Two key theories have been proposed to explain the role of HRV as a determinant of autonomic flexibility: Porges' Polyvagal Theory (Porges 1995, 2001, 2007) and Thayer and colleagues' Neurovisceral Integration Perspective (Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer & Lane, 2000).

The Polyvagal Theory (PVT). First, the PVT, proposed by Porges (2007), is based in an evolutionary framework. According to this theory, physiological and behavioral adaptivity are accounted for through a series phylogenetic changes in the neural structures regulating the autonomic nervous system. Porges theorized that the human ANS evolved in three stages to support survival through activating different classes of behavior (Porges, 2003, 2007) as shown in Table 1.

Table 1

Phylogenetic Stages of the Polyvagal Theory

Stage	ANS Component	Related Behaviors	Anatomical Structure
III	Myelinated vagus (ventral vagal complex)	Social communication, self-soothing and calming, arousal inhibited	Nucleus ambiguous
II	Sympathetic-adrenal system	Mobilization (active avoidance)	Spinal cord
I	Unmyelinated vagus (dorsal vagal complex)	Immobilization (death feigning, passive avoidance)	Dorsal motor nucleus of the vagus

Note. Adapted from The Polyvagal Perspective, by S.W. Porges, 2007, *Biological Psychology*, *74*(2), p. 23.

According to Porges (2007), each of these stages was characterized by the development of an autonomic structure which plays a role in social processes, the first of which was the dorsal vagal complex (DVC), characterized by a slow-responding, unmyelinated vagus nerve through which primary vagal motor (i.e., efferent) fibers are connected with organs located below the diaphragm, enabling an organism to respond to danger or threat through immobilization. Activation of the immobilization or "freeze" response is characterized by decreased muscle tone, reduced cardiac output to reserve metabolic demands and changes in bowel and urinary function (e.g., reflexive defecation and urination) in order to reduce metabolic demands associated with digestion. Together, this activity represents an attempt to reduce physiological demands to the least amount necessary for survival; in humans, such a response may be experienced as a disembodied dissociative state/loss of consciousness.

The PVT asserts that next, physiological changes associated with mobilization through SNS activation, including the "fight or flight" response (e.g., increased muscle tone, shunting of blood from periphery, inhibited gastronintestinal function, dialated brochi, increased heart and

respiration rates), which prepare the body to respond to threats by engaging in behaviors supporting safety and survival.

Lastly, the ventral vagal complex (VCC) was acquired, providing a neural platform to support prosocial behavior and social connectedness. According to the PVT, this is achieved through linking neural regulation of visceral states, which support homeostasis and facial expressivity to receptive and expressive domains of communication (i.e., prosodic vocalizations (e.g., intonation, rhythm) and enhanced ability to listen to voices, respectively). Further, the motor component of the VCC, originating in the nucleus ambiguus, coordinates and regulates facial and head muscles with the heart and brochi, which enhance prosocial engagement and promote flexible and adaptive response to environmental challenges, including social interactions (Porges, 2003). Porges theorized that activation of the SNS might temporarily inhibit the VCC to facilitate immediate action. According to the PVT, the role of afferent pathways (i.e., those comprised of sensory nerve fibers which carry nerve impulses away from sensory stimuli and towards the central nervous system and brain [Marieb & Hoehn, 2013]) are key. The VCC includes afferent fibers which terminate in the nuclei of the facial and trigeminal nerves as well as those cranial nerves which support social behaviors such as facial expression, head turning, listening, and vocalization. Through this connection, cardiac activity is linked with social behavior (Porges 1997, 2001).

Such differences in physiological states aligning with each of these neural platforms support different classes of behavior. A physiological state of mobilization, driven by vagal withdrawal (and in turn, withdrawal of SNS inhibition), would support behaviors of fight or flight. Alternatively, a physiological state driven by increased parasympathetic influence would support behaviors associated with social engagement.

According to the PVT, these neural platforms are organized in a hierarchical fashion and engage in accordance with Jacksonian principle of dissolution, whereby higher (i.e., phylogenetically newer) structures inhibit lower (i.e., phylogenetically older) structures, such that when higher structures are ineffective, lower structures are activated (Jackson, 1958). Thus, activation of a second neural platform and associated defensive behaviors follow only when the VCC has failed to mitigate a presenting threat. As a result, the source nuclei of primary vagal pathways which regulate the heart shifted from the dorsal motor nucleus to the nucleus ambiguous, resulting in the development of a face-heart connection and the core of a social engagement system whereby visceral state is partially regulated by social interaction (Porges, 2009). Further, the PVT asserts that afferent fibers terminating in facial and cranial nerves mediate facial expression, head turning, vocalization, listening, and other socially relevant behaviors. This connection provides a mechanism through which cardiac function is connected with social behavior.

In addition to physiological and accompanying behavioral changes associated with each neural platform, Porges (1999) asserted that emotions are also governed by these processes. More specifically, the PVT posits that the SNS is associated with emotions such as fear or anger which promote protective behaviors, whereas the VCC is associated with social connectedness/pro-social behavior. Porges (2001) asserted that RSA is a marker of VCC activity (i.e., higher order processes) and thus capacity for efficient and flexible functioning.

Neurovisceral integration model (NIM). Similarly, the NIM underscores the role of vagally mediated inhibition of autonomic arousal in emotional expression and regulation; like the PVT, it maintains that HRV represents a marker of flexibility and regulated emotional responding in general. The perspective, however, emphasizes the neuroanatomical connection

between the ANS and brain regions associated with emotional processing, rather than the neural connection between the vagus and facial nerves (Thayer, 2006). Rather than placing emphasis on the vagal system, the NIM emphasizes the role of the CAN, viewing this system as a dynamic command center which governs cognitive, behavioral, and physiological elements in order to regulate emotion (Hageman, Waldstein, & Thayer, 2003). Thayer and Lane (2000) observed that the CAN possesses many features of a "nonlinear dynamical system," including components which are reciprocally interconnected and numerous parallel, distributed pathways. Accordingly, these features allow for continuous positive and negative feedback interactions, integration of autonomic responses, and multiple avenues through which a response may be achieved. Such capabilities enable the CAN to support regulated emotional responses by flexibly adjusting physiological arousal to evolving environmental demands, including integration of physiological responses involved in emotional expression, goal-directed behavior, and homeostatic regulation (Benarroch, 1993).

At the crux of the NIM, this dynamic interplay is seen to influence the experience of emotion, which has been characterized by Hagemann and colleagues (2003) as "an organismic response to an environmental event that facilitates the rapid mobilization for action" (p. 44). Emotion, which is dependent on the dynamic CAN, allows for goal-directed behavior in the service of flexible adaptation of the organism to changing environmental demands, if and when multiple systems are efficiently engaged. As such, Thayer and colleagues view thwarted or inefficient, inflexible emotional and behavioral responses as due to deficits in the CAN (Thayer & Lane, 2000).

Key to the functionality of the CAN are inhibitory processes governed by the prefrontal cortex, which has a prominent role in both inhibition and executive function. As previously

discussed, the CAN is both reciprocally and peripherally connected to the heart via sympathetic and vagal pathways, and thus, the prefrontal cortex may exert inhibitory control on subcortical structures enabling an individual to flexibly and adaptively respond to demands in the environment (Zahn et al., 2016). It has been proposed that under times of stress, the prefrontal cortex "goes offline," allowing automatic, prepotent processes to govern behavior (Arnsten & Goldman-Rakic, 1998), as opposed to adaptive responses (e.g., delayed response, cognitive flexibility; Thayer et al., 2009). Thus, from the perspective of the NIM, HRV is considered a proxy for the CAN and associated cortical activity to regulate the timing and magnitude of behavioral and emotional responses through inhibition (Thayer, 2006). Indeed, studies have evidenced an association between HRV and executive ability, whereby higher HRV has been linked to faster reaction time and accuracy in tasks of cognitive performance (e.g., the Stroop task; Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004; Hansen, Johnsen, & Thayer, 2003).

The PVT and NIM. Both the PVT and NIM recognize HRV as informative about the capacity for emotional responding and underscore the role of the PNS in inhibiting autonomic arousal in emotional expression and regulation. Each posit that lower parasympathetic cardiac control associated with decreased HF-HRV and elevated LF-HRV contributes to rigid responding which characterizes pathological anxiety (Akselrod et al., 1981; Pittig, Arch, Lam, & Craske, 2013). Additionally, both are supported by evidence that prefrontal cortical substrates involved in top-down self-regulation (i.e., effortful/executive control processes) also influence cardiac activity through the parasympathetic nervous system (Bridgett, Burt, Edwards, & Deater-Deckard, 2015). The models differ in that the NIM underscores the role of the prefrontal cortex in inhibitory processes via vagal pathways, whereas the PVT highlights the evolution of a

myelinated vagus in promoting social engagement, communicating and the cultivation of relaxed behavioral states also through inhibitory processes.

HRV measurement and interpretation. Historically, HRV has been calculated through analysis of QRS complexes obtained via electrocardiogram (ECG; see Figure 1). As previously discussed, HRV analysis relies on the use of inter-beat intervals, or R-R intervals, which are differences between successive R-wave occurrence times, calculated via the following formula: $RR_n = t_n - t_{n-1}$ (Task Force of the European Society of Cardiology, 1996). After collection, the series of R-R intervals must be corrected for abnormal beats and artifacts (see Kamath & Fallen, 1995). More recently, technological advances have enabled measurement of HRV through "wearable devices" (Georgiou et al., 2018; Peake, Kerr, & Sullivan, 2018), which, rather than electrocardiography, use plethysmography, a simple and low-cost method for detecting volumetic changes in the peripheral blood circulation at the skin surface, through which R-R intervals may be captured. R-R intervals derived from photoplethymsmography have been shown to be strongly correlated to those obtained via ECG (Giardino, Lehrer, & Edelberg, 2002).

From R-R intervals, two types of analyses may be used to analyze HRV: time domain and frequency domain. Time domain (TD) analyses yield information about general HRV via standard deviation of normal to normal R-R intervals (SDNN), or differences between R-R intervals (e.g., root mean square of successive differences [RMSSD], number of pairs of adjacent R-R intervals differing by more than 50 milliseconds [NN50], or ratio of NN50 to all R-R intervals expressed as a percentage [pNN50]). Within the extant psychological literature, RMSSD is the most commonly reported time domain index of HRV (e.g., Brosschet, Gerin, & Thayer, 2006; Hansen et al., 2003; Johnsen et al. 2003; Kemp, Quintana, Kuhnert, et al., 2012; Ottaviani, Meeten, Lonigro, Tarvainen, & Couyoumdjian, 2015), as a marker of parasympathetic

activity. Although TD indices are straightforward to calculate, overall, they are limited due to lack of discrimination between effects of sympathetic and parasympathetic autonomic branches (Kuusela, 2013). Further, RMSSD has been shown to be strongly correlated (r = .93) with HF absolute power (Ernst, 2014) and thus is likely not qualitatively more informative than frequency domain indices.

Frequency domain analyses provide detailed information about dynamics and frequency components of HRV and allow sympathetic and parasympathetic contributions of HRV to be identified (Achten & Jeukendrup, 2003). In frequency domain methods, a power spectrum density (PSD) estimate is calculated for the R-R interval series, which represents the signals power intensity in the frequency domain. PSD estimation may be computed using one of two techniques for decomposing the variance in the frequency domain (ms2/Hz), thus converting the signal from a time domain to a frequency domain and producing a power spectrum (Ernst, 2014): fast Fourier Transformation (FFT) or autoregressive (AR) modeling (Marple, 1987). Findings from a detailed comparison of the approaches by Cerutti, Bianchi, and Mainardi (1995) indicated that the methods yield comparable results (Task Force of the European Society of Cardiology, 1996). Of the two, FFT is most commonly used in studies of anxiety and HRV (e.g., Keary, Hughes, & Palmieri, 2009; Pittig et al., 2013).

The Task Force of the European Society of Cardiology (1996) has put forth specific guidelines for frequency-domain computations of HRV, whereby spectral power is divided in high frequency (HF-HRV; 0.15–0.40 Hz), low frequency (LF-HFV; 0.04 –0.15 Hz), and very low frequency (VLF-HRV; 0.00–.04 Hz (see Figure 4). These analyses are based on the observation that HRV is composed of well-defined rhythms that align with different regulatory mechanisms of cardiovascular control and provide measurement of high frequency, whereby HF-

HRV represents the parasympathetic nervous system output. There is considerably more controversy surrounding LF-HRV; some argue that LF-HRV reflects fluctuations of sympathetic input to the SA node (Malliani, Pagani, Lombardi, & Cerutti, 1991), whereas others assert that LF rhythms reflect the fluctuating influence of both sympathetic and parasympathetic influence (Berntson et al., 1997).

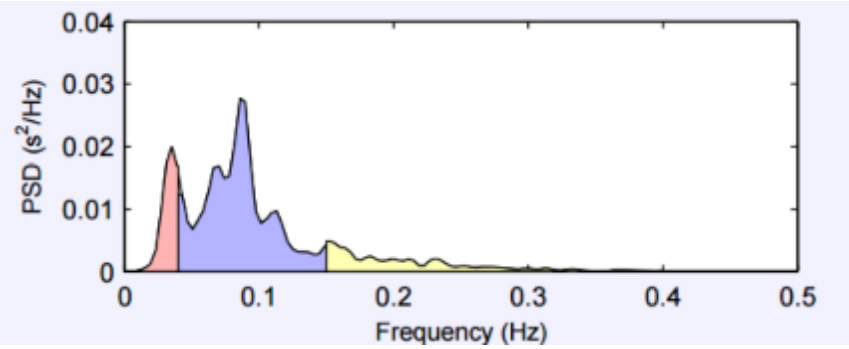

Figure 4. An example of a HRV power spectrum. Very low-frequency (VLF-HRV) is shown in red, low frequency (LF-HRV) in blue, and high-frequency (HF-HRV) in yellow.

A number of frequency-domain measures may be extracted from the PSD estimate for each frequency band, including absolute and relative powers of VLF-HRV, LF-HRV, and HF-HRV in normalized units; LF/HF power ratio; and peak frequencies for each band. Normalized units (n.u.) represent the relative value of each power component in proportion to the total power minus very low frequency (VLF; 100.0 * HF Power / [Total Power - VLF Power]; Task Force, 1996). These measures are most commonly used in empirical work, as they are normally distributed by removing differences in overall variance across (Berntson et al., 1997) and thus can be used in parametric statistics. Normalized units are seen to be beneficial as they represent the controlled and balanced behavior of the sympathetic and vagal branches of the nervous system (Task Force, 1996). Some have argued that use of these parameters is less than ideal, however, as HF-HRV normalized units (HF-HRV n.u.) and LF-HRV normalized units (LF-HRV

n.u.) are perfectly linearly related and thus computationally identical, so analyzing both values provides no additional information over the other. Thus, it is recommended that normalized units always be reported with absolute values of the LF and HF to best describe the distribution of power (Task Force, 1996).

Clinical implications of HRV. In summary, healthy activity in many physiological processes is characterized by variability, seen to reflect multiple ongoing processes, including inhibitory processes. Pathological functioning, including psychopathological functioning, on the other hand, is characterized by reduced flexibility and predictability (Friedman, 2007), which may be due to failures in inhibitory mechanisms (Thayer et al., 2000, 2009). Numerous studies have provided support for the PVT and NIM, by demonstrating decreased flexibility via lower HF-HRV among clinical samples relative to controls (e.g., Chalmers et al., 2014). This is not surprising, since failures of inhibition are associated with the behavioral rigidity and dysregulation which characterize a host of psychological disorders, including obsessive compulsive disorder, attention-deficit hyperactive disorder, anxiety, depression, and schizophrenia (Thayer et al., 2009). Indeed, relative to healthy controls, lower HRV has been demonstrated in individuals with depression (e.g., Kemp et al., 2010; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012), borderline personality disorder (Koenig, Kemp, Feeling, Thayer, & Kaess, 2016), and alcohol use disorders (e.g., Ingjaldsson, Laberg, & Thayer, 2003; Quintana, McGregor, Guastella, Malhi & Kemp, 2013) in addition to anxiety symptoms and pathology broadly (e.g., Friedman, 2007).

With regards to anxiety disorders, Pittig and colleagues (2013) found significant reductions in HF-HRV (reported as normalized units) for PD, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD) participants

relative to controls at rest. Others have found evidence for diminished HF-HRV among individuals with GAD (Lyonfields, Borkovec, & Thayer, 1995; reported as mean successive differences [MSD]), comorbid major depressive disorder and GAD (reported as SDNN, RMSSD, HF absolute power and LF/HF absolute power ratio; Kemp, Quintana, Kuhnert, et al., 2012), specific phobias (reported as RMSSD; Johnsen et al., 2003), PTSD (reported as normalized units; Cohen et al., 1997), and PD (Klein, Cnaani, Harel, Braun, & Ben-Haim, 1995). Alvarenga, Richards, Lambert, and Elser (2006) found significantly lower HF-HRV and higher LF-HRV (reported as absolute power via LF/HF) among PD patients, relative to controls. A recent meta-analysis of 36 studies found that, relative to controls, HF-HRV was lower among individuals with anxiety disorders (Hedges' g = -0.29, $p < 0.001$; Chalmers et al., 2014). Although this effect size was small-moderate, it is worth noting that when investigators explored associations by specific pathology, rather than anxiety disorders overall, findings revealed more nuance. GAD participants evidenced lower HF-HRV (Hedges' g = -0.56; $p < 0.001$) in comparison with controls. Significant relationships were also found for SAD (Hedges' g = -0.47, p = .001), PD (Hedges' g = -0.22, p = .30), and PTSD (Hedges' g = -0.29, p = .049).

It may also be that differences between clinical samples and healthy controls are better accounted for by general constructs which underlie psychopathology. Chalmers and colleagues (2016) reported that HF-HRV was significantly lower for "high worriers," relative to "low worriers," (Hedges' g = -0.75, p = .001) regardless of whether individuals were diagnosed with an anxiety disorder or not. Further, there is evidence to suggest that HF-HRV is significantly lower among "high-worrying" individuals, relative to "low worriers" (Brosschot et al., 2006) and appears to negatively impact "efforts to inhibit thoughts" (Ottaviani et al., 2015). Relatedly, in a study of GAD patients, Ottaviani et al. (2016) found that HF-HRV, indexed via RMSSD, was

significantly lower among those with higher perseverative cognition. Other work has shown that individuals with higher HRV report a lower incidence of intrusive thoughts (Ingjaldsson et al., 2003). as well as greater success in tasks of active thought suppression (Gillie, Vasey, & Thayer, 2015).

The aforementioned literature has led many to view HRV as an index of emotion regulation broadly (e.g., Appelhans & Luecken, 2006; Beauchaine & Thayer, 2015). This contention has been supported by studies linking autonomic function to executive ability, purported to underlie emotion regulation (Zelazo & Cunningham, 2007). Literature has evidenced an association between HRV and executive inhibitory ability, whereby lower HRV has shown associations with poorer performance on neuropsychological tasks of attention and reaction inhibition, including computerized versions of continuous performance and working memory tasks (Hansen et al., 2003, 2004) and Stroop, Go/No-Go (Thayer et al., 2009).

HRV and challenge paradigms. Research investigating HRV in the context of challenge paradigms, including the Trier Social Stress Task (e.g., Kircanski, Waugh, Camacho, & Gotlib, 2016; Taylor et al., 1996), mental arithmetic tasks (e.g., Hu, Lamers, de Gues, & Penninx, 2016; Godfrey et al., 2019), and paced breathing exercises (e.g., Godfrey et al., 2019) also lends support to the idea of HRV as a biomarker of emotion regulation. In general, studies have demonstrated HF-HRV to decline during exposure to stressful tasks. For example, Godfrey and colleagues (2019), observed significantly lower HF-HRV (reported in normalized units of absolute power) during a mental arithmetic task, relative to baseline. Sheffield et al. (1998) identified significantly decreased HF-HRV (reported in normalized units of absolute power) during a social stress task, relative to baseline. A recent meta-analysis of studies investigated findings associated with short-term HRV readings collected during challenge paradigms. Results

indicated that in general, HF-HRV (reported via absolute power) was significantly lower during periods of mental stress (Castaldo et al., 2015).

Challenge paradigms have also been heavily utilized in investigations of HRV among individuals with anxiety disorders. Pittig et al. (2013) found that HF-HRV was lower among participants with GAD, OCD, PD and SAD relative to healthy controls both at rest and during behavioral challenges. Thayer, Friedman, and Borkovec (1996) also found that compared with controls, GAD generally had both lower HF-HRV (reported as MSD, R-R intervals, HF-HRV and LF-HRV absolute power) at baseline, rest, and during an experimental 10-minute worry period. Keary and colleagues (2009) investigated HRV differences in women with PTSD, in comparison with age and gender-matched controls, both at rest and during speech challenges. Although findings did not evidence group differences during rest, an increase in LF-HRV was evident among PTSD participants during challenges in comparison with controls. Furthermore, PTSD participants evidenced greater reductions in HF-HRV (reported as absolute values) during stress tasks relative to controls (Keary et al., 2009).

To date, two studies have investigated HRV clinical samples comprised of PTSD and PD patients. Cohen and colleagues (2000) investigated PTSD alongside PD participants at rest and during a speech task. At rest, both groups demonstrated higher LF-HRV and lower HF (reported as absolute values) relative to controls. Interestingly, during a stressful task, PD and control groups demonstrated increased LF-HRV and decreased HF-HRV, whereas PTSD participants did not. Investigators attributed this lack of response to chronic autonomic overstimulation amongst PTSD participants, thus restricting ANS capacity to respond to further stress (Cohen et al., 2000). Blechert, Michael, Grossman, Lajtman, and Wilhelm (2007) also investigated PD and PTSD alongside controls, both at rest and in response to stress (i.e., threat of electric shock).

Findings indicated that HF-HRV (reported as raw R-R intervals) among PTSD participants was lower at rest; no changes were observed during the stress period among PD, PTSD, or control participants (Blechert et al., 2007).

AS and HRV. To date, few studies have investigated a potential relationship between AS and HRV, two of which have been undertaken by Schmidt and colleagues (2000, 2001). The first, undertaken in 2000, was part of a genetic investigation whereby AS and variation across the serotonin transporter 5-HTT gene were evaluated following a CO2 challenge. Findings indicated that AS, as measured via the Anxiety Sensitivity Index (ASI), predicted HRV reductions following the challenge paradigm (Schmidt et al., 2000). Schmidt, Santiago, and Wernicke (2001), later investigated physiological and interoceptive predictors of AS, following orthostatic and CO2 inhalation challenges. HRV did not emerge as related to AS or as a predictor of AS, whereas accuracy in detecting heart beats, greater tonic heart rate and greater diastolic blood pressure reactivity were.

Authors in each of these suspected that use of a community-based sample may have attenuated findings, describing it as "super" normal: Significant psychiatric and medical history were thoroughly screened, and thus, participants evidenced significantly lower AS than other community, "nonclinical" samples. They also noted that community-based recruitment yielded a higher mean sample age (i.e., $M = 27$) than that found in college samples. The authors postulated that at this stage, many of the participants may have passed through a significant portion of the critical life time points at which anxiety might be expected to manifest (Schmidt et al., 2000, 2001). Thus, the authors concluded that the relative risk for anxiety was low in these samples, and thus influenced findings. Additionally, it is worth noting that these investigations reported on a general measure of HRV, rather than reporting on specific indices used in analyses.

Thus, information about parasympathetic and sympathetic influence, as quantified via LF-HRV and HF-HRV power estimates, could not be extracted from the report. HRV data was collected over one-minute intervals, which is not consistent with the recommendations of the Task Force of the European Society of Cardiology (1996).

More recently, Dodo and Hashimoto (2017) investigated HRV in low and high AS, participants before, during, and after a cold pressor task, designed to induce discomfort. Participant AS was characterized using the Japanese version of the ASI. Results indicated both groups to evidence significantly lower HRV during the cold pressor task, relative to baseline. Following the task, during the "recovery" period, low AS participants exhibited significantly higher HRV than high AS participants.

Assessment. As noted above, investigations into AS and HRV used the ASI (Peterson & Reiss, 1987) to characterize groups of AS, which is not likely the most reliable of assessment methods. Although the ASI demonstrates solid psychometrics such as test-retest reliability (e.g., Maller & Reiss, 1992), internal consistency (e.g., Cox, Endler, Norton, & Swinson, 1991), and convergent validity (e.g., Peterson & Reiss, 1987), its subscales do not. The physical subscale has been shown to have the strongest internal consistency (e.g., Zvolensky et al., 2001), followed by the cognitive subscale (Zvolensky et al., 2001). The social concerns subscale has shown lower internal consistency, (Schmidt, Lerew, & Jackson, 1999), which may be due its small item number (Zvolensky et al., 2001). Additionally, the ASI has shown substantial instability with regards to its factor structure. Evidence from both exploratory (EFA) and confirmatory factor analyses (CFA) have failed to reach a consensus regarding its underlying factor structure, yielding support for one- (e.g., Norton, De Coteau, Hope, & Anderson, 2004; Taylor, Koch, & McNally, 1992), two- (e.g., Asmundson, Frombach, & Hadjistavropoulos,1998), three- (e.g.,

Stewart et al., 1997; Carter, Marin, & Murrell, 1999) and four-factor solutions (e.g. Cox, Parker, & Swinson, 1996). Others' findings have supported a hierarchical factor structure, consisting of three lower order factors (i.e. [a] fear of physical sensations, [b] fear of cognitive dyscontrol, and [c] fear of socially observable anxiety reactions) and one overarching general AS higher order factor (e.g., Jurin, Jokic-Begic, & Korajlija, 2012; Zinbarg, Mohlman, & Hong, 1999).

The more recently developed Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007), appears to be a more robust measure of AS. It demonstrates improved internal consistency which extends to subscales (Taylor et al., 2007; Osman et al., 2010) and preliminary factor analyses have shown it to possess increased factorial stability: as indicated via both EFA (Escocard, Fioravanti-Bastos, & Landeira-Fernandez, 2009) and CFA (Taylor et al., 2007; Wheaton, Deacon, McGrath, Berman, & Abramowitz, 2012; Petrocchi, Tenore, Couyoumdjiian, & Gragnani, 2014), with evidence converging to support a three-factor, hierarchical model.

Conclusions

Taken together, AS and HRV represent two constructs which have come to be seen as transdiagnostic risk factors for psychopathology. AS is a well-established predictor of fear response. Indeed, a vast literature has demonstrated high AS individuals to exhibit increased subjective distress (e.g., Brown et al., 2003; Zinbarg et al., 2001) and sympathetic activation (e.g., Beck et al., 1996; Forsyth, Eifert, & Canna, 2000) in response to behavioral challenge paradigms. Few studies to date have investigated the relationship into how AS might be related to parasympathetic activation. HRV, which represents a non-invasive biomarker of ANS activity, has also been heavily researched in the context of challenge paradigms, whereby clinical and healthy control groups alike have demonstrated decreases in HF-HRV in response to stress (e.g., Chalmers et al., 2016; Dodo & Hashimoto, 2019). Like AS, there is a strong literature

evidencing an association between decreased HRV and psychopathology (e.g., Beauchaine & Thayer, 2015; Friedman, 2007). At present, few studies have investigated a plausible relationship between AS and HRV. Those of which have done so have evidenced mixed findings and warrant additional investigation.

Goals and Hypotheses

Goals. A study was proposed with the primary goal of exploring a plausible relationship between AS and HRV. While these variables have been vastly investigated in the context of challenge paradigms independently, literature investigating a relationship between them is limited. It was proposed that participants with normative and high AS be exposed to three challenge paradigms designed to target each of the three dimensions of AS (i.e., cognitive, physical, social). To date, the majority of AS-focused studies have utilized physical tasks (i.e., CO2 inhalations and hyperventilation; e.g. Gregor & Zvolensky, 2008; Rapee & Medoro, 1994). However, since the literature suggests that AS domains possess challenge-specific predictive utility (e.g., Brown et al., 2003), use of multiple challenge paradigms was thought to be beneficial in delineating the relationship of HRV to challenge-induced stress, since high AS participants may be elevated across one or more ASI-3 domains. Thus, it was proposed that participants be presented with multiple challenges to increase the likelihood that stress and fearful responding be evoked during HRV recordings. It was proposed that HRV be investigated at rest, and during each challenge in order to determine whether groups evidenced differences (a) at each time point (i.e., baseline and during behavioral challenges) and (b) in the magnitude of HRV change observed during each challenge, relative to baseline.

In addition to providing valuable insights into group differences (i.e., whether high and normative AS participants respond differentially to stress evoked via challenges), the study had a

secondary goal. Use of the ASI-3 is relatively novel to the AS challenge literature. Thus, the present study aimed to investigate the predictive utility of AS, as indexed by the ASI-3. Subjective distress would be measured at baseline and following each challenge, with the goal of evaluating whether differences in normative and high groups emerged.

Primary hypotheses. The following set of primary hypothesizes were proposed in order to address the main research questions of this study, delineating a posited relationship between high AS and diminished parasympathetic activity, indexed by diminished HF-HRV and elevated LF-HRV:

1. High AS individuals will demonstrate significantly lower HF-HRV and a trend toward higher LF-HRV at rest, relative to individuals with normative AS.
2. High AS individuals will demonstrate significantly lower HF-HRV during the cognitive challenge relative to individuals with normative AS.
3. High AS individuals will demonstrate significantly lower HF-HRV during the physical challenge relative to normative AS individuals.
4. High AS individuals will demonstrate significantly lower HF-HRV during the social challenge relative to normative AS individuals.
5. High AS individuals will demonstrate greater *decreases* in HF-HRV relative to normative AS individuals during the cognitive challenge.
6. High AS individuals will demonstrate greater *decreases* in HF-HRV relative to normative AS individuals during the physical challenge.
7. High AS individuals will demonstrate greater *decreases* in HF-HRV relative to normative AS individuals during the social challenge.

Secondary hypothesis. A secondary hypothesis was proposed in order to evaluate the degree to which AS is associated with subjective distress. It was hypothesized that high AS individuals will report increased subjective distress following cognitive, physical, and social behavioral challenges, relative to low normative AS individuals.

Method

Screening Phase

Participants. After obtaining IRB approval (see Appendix A), participants were recruited on the campus of Eastern Michigan University through multiple methods, including an online subject recruitment site, fliers (see Appendix B) around campus (e.g., dormitory and academic building common areas), brief classroom presentations (see Appendix C) and one mass email sent to a randomized group of Eastern Michigan University students currently enrolled in coursework. Those interested in participating in the screening portion of the study were directed a brief, online questionnaire (see Appendix D) which included the Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007) and a series of questions addressing inclusion and exclusion criteria.

Procedures. Participants were provided access to the study via hyperlink, which first directed them to an informed consent form to review (see Appendix E). After clicking through pages of the consent form, participants were asked to check yes or no in response to the following question: "I have read this form. I have had an opportunity to ask questions and am satisfied with the answers I received. I give my consent to participate in this research study." Participants provided consent by clicking "yes" in response to this question. They were then directed to the screening questionnaire at the end of which they were asked to respond "yes" or "no" to the following question: "I am interested in completing an hour-long follow up to the study through which they could earn a $25 Amazon gift card and, if applicable, research credit." Those who responded "yes" were asked to list their name, email, and mobile phone number. Screening procedures were ongoing until all the full sample (n = 120) completed the in-person portion of the study. See Figure 5 for a summary of screening results.

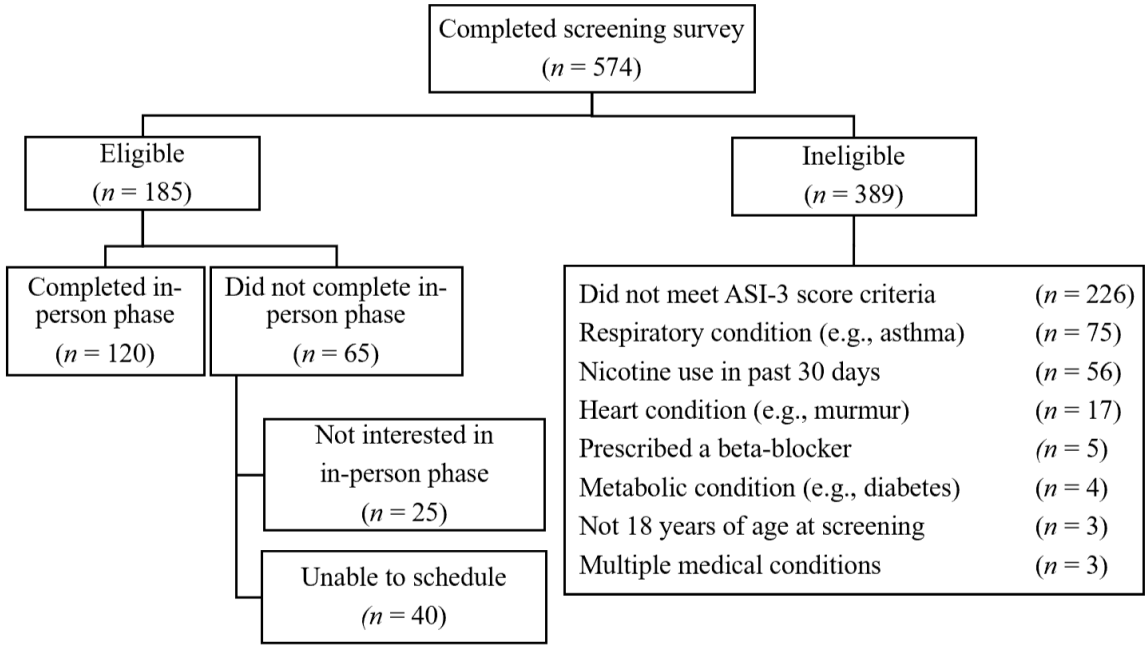

Figure 5. Summary of screened participants

In-Person Phase

Participants. Screening data was reviewed to identify individuals who met eligibility criteria for participation in the in-person phase of the study. Given the association between diabetes and compromised autonomic function (Ewing & Clarke, 1982), individuals with diabetes were excluded from participating in the in-person portion of the study. Further, given that research has linked nicotine use (i.e., via oral ingestion or inhalation) to reduced heart rate variability (HRV) and parasympathetic modulation (Dinas, Koutedakis, & Flouris, 2013; Sjoberg & Saint, 2011), those reporting use of nicotine (i.e., via chewing or cigarette tobacco, electronic cigarette use, or through use of smoking cessation aids such as nicotine patches or gum [e.g., Nicorette]) within the past thirty days were excluded from study participation. Further, given the embedded study hyperventilation challenge, those with a history of respiratory problems or conditions were excluded from participation. Furthermore, individuals with cardiac problems or

conditions, including a history of heart murmur or congenital heart disease, or who were taking beta-blockers for any reason were excluded from study participation. Individuals were required to be ≥ to 18 years of age to participate in the in-person portion of the study.

In order to explore differences between individuals with high and low levels of anxiety sensitivity (AS), cut-points for study inclusion were defined as follows: those scoring greater than or equal to one standard deviation above the mean (i.e., ≥ 23) on the ASI-3 (Taylor et al., 2007; *M* = 12.8, *SD* = 10.5) were recruited as "high" AS participants and those scoring less than or equal to one standard deviation below the mean (i.e., ≤ 2) the mean were recruited as "low" AS participants. However, after one month of study recruitment, a total of 126 individuals completed the online screener for the study, and while 31% of completers met inclusion/exclusion criteria and scored ≥ 23 on the ASI-3 (Taylor et al., 2007), none met criteria for "low" AS (ASI-3 score ≤ 2). Assuming a normal distribution, 31.8% of participants would fall within proposed study inclusion range, and although 31% did meet study criteria, these were all on the high side of the distribution. Thus, it was thought that ASI-3 cut-points were problematic and potentially overly stringent, since obtaining a score of 2 or less on the ASI-3 would require endorsing only a small amount of AS in response to one or two questions at the most. Therefore, study criteria were amended and individuals with "normative" AS (i.e., those scoring ≤ the mean 12) were recruited for comparison.

Individuals who satisfied screening criteria and expressed interest in the in-person portion of the study were contacted to set up a time for participation. A power analysis using G*Power 3.1 was completed assuming a medium effect size, *d* = .5 as recent work has shown a medium effect size for the association between HRV and various anxiety disorders (Hedge's *g* = -.47,

-.56; Chalmers et al., 2014) as well as AS-related variables such as emotional dysregulation (Cohen's d = 0.52; Williams et al., 2015) and trait anxiety (Cohen's *d* =0.52; Miu, Heilman, & Miclea, 2009). A sample size of 120, with 60 in each group, was estimated to achieve power of .8 with alpha set to .05 (two-tailed).

Procedures. Individuals who were responsive to outreach were scheduled to meet with the principal investigator in the study lab for approximately one hour. Prior to undergoing study procedures, participants were provided an informed consent form (see Appendix F). The principal investigator reviewed the form with each participant and answered questions presented. Upon provision of consent, each participant was assigned a study participation code, to be used as a unique identifier on all study documents. Participants were then fitted with a Polar® H7 Heart Rate Monitor. Appropriate fitting of the Polar® H7 was demonstrated systematically by the researcher; participants were instructed align device electrodes with their sternum, against their skin, in accordance with instructions in the Polar® H7 Heart Rate Monitor Manual. Then, Polar® H7 electrodes were moistened according to manual instructions and participants were allowed 2-5 minutes in privacy to affix the device as instructed. Appropriateness of fit was then assessed via brief remote recording through use of the Polar® V800.

Once fitted with the H7 chest strap, participants were presented with a series of questionnaires, including the subjective units of distress scale (SUDS; see Appendix G), demographics questionnaire (see Appendix H), ASI-3 (Taylor et al., 2007; see Appendix I), and PROMIS® Emotional Distress measures of anxiety and depression (see Appendix J). Participants were then asked to undergo three brief behavioral challenges: cognitive, physical, and social in nature. During each challenge, a brief recording of HRV (i.e., R-R interval data) was collected through use of the Polar® V800 and H7. Participants were asked to complete the

SUDS following each challenge. A 10-minute break was allotted between each behavioral challenge. Following completion of the three behavioral challenges, a debriefing sheet (see Appendix K) was provided to study participants. The principal investigator answered any questions posed by participants and provided each with a $25 Amazon Gift Card as compensation for their time.

Measures

Demographic information. Each participant was asked to complete a brief questionnaire with items addressing socioeconomic status, education, and employment, in order to provide general information about the sample.

PROMIS® (Patient-Reported Outcomes Measurement Information System). Participants were additionally asked to complete select measures from the PROMIS®. The PROMIS® is a set of measures designed to yield rapid and accurate measurement of physical, mental, and social health in adults and children (Ader, 2007). Measures were selected to obtain information about depression and anxiety symptoms known to be associated with elevated AS and decreased HF-HRV.

PROMIS® Emotional Distress---Anxiety. The short form PROMIS anxiety tool is a four-item measure of fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). It has demonstrated adequate reliability and validity, including internal consistency (Chronbach's $\alpha = .89$) as well as construct validity, correlating strongly with the Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006; Kroenke, Yu, Wu, Kean, & Monaha, 2014) and the Mood and Anxiety Screening Questionnaire (MASQ; Watson & Clark, 1991; $r = .80$, Pilkonis et al., 2011). It has been reported to be a reasonable option for

brief screening (Kroenke et al., 2014). Scores range from 4 to 20 points and a score of 8 is recommended as an optimal screening cut-point for anxiety (Kroenke et al., 2014).

PROMIS® Emotional Distress---Depression. The short form PROMIS depression tool is a four-item measure of negative mood (sadness, guilt), views of self (self- criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). It has been reported to be a reasonable option for brief screening (Kroenke et al., 2014), demonstrating adequate reliability and validity, including internal consistency (Chronbach's $\alpha = .93$) as well as construct validity, correlating strongly ($r = .75$) with the Patient Health Questionnaire-9 (PHQ-9; Kroenke & Spitzer, 2002; Kroenke et al., 2014) and Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977; $r = .77$; Pilkonis et al., 2011). Scores range from 4 to 20 points and a score of 8 is recommended as an optimal screening cut-point for depression (Kroenke et al., 2014).

Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007). The ASI-3 was additionally completed by participants prior to engaging in behavioral challenges. The ASI-3, as previously noted, is the most recently developed self-report measure of AS and is comprised of 18 items. Participants report on a 5-point Likert scale from 0 (*very little*) to 4 (*very much*), expressing the extent to which they agree with each item (e.g., "It is important for me not to appear nervous," "When I notice my heart skipping a beat, I worry that there is something seriously wrong with me"). Total scores range from 0 to 72 and are calculated by summing the point values for each question.

A comprehensive psychometric analysis published by Taylor et al. (2007) has shown the ASI-3 to possesses strong psychometric properties. Although Taylor and colleagues

acknowledged an AS hierarchical factor structure when describing their development of the measure, they neglected to report on psychometrics of an overarching higher order AS (i.e., total ASI-3 score), focusing instead on psychometrics of lower order domains. Their initial validation efforts indicated that ASI-3 subscales indeed possess strong internal consistency (physical concerns, a = .76 - .86; cognitive concerns, a = .79 - .91; social concerns, a = .73 - .86). Subsequent analyses by independent researchers did investigate the total ASI-3 score and found it to possess strong internal consistency (α = .90; Osman et al., 2010), which has held up in a variety of cultures, including: African American (a = .90; Williams, Abramowitz, & Olatunji, 2012), German (α = .92; Kemper, Lutz, Bähr, Ruddel, & Hock, 2012) and Italian (α = .87 - .92; Petrocchi et al., 2014) samples. The ASI-3 has also shown strong convergent validity with appropriate measures (e.g., r = .61 with the State Trait Anxiety Inventory; Spielberger, Gorsuch, & Lushene, 1970; r = .64 with the Fear of Negative Evaluation Scale; Kemper et al., 2012).

Subjective Units of Distress Scale (SUDS). The SUDS (Wolpe, 1958) was developed to index self-reported anxiety in the moment. The SUDS is a Likert-type scale ranging from 0 (*no anxiety*) to 100 (*extreme anxiety*) in subjective ratings of anxiety. The SUDS was completed by participants prior to and just after each challenge.

Behavioral Challenges

In order to evaluate HRV and AS under varying conditions of stress, designed to tap into each facet of AS measured by the ASI-3, participants were presented with three challenges, counterbalanced in presentation in order to control for order effects.

Cognitive challenge. Participants were presented with a computerized version of the Paced Auditory Serial Addition Task (PASAT) as a cognitive challenge. The PASAT is a task of neuropsychological functioning which coincidentally also produces high levels of distress and

anxiety for those completing the task (Tombaugh, 2006). The PASAT-C (Lejuez, Kahler, & Brown, 2003) is a brief computerized version of the task which was adapted for use in behavioral challenge paradigms and has been shown to induce psychological distress (e.g., self-reported anxiety, difficulty concentrating, and irritability) as well as physiological arousal (e.g., increased skin conductance and heart rate; Lejuez et al., 2003). During the task, numbers are sequentially flashed on a computer screen, and participants are instructed to sum the digits and then click on the correct answer using a mouse. They are then instructed to ignore the sum and add the following number with the previously presented number. When the participant provides a correct answer, a point is earned and when an error is made, an "explosion" sound is played. The speed of the task increases over time, and although the package can be programmed with a discontinue button, this option was not be presented in order that all participants undergo the same challenge duration. The "explosion" sound was presented at 68 decibels.

Physiological challenge. Participants were presented with a brief hyperventilation exercise as a physiological challenge. The exercise was modeled after procedures used by Brown and colleagues (2003) in an investigation into the predictive utility of ASI factors. Participants were instructed to take full vital capacity breaths every 2 seconds for a total of 120 seconds (i.e., two minutes). The rate of breath was paced using a recording of a female voice announcing the words ''inhale'' and ''exhale.'' Prior to starting the exercise, the investigator modeled the procedure and answered questions posed by participants.

Social challenge. A socially stressful task based on the Trier Social Stress Task (Kirschbaum, Pirke, & Hellhammer, 1993) was additionally presented to participants. Participants were instructed to develop and perform a 15-minute speech concerning "their most undesirable characteristic" and were informed that the speech would be videotaped and evaluated

by a group of students and faculty. Participants were given ten minutes to prepare the speech and were reminded of the task after a period of five minutes. Following the 10-minute period, participants were informed that they did not actually have to perform the speech. The Trier Social Stress Task has been utilized in prior work investigating AS alongside indices of SNS arousal (e.g., heart rate change, skin conductance; Conrod, 2006) but not alongside HRV.

Physiological Measurement of HRV

A Polar® V800 with a Polar® H7 heart rate sensor was utilized to record R-R intervals for each participant at baseline and during each challenge. The Polar® V800/H7 combination functions in accordance with standards put forth by the Task Force of the European Society of Cardiology (1996), recording R-R intervals at a 1,000 Hz sampling rate. Recent research by Giles, Draper, and Neil (2015) has supported the validity of the Polar® V800/H7 combination in producing R-R interval recordings consistent a traditional Biopac ECG, commonly used in psychophysiological studies targeting HRV and anxiety (e.g., Blechert et al., 2007; Keary et al., 2009; Miu et al., 2009). Increasingly, the Polar® V800 with a Polar® H7 heart rate sensor combination has been utilized in psychophysiological studies (e.g., Colzato, Jongkees, de Wit, van der Molen, & Steenbergen, 2018).

R-R interval recordings were collected at four time points (i.e., baseline and during each behavioral challenge) in five-minute increments, in accordance with standards of the Task Force of the European Society of Cardiology (1996). For the two-minute hyperventilation challenge, R-R interval recordings were completed during the challenge and through three minutes post. A Polar V800 watch and H7 chest strap were utilized to initiate and end recordings. The V800 wirelessly receives HR data from the H7 chest strap, which may be extracted through synching the device with the Polar Flow web application. Raw data were extracted from the Polar Flow

web application as text files and imported into Kubios HRV software for analysis (Premium Version 3.0, 2017, Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland, MATLAB; Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).

Kubios HRV analysis software contains an artifact correction method which identifies beats that are too long or short and corrects them by interpolating new values to the RR time series from a time varying threshold, based on a time series consisting of differences between successive RR interval, which Kubios refers to as "dRR." According to the Kubios manual, the automatic correction method enables ectopic and normal beats to be separated, as for each beat, a quartile deviation of the 90 surrounding beats is calculated and multiplied by factor 5.2. Beats within this range cover 99.95% of all beats if the RR series is normally distributed. However, RR intervals are often not normally distributed, and thus some normal beats may exceed the threshold, so an embedded decision algorithm is used to detect artefact beats. Ectopic beats form negative-positive-negative (NPN) or positive-negative-positive (PNP) to the dRR series. Similarly, long beats form positive-negative (PN) and short beats negative-positive (NP) patterns to the dRR series. Only these segments from the dRR series are classified as artefact beats. Missed or extra beats are detected by comparing current RR values with median of the surrounding 10 RR interval values (medRR). Detected ectopic beats are corrected by replacing corrupted RR times by interpolated RR values. Similarly, too long and short beats are corrected by interpolating new values to the RR time series. Missed beats are corrected by adding new R-wave occurrence time and extra beats are corrected by removing extra R-wave detection and recalculating RR interval series. According to the Kubios brochure, this correction algorithm has been validated using the MIT-BIH arrhythmia database, showing 97.0% accuracy in detecting

ectopic beats and 99.9% accuracy in identifying normal beats (Kubios brochure, publication under review).

Kubios also contains an embedded smoothness priors detrending option. De-trending is seen to be an important step in HRV analysis as it relates to the stationarity of the recording, or the stability of the signal. Stationarity, for example, can mean that there is no shifting in the base level of the signal or that the amplitude distribution, spectrum, and autocorrelation function of the signal do not change, as a function of time. The "trend" in R-R interval series represents a sign of non-stationarity, which can be removed by subtracting the trend from the data (Kuusela, 2013). It is recommended that trends be removed from HRV data in order to decrease contributions from lowest frequencies, allowing analyses to focus on faster oscillations (Kuusela, 2013). Kubios automatic correction and detrending options were utilized in HRV analyses for the study.

It was proposed that high-frequency heart rate variability (HF-HRV) and low-frequency heart rate variability (LF-HRV) normalized units (n.u.) from FFT frequency domain output be extracted for use in the present study. Use of FFT-derived measures were selected since they yield similar results to the alternative of AR techniques but are more commonly used in investigations of psychopathology (e.g., Keary et al., 2009; Pittig et al., 2013).

Study Design

The study utilized a repeated measures design with one between-subjects factor: high versus normative AS. The within-subjects factor consisted of HRV levels recorded at baseline and again during each of the three challenges. To minimize carry-over effects, the challenges were counterbalanced in presentation, and a rest period of 10 minutes between each challenge was allotted to each participant.

Planned Analyses

Primary hypotheses.

Hypothesis 1: High AS individuals will demonstrate significantly lower HF-HRV and a trend toward higher LF-HRV at rest, relative to individuals with normative AS. It was initially proposed that Hypothesis 1 be tested by using an independent samples t-test, where the outcome was HRV measured at baseline.

Hypotheses 2-4: High AS individuals will demonstrate significantly lower HF-HRV during the behavioral challenges, relative to normative AS individuals. It was initially proposed that Hypotheses 2-4 be tested using a repeated measures ANOVA with HF-HRV measured at baseline and during each challenge, whereby the within-subjects factor (the repeated measures) would be interacted with the between-subjects factor (normative or high AS) to determine if group differences varied significantly depending on the challenge. Determinations of statistical significance (alpha = .05) would employ the Greenhouse-Geisser correction for deviations from sphericity. It was proposed that planned contrasts for simple effects be presented for a significant interaction and/or main effect for the between-subjects factor, in order to identify which challenges produced significant results (i.e., if AS category significantly differentiated HRV levels during the cognitive challenge [H2], during the social challenge [H3], and during the physical challenge [H4]). Simple effects analysis revealing statistically significant differences in HRV scores by group during the respective challenge would result in rejection of the null hypothesis.

Hypotheses 5-7: High AS individuals will demonstrate greater decreases in HF-HRV relative to normative AS individuals during behavioral challenges. It was initially proposed that change scores be calculated to represent the differences in HRV scores between baseline and

each challenge. That is, the change score during the cognitive challenge would be $Change_{cognitive} = HRV_{cognitive} - HRV_{baseline}$, the change score for the physical challenge will be $Change_{physical} = HRV_{physical} - HRV_{baseline}$, and the change score for the social challenge will be $Change_{social} = HRV_{social} - HRV_{baseline}$. It was proposed that a repeated measures ANOVA be fit using each change score as the within-subjects factor with AS category as the between-subjects factor. The null hypotheses would be rejected if a significant difference in HRV change scores between the two AS groups for the respective challenges emerged.

Secondary Hypothesis: High AS individuals will report increased subjective distress following behavioral challenges, relative to normative AS individuals. It was proposed that change scores be calculated to represent the differences in SUDS between baseline and following each challenge. That is the change score during the cognitive challenge would be $Change_{cognitive} = SUDS_{post} - SUDS_{pre}$, the change score for the social challenge would be $Change_{social} = SUDS_{post} - SUDS_{pre}$, and the change score for the physical challenge would be $Change_{physical} = SUDS_{post} - SUDS_{pre}$. A repeated measures ANOVA would be fit using each change score as the within-subjects factor with AS level as the between-subjects factor. A significant estimate (applying the Greenhouse-Geisser correction) for either the within-between interaction or the between-subjects main effect would be again followed up with simple effects.

Correlational Analyses

Finally, it was proposed that correlational analyses be utilized in order to evaluate relationships between psychosocial variables. Correlations would also be used to assess test-retest reliability of the ASI-3 for administrations completed during online screening and the in-person portion of the study.

Amended Analysis Plan

When analyses were undertaken, it became clear that the SPSS procedure for performing repeated-measures ANOVA did not report the necessary contrasts for testing Hypotheses 2-4. It could test Hypotheses 5-7 by using simple contrasts with baseline as the reference category. This approach obviates the need to calculate change scores because the simple effects are already testing change from baseline. Therefore, the data analysis plan for Hypotheses 2-4 was amended whereby a MANOVA was fit to evaluate differences in HRV measured during cognitive, physical, and social challenges between groups. Levene's and Box's tests were utilized in order to ensure that assumptions of equality of variance and covariance were not violated. The MANOVA omnibus test statistic was evaluated in order to determine if an overall difference between high and normative AS groups was present. A significant result (alpha = .05) was followed by a review of univariate ANOVA results in order to determine upon which behavioral challenge/s groups significantly differed. In order to control for type I error, a Bonferroni correction was applied to univariate results. Significant differences in groups resulted in rejection of the null hypothesis.

Hypotheses 5-7 and secondary hypotheses were tested using methodology originally proposed for Hypotheses 2-4. The tests of the within-subjects simple contrasts for the interaction term assessed whether the change from baseline was significantly different between groups for each of the challenges.

Results

Missing Data

In-person study questionnaires were inspected for missing data at the time of completion, and thus there was little missing data. However, due to placement of one item (i.e., reported age), 13 participants failed to provide a response, which remained unknown to the principal investigator until data was entered into SPSS at a later date. Since participants had not provided consent for future contact, data was unable to be recovered by the principal investigator. There was no other missing data.

Study Sample

Screened participants who presented to complete the in-person portion of the study (N = 120) were predominantly female, White, and on average, 23.5 years old, ranging from 18-63. Normative anxiety sensitive (AS)-screened participants (M = 25.84, SD = 9.8) were significantly older than high AS-screened participants (M = 21.44, SD = 4.2), $t(105) = 3.09$, $p < .001$. Most participants (92.5%) were enrolled in coursework at the time of participation, taking an average of 10.1 credit hours (SD = 5.7). Of those currently enrolled in coursework, high AS-screened participants were enrolled in significantly more credit hours (M = 11.82, SD = 5.18) than normative AS-screened participants (M = 8.04, SD = 5.57), $t(110) = -3.7$, $p < .01$, although normative AS-screened participants had completed significantly more (M = 73.2 SD = 40.8) credit hours at the time of participation, as compared with high AS-screened participants (M = 56.5, SD = 37.9), $t(101) = 2.2$, $p < .05$. Additional demographic information is shown in Table 2.

Table 2

Demographics for Eligible Participants by Group at Time of Screening

	Total Sample (N = 120)		High AS (n = 60)		Normative AS (n = 60)	
	N	(%)	*n*	(%)	*n*	(%)
Gender						
Female	78	(64.5)	46	(76.7)	32	(53.3)
Non-cisgender	1	(8.0)	1	(1.7)		
Ethnicity						
Hispanic/Latino	6	(5.0)	2	(3.3)	4	(6.7)
Race (check all that apply)						
White	84	(69.4)	40	(66.7)	44	(73.3)
Black/African American	19	(15.7)	9	(15.0)	10	(16.7)
Hispanic/Latino	5	(4.1)	2	(3.3)	3	(5.0)
Native American/American Indian	5	(4.1)	3	(5.0)	2	(3.3)
Asian	11	(9.1)	6	(10.0)	5	(8.3)
Middle Eastern	5	(4.1)	4	(6.7)	1	(1.7)
Indian	1	(0.8)	1	(1.7)		
Mixed race	1	(0.8)	1	(1.7)		
Self-reported socio-economic status						
We have barely enough to get by	3	(2.5)	2	(3.3)	1	(1.7)
more	22	(18.2)	9	(15.0)	13	(21.7)
We are solidly middle class	59	(48.8)	27	(45.0)	32	(53.3)
We have plenty of "extras"	32	(26.4)	19	(31.7)	13	(21.7)
Don't know/unsure/prefer not to say	4	(3.3)	3	(5.0)	1	(1.7)
Student status						
Enrolled in courses	111	(91.7)	60	(100.0)	51	(85.0)

Participants completed a number of psychosocial measures at baseline, results of which are summarized in Table 3. Of the entire sample, 29 participants (24.2%) met the PROMIS® Emotional Distress cutoff of 8 for depression, 25 (86.2%) of whom were from the high AS-screened group. Of the entire sample, 36 participants (30.0%) met the PROMIS® Emotional Distress cutoff of 8 for anxiety, 33 (91.67%) of whom were from the high AS-screened group. High AS-screened participants evidenced significantly higher scores on the PROMIS indices of anxiety ($t(118) = -6.00$, $p = .00$) and depression ($t(118) = -9.26$, $p = .00$).

Table 3

Descriptve Statistics for Psychosocial Variables for AS-Screened Groups

	High AS at screening (N = 60)			Normative AS at screening (N = 60)		
Measure	*M (SD)*	Range	Chronbach's α	*M (SD)*	Range	Chronbach's α
ASI-3, screening	35.12 (10.87)	23-66	0.83	7.85 (3.19)	1-12	0.31
ASI-3, in-person	35.48 (10.53)	18-64	0.84	12.38 (7.34)	1-31	0.83
PROMIS® Anxiety	8.00 (3.15)	1-15	0.73	3.23 (2.45)	0-10	0.68
PROMIS® Depression	6.27 (3.82)	0-15	0.88	2.64 (2.67)	0-10	8.23

Preliminary screening of relationships between psychosocial variables revealed the Anxiety Sensitivity Index-3 (ASI-3) to demonstrate strong test-retest reliability *(r* = .86) between screening and the in-person portion of the study, whereby the mean time difference was 23 days (*SD* = 19.3), ranging from 2-141 days. However, of the 60 participants who met criteria for high AS (i.e., ASI-3 ≥ 23) at the time of screening, four no longer met this criterion during the in-person portion of the study. Of the 60 participants who met criteria normative AS, 25 no longer met criteria (i.e., ASI-3 ≤ 12) during the in-person portion of the study.

ASI-3 subscales. In order to further evaluate ASI-3 scores completed at screening and in-person, participant subscale (i.e., cognitive, physical, and social concerns) scores were computed. See Appendix L for a list of ASI-3 items and the subscale to which each item corresponds. "High" and "normative" subscale scores were classified according to published norms (i.e., cognitive [*M* = 2.7, *SD* = 3.8], physical [*M* = 4.2, *SD* = 4.2], and social [*M* = 5.9, *SD* = 4.7] Taylor et al., 2007), whereby scores ≥ 1 *SD* above the published mean on each subscale were characterized as "high" and scores at or below the published means on each subscale were characterized as "normative." Thus, participants with cognitive subscale scores ≥ 6.5, physical subscale scores ≥ 8.4, and social subscale scores ≥ 10.6 were classified as "high" on the subscale. Descriptive statistics for subscale scores are presented in Table 4. Participants with

cognitive subscale scores ≤ 2.7, physical subscale scores ≤ 4.2, and social subscale scores ≤ 5.9 were classified as "normative" on the subscale.

Table 4

Descriptive Statistics for ASI-3 Subscale Scores

Measure	*M(SD)*	Range	Chronbach's α	High *N (%)*	Normative *(N) %*
ASI-3 cognitive subscale					
Screening	5.85 (6.06)	0 – 22	0.92	46 (38.33)	52 (43.33)
In-person	6.71 (5.73)	0 – 22	0.92	57 (47.50)	39 (32.50)
ASI-3 physical subscale					
Screening	5.35 (5.37)	0 – 22	0.87	32 (26.67)	73 (60.83)
In-person	6.25 (5.15)	0 – 21	0.86	39 (32.50)	54 (45.00)
ASI-3 social subscale					
Screening	10.28 (6.38)	0 – 24	0.88	53 (44.16)	37 (30.83)
In-person	10.98 (6.14)	0 – 24	0.88	60 (50.00)	25 (20.83)

Note. Subscale scores ≥ *SD* above the mean were classified as high; scores ≤ or equal to the mean were classified as normative.

Of the 60 participants who were categorized as high AS at screening, 25 (41.67%) had three elevated subscales, 20 (33.33%) had two elevated subscales, and 15 (25.0%) had one elevated subscale: three on the cognitive subscale, two on the physical subscale, and 10 on the social subscale. Of the 60 participants who were categorized as normative AS at screening, one participant was elevated on the cognitive subscale only.

Of the 61 participants who were categorized as high AS during the in-person portion of the study, 31 (50.82%) had three elevated subscales, 19 (31.15%) had two elevated subscales, and 11 (18.03%) had one elevated subscale: three on the cognitive subscale, one on the physical subscale, and seven on the social subscale. Of the 35 participants who were categorized as

normative AS during the in-person portion of the study, one participant was elevated on the social subscale only.

Internal consistency of ASI-3 scores. Chronbach's alpha reflected high internal consistency for ASI-3 subscales derived from both screening and in-person administrations. Internal consistency was likewise acceptable for both high AS-screened scores and in-person scores, although normative AS-screened scores demonstrated markedly lower reliability (α = .0.31) with normative AS in-person (0.83). Thus, given that total ASI-3 in-person scores likely provided a more reliable representation of AS, it was decided that AS in-person groups, rather than AS-screened groups would be used as the between-subjects variable used in answering primary research study questions. AS in-person group demographics and descriptive statistics for psychosocial variables and subjective units of distress scale (SUDS) are presented in Tables 5 and 6.

Table 5

Demographics for High and Normative AS In-Person Groups

	High AS (N = 61)		Normative AS (N = 35)	
	N	(%)	*N*	(%)
Gender	45	(73.8)	17	(48.6)
Female	1	(1.6)		
Non-cisgender				
Ethnicity				
Hispanic/Latino	3	(4.9)	3	(8.6)
Race (check all that apply)				
White	43	(70.5)	25	(71.4)
Black/African American	11	(18.0)	5	(14.3)
Hispanic/Latino	3	(4.9)	2	(5.7)
Native American/American Indian	3	(4.9)	1	(2.9)
Asian	4	(6.6)	3	(8.6)
Middle Eastern	4	(6.6)	1	(2.9)
Indian	1	(1.6)		
Mixed race	1	(1.6)	1	(2.9)
Self-reported socio-economic status				
We have barely enough to get by	2	(3.3)	0	(0.0)
We have enough to get by, but no more	11	(18.0)	7	(20.0)
We are solidly middle class	26	(42.6)	21	(60.0)
We have plenty of "extras"	19	(31.1)	6	(17.1)
Don't know/unsure/prefer not to say	3	(8.6)	1	(2.9)
Student status				
Enrolled in courses	60	(98.4)	33	(94.3)

Independent samples t-tests were utilized to explore differences between AS in-person groups. Participants categorized as high AS during the in-person portion of the study evidenced significantly higher scores on PROMIS indices of anxiety, $t(94) = -10.83$, $p = .00$, and depression, $t(94) = -6.41$, $p = .00$. For age, Levene's test revealed that the assumption of homogeneity of variances had been violated, $F(1,81) = 7.62$, $p = .01$. Therefore, a t statistic not assuming homogeneity of variance was computed. Results indicated that those in the normative

AS group were significantly older (M = 26.67, SD = 10.53) than those in the high AS group (M = 22.00, SD = 6.97), t(37.36) = 2.09, p = .04. Of those currently enrolled in coursework, high AS participants were enrolled in significantly more credit hours (M = 11.57, SD = 5.35) than normative AS participants (M = 7.67, SD = 5.35), t(91) = -3.36, p = .001. Normative AS participants had completed significantly more (M = 74.20 SD = 41.72) credit hours at the time of participation, than high AS-screened participants (M = 57.16, SD = 38.07), although this difference was not statistically significant t(84) = 1.91, p = .06.

Table 6

SUDS at Baseline and Post-Behavioral Challenges for AS In-Person Groups

	High AS (N = 61)		Normative AS (N = 35)	
	M (SD)	Range	*M (SD)*	Range
Baseline	26.07 (14.26)	0-60	12.86 (8.94)	0-30
Post-cognitive	56.31 (19.75)	10-90	24.86 (16.52)	0-70
Post-physical	44.26 (23.13)	0-90	21.14 (16.76)	0-70
Post-social	50.82 (20.90)	0-90	22.71 (14.16)	0-60

HRV Data Cleaning and Analysis.

In accordance with recommendations put forth by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996; Shaffer & Combatalade, 2013), HRV data was visually inspected for extreme artifacts (R-R intervals >3) and when possible, trimmed. Task Force recommendations specify that while a five-minute recording is optimal, a minimum recording of one minute is sufficient to estimate the high-frequency heart rate variability (HF-HRV) component and at least two minutes enough to estimate the low-frequency heart rate variability (LF-HRV) component. Therefore, trimmed recordings with ≥ two minutes of uninterrupted recording were retained for analyses. A total of nine recordings were deleted due to multiple artifacts without unbiased recording periods

of $\geq$ two minutes. Of the deleted recordings, six were from the high AS group: one during baseline, one during cognitive, two during physical, and two during social. Three of the recordings were from the normative AS group: two during the social challenge and one during cognitive.

Kubios automatic correction algorithm and smoothness priors detrending options were applied to remaining HRV recordings. HRV data was then exported to an SPSS-readable batch file (see Appendix M). Data was once again inspected and recordings with more than 5% corrected errors were deleted in order to reduce effects from editing (Peltola, 2012; Tarvainen, Lipponen, Niskanen, & Ranta-aho, 2017). A total of 29 recordings were deleted due to > 5% corrected artifacts. Of these recordings, nine were from the high AS group: three during baseline, four during the cognitive challenge, one during physical, and one during social. Twenty of the recordings were from the normative AS-screened group: five during baseline, four during the cognitive challenge, five during physical, and six during social.

Consideration of additional HRV indices. In order to further evaluate research questions, additional HRV indices captured via Kubios were considered for use in exploratory analyses. As previously noted, normalized units were initially thought to be beneficial for use in parametric statistics, since difference in overall variance has been removed (Berntson et al., 1997). However, HF-HRV and LF normalized units are perfectly linearly related and thus computationally identical, so use of both values to answer study questions would be redundant. Therefore, in order to more thoroughly evaluate the role of HRV alongside AS, other frequency-domain indices of HRV provided by Kubios (i.e., HF and LF indices of absolute power reported in milliseconds and via log-transformed values) were considered for use in exploratory analyses

to supplement information provided by normalized units (i.e., HF n.u., LF n.u.). Results of all HRV indices are summarized below in Table 7.

Table 7

HRV Indices at Baseline and During Behavioral Challenges

	High AS			Normative AS		
Baseline	(*N* = 57)	*M (SD)*	Range	(*N* = 32)	*M (SD)*	Range
HF log		5.93 (1.51)	2.66 - 9.55		6.10 (1.57)	1.53 - 9.07
LF log		6.42 (0.96)	3.65 - 8.65		6.80 (1.32)	4.20 - 9.23
HF n.u.		39.61 (19.22)	6.01 - 89.85		34.69 (14.79)	6.49 - 67.27
LF n.u.		60.28 (19.25)	9.95 - 93.96		65.22 (14.80)	32.70 - 93.50
During Cognitive	(*N* = 55)	*M (SD)*	Range	(*N* = 33)	*M (SD)*	Range
HF log		5.63 (1.29)	2.69 - 8.84		5.68 (1.46)	0.18 - 8.83
LF log		6.27 (0.97)	3.09 - 8.13		6.24 (1.21)	3.10 - 9.00
HF n.u.		36.55 (19.95)	7.14 - 89.08		38.25 (17.09)	5.09 - 77.45
LF n.u.		63.26 (20.04)	10.71 - 92.85		61.65 (17.11)	22.50 - 94.89
During Physical	(*N* = 57)	*M (SD)*	Range	(*N* = 32)	*M (SD)*	Range
HF log		6.01 (1.22)	3.09 - 8.73		5.73 (1.47)	2.42 - 9.13
LF log		6.53 (0.86)	4.30 - 8.41		6.68 (0.89)	4.47 - 8.24
HF n.u.		39.22 (19.81)	3.76 - 87.82		31.14 (21.61)	10.32 - 91.60
LF n.u.		60.74 (19.82)	12.16 - 96.23		68.82 (21.62)	10.32 - 91.60
During Social	(*N* = 58)	*M (SD)*	Range	(*N* = 31)	*M (SD)*	Range
HF log		5.85 (1.39)	3.00 - 9.16		5.85 (1.51)	1.02 - 8.72
LF log		6.43 (0.85)	5.01 - 8.25		6.55 (1.13)	4.06 - 8.63
HF n.u.		37.72 (19.42)	7.39 - 88.63		35.12 (15.87)	4.59 - 71.67
LF n.u.		62.20 (19.46)	11.26 - 92.53		64.79 (15.86)	28.26 - 95.39

Note : HF log and LF log refer to log-transformed values of high frequency and low frequency absolute power; HF n.u. and LF n.u. refer to high frequency and low frequency normalized units

HF and LF indices of absolute power reported in milliseconds squared (ms^2) revealed skewedness (see Appendices N-O). Therefore, Kubios-generated indices of log-transformed absolute power (i.e., HF log and LF log), which met assumptions for normality, were selected for use in exploratory analyses.

Statistical Analyses

Statistical analyses were computed using SPSS 24. Prior to analyses, data histograms were visually screened to ensure that assumptions of normality were not violated. Assumptions for specific tests were also assessed: for planned repeated measures ANOVAs, sphericity was systematically assessed via Mauchley's test and corrected with Greenhouse-Geisser estimate; for planned MANOVAs, Levene's and Box's tests were reviewed to assess equality of variance and covariance, respectively, in order to ensure that assumptions of homogeneity of covariance and variance were not violated.

Hypotheses 1: Group Differences in HF-HRV and LF-HRV at Baseline

Planned analysis of HF-HRV: HF n.u. An independent samples t-test was performed to evaluate Hypothesis 1, whereby it was posited that high AS participants would exhibit significantly lower HF n.u at baseline than normative AS participants. Levene's test indicated that the assumption of homogeneity of variance had not been violated, F (1,87) = 2.79, p = .10. Independent samples t-test results indicated that differences between groups were not statistically significant, t(87) = -1.25, p = .21.

Planned analysis LF-HRV: LF n.u. An independent samples t-test was performed to further evaluate Hypothesis 1, which posited that high AS participants would exhibit a trend toward higher LF n.u. than normative AS participants at baseline. Levene's test indicated that the assumption of homogeneity of variance had not been violated, F (1,87) = 2.84, p = .10). Independent samples t-test results indicated that differences between groups were not statistically significant, t(87) = 1.25, p = .21.

Exploratory analysis of HF-HRV: HF log. An independent samples t-test was utilized to explore HF-HRV, as indexed by HF log. Levene's test indicated that the assumption of

homogeneity of variances had not been violated, $F(1,87) = 0.07$, $p = .80$. Independent samples t-test results indicated that differences between groups were not significant, $t(1,87) = 0.49$, $p = .62$.

Exploratory analysis of LF-HRV: LF log. An independent samples t-test was utilized to explore LF-HRV, as indexed by LF log. Prior to evaluating results, Levene's test results were reviewed; they revealed that the assumption of homogeneity of variances had been violated, $F(1,87) = 4.98$, $p = .03$. Therefore, a *t* statistic not assuming homogeneity of variance was computed. Results indicated that although LF log was higher for normative AS participants ($M = 6.80$, $SE = 0.23$) than high AS participants ($M = 6.42$, $SE = 0.13$), the difference was not statistically significant, $t(1,49.54) = 1.44$, $p = .16$.

Hypotheses 2-4: Group Differences in HF-HRV at Each Challenge

Planned analysis of HF-HRV: HF n.u. A one-way MANOVA was fit to test Hypotheses 2-4, which posited that normative AS participants, relative to high AS participants, would demonstrate significantly higher HF-HRV (as measured via HF normalized units [n.u.]). AS group served as the independent variable; HF n.u. recorded during each behavioral challenge served as the dependent variables. A non-significant omnibus effect was observed, Pillai's Trace = 0.06, $F(3,78) = 1.53$, $p = .21$, partial $\eta^2 = 0.06$, indicating that differences in HF-HRV (i.e., HF n.u.) between groups were not significant.

Exploratory analysis of HF-HRV: HF log. In order to further evaluate possible differences between groups, an exploratory one-way MANOVA was fit, utilizing HF-HRV log-transformed absolute power (i.e., HF log) at each challenge as the dependent variables. Results revealed a non-significant omnibus effect, Pillai's Trace = .02, $F(3,78) = 0.48$, $p = .70$, partial $\eta^2 = .02$.

Hypotheses 5-7: Group Differences in HF-HRV Change

Planned analysis: HF n.u. change. A repeated measures ANOVA, with AS group serving as the between-subjects factor and HF n.u. as the within-subjects factor, was utilized to test Hypotheses 5-7, whereby it was posited that, relative to normative AS participants, those with high AS would demonstrate significantly greater decreases in HF-HRV (as measured via HF n.u.), between baseline and each behavioral challenge. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of HF n.u., $X^2(5) = 31.51$, $p < .001$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .77$). Results, summarized in Table 8, evidenced an interaction between HF n.u. and group membership which trended toward significance, F (2.31, 177.68) = 2.29, $p = .10$. Contrasts were inspected but interpreted with caution given the non-significant interaction effect. Results revealed that groups differed the most with regards to HF n.u. between baseline and cognitive challenge readings, as shown in Table 9. An inspection of the interaction graph, shown in Figure 6, revealed that normative AS participants exhibited an increase in HF n.u. during the cognitive challenge from baseline, whereas high AS participants exhibited a decrease in HF n.u. during the cognitive challenge from baseline. Relative to baseline, normative AS and high AS participants both evidenced decreases during the physical challenge. The high AS group evidenced a decrease in HF n.u. during the social task, relative to baseline, whereas the normative AS group evidenced a slight increase.

Table 8

ANOVA Summary Evaluating HF n.u. Across Challenges

	MS	*df*	*F*	*p*	Partial η^2
HF n.u.	231.59	2.31	1.05	0.36	0.01
HF n.u.*AS	1159.74	2.31	2.29	0.10	0.03
Error	220.00	177.68			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Table 9

Summary of Within-Subjects Contrasts for HF n.u.

				MS	*df*	*F*	*p*	Partial η^2
HF n.u	Baseline	vs.	Cognitive	22.79	1	0.10	.33	.03
	Baseline	vs.	Physical	650.84	1	1.30	.25	.02
	Baseline	vs.	Social	85.71	1	4.43	.50	.06
HF n.u. * AS	Baseline	vs.	Cognitive	894.45	1	4.00	.05	.05
	Baseline	vs.	Physical	263.43	1	0.53	.47	.07
	Baseline	vs.	Social	190.75	1	1.03	.31	.01
Error	Baseline	vs.	Cognitive	223.56	77			
	Baseline	vs.	Physical	499.97	77			
	Baseline	vs.	Social	184.58	77			

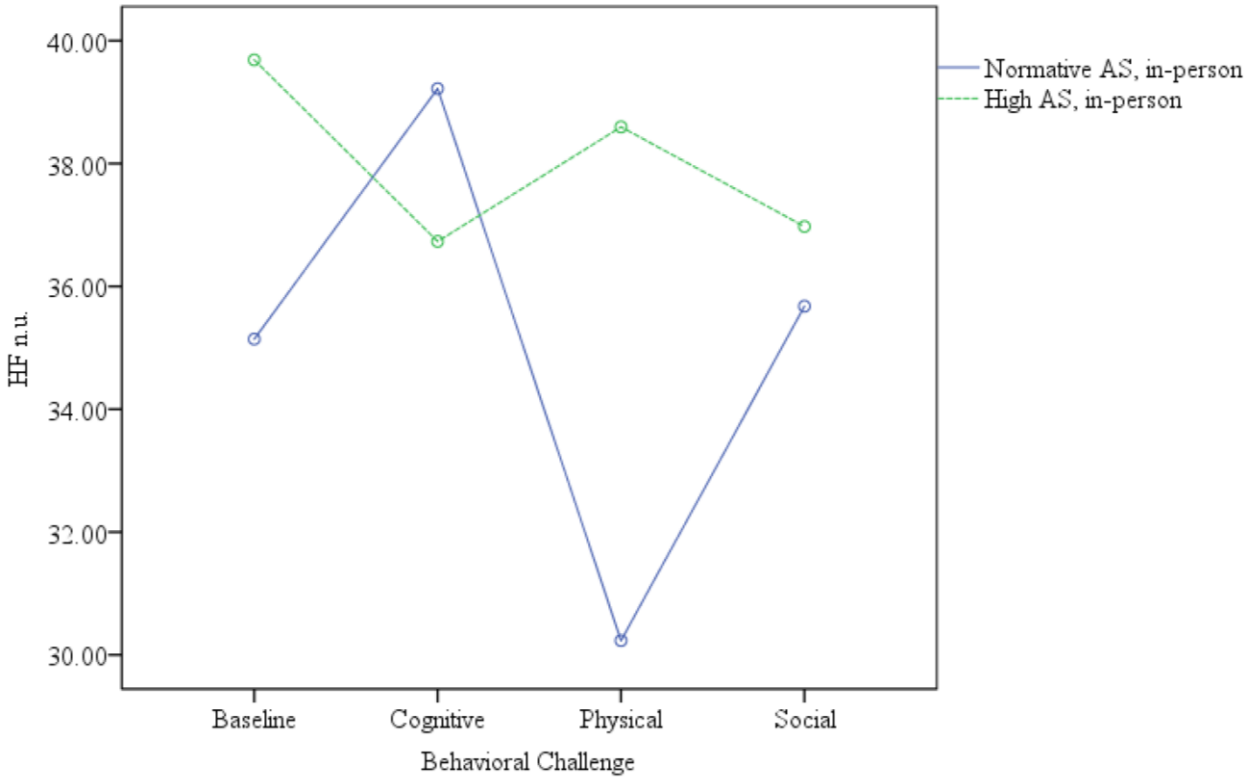

Figure 6. HF-HRV normalized units (HF n.u.) at baseline and during each behavioral challenge for normative and high AS participants.

Exploratory analysis: HF log change. A repeated measures ANOVA, with HF log serving as the within-subjects factor, was performed. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of HF log, $X^2(5) = 21.09$, $p = .001$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .83$). Results, summarized in Table 10, revealed a significant main effect F (2.49, 191.71) = 4.16, $p = .01$ of the repeated-measures factor, and a non-significant interaction between AS group and the within-subjects factor, F (2.49, 191.71) = 2.21, $p = .10$. In order to further explore these associations, simple contrasts were examined. Results are summarized in Table 11. Notably, contrasts revealed that for the main effect of HF log, relative to baseline, significant changes in HF log were evidenced during cognitive and social recordings. In addition, the

results revealed that high and normative AS participants differed most in terms of HF log change between baseline and physical challenges. Inspection of the interaction graph (see Figure 7) revealed that normative participants evidenced a decrease in HF log during the physical task, relative to baseline, whereas high AS participants evidenced a slight increase. Relative to baseline, both groups evidenced decreased HF log during cognitive and social challenges.

Table 10

ANOVA summary evaluating HF Log Across Challenges

Effect	*MS*	*df*	*F*	*p*	Partial η^2
HF log	1.93	2.49	4.16	.01	.05
HF log*AS	1.02	2.50	2.21	.10	.03
Error	0.46	191.71			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Table 11

Summary of Within-Subjects Contrasts for HF Log

				MS	*df*	*F*	*p*	*Partial* η^2
HF log	Baseline	vs.	Cognitive	9.27	1	16.81	.00	.18
	Baseline	vs.	Physical	2.60	1	2.64	.11	.03
	Baseline	vs.	Social	4.04	1	7.93	.01	.09
HF log* AS	Baseline	vs.	Cognitive	1.38	1	2.50	.12	.03
	Baseline	vs.	Physical	4.81	1	4.88	.03	.06
	Baseline	vs.	Social	0.48	1	0.94	.34	.01
Error	Baseline	vs.	Cognitive	0.55	77			
	Baseline	vs.	Physical	0.98	77			
	Baseline	vs.	Social	0.51	77			

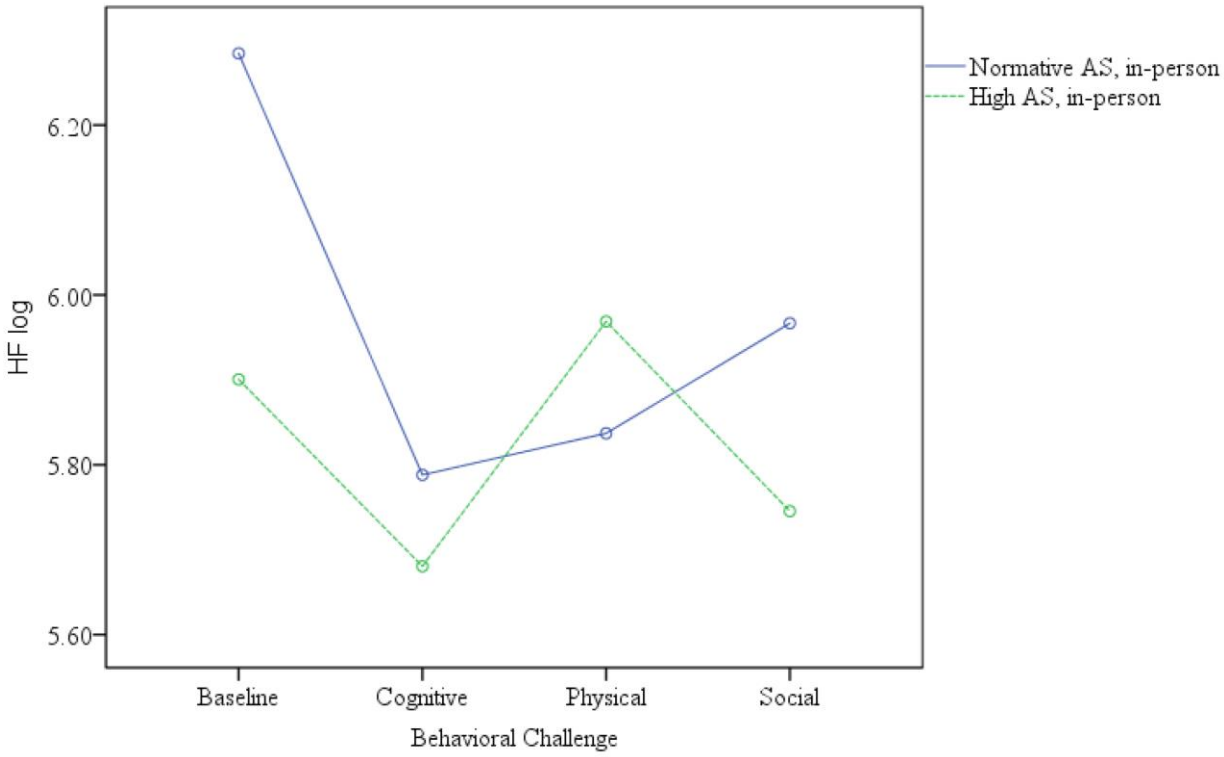

Figure 7. HF-HRV log-transformed absolute power (HF log) at baseline and during each behavioral challenge for normative and high AS participants

Exploratory analysis: HF log change for three AS groups. In order to further explore the significant main effect for HF log change, AS participants were re-categorized into three groups: those who met criteria for normative anxiety (i.e., $M \leq 12$) at both screening and in-person (i.e.," always normative"), those who met criteria for normative AS only at screening (i.e., "sometimes normative"), and those who never met criteria for normative AS (i.e., "never normative"). Descriptive statistics for HRV indices across these three categories are presented in Table 12.

Table 12

HRV Indices at Baseline and During Behavioral Challenges, Across Three AS Categories

	Never Normative			Sometimes Normative			Always Normative		
	N	*M (SD)*	Range	*N*	*M (SD)*	Range	*N*	*M (SD)*	Range
Baseline									
HF log	57	5.90 (1.47)	2.66 - 9.55	23	6.45 (1.14)	2.93 - 9.09	32	6.10 (1.57)	1.53 - 9.07
LF log	57	6.40 (0.94)	3.65 - 8.65	23	6.90 (0.80)	5.23 - 8.18	32	6.80 (1.32)	4.20 - 9.23
HF n.u.	57	39.03 (18.85)	6.01 - 89.85	23	40.66 (18.40)	9.09 - 71.13	32	34.69 (14.79)	6.49 - 67.27
LF n.u	57	60.86 (18.89)	9.95 - 93.96	23	59.25 (18.38)	28.86 - 90.85	32	65.22 (14.80)	32.70 - 93.50
Cognitive									
HF log	55	5.58 (1.30)	2.69 - 8.84	22	5.97 (0.87)	4.15 - 7.33	33	5.68 (1.46)	0.18 - 8.83
LF log	55	6.19 (1.02)	3.09 - 8.13	22	6.42 (0.72)	5.02 - 8.23	33	6.24 (1.21)	3.10 - 9.00
HF n.u.	55	37.07 (19.75)	7.14 - 89.08	22	39.83 (16.31)	12.36 - 75.36	33	38.25 (17.09)	5.09 - 77.45
LF n.u	55	62.76 (19.85)	10.71 - 92.85	22	59.99 (16.25)	24.60 - 87.64	33	61.65 (17.11)	22.50 - 94.89
Physical									
HF log	57	6.07 (1.24)	3.09 - 8.73	23	6.27 (0.78)	4.36 - 7.77	32	5.74 (1.47)	2.42 - 9.13
LF log	57	6.55 (0.86)	4.30 - 8.41	23	6.95 (0.83)	5.25 - 8.22	32	6.68 (0.89)	4.47 - 8.24
HF n.u.	57	40.16 (20.31)	3.76 - 87.82	23	35.58 (17.54)	12.99 - 71.83	32	31.14 (21.61)	8.39 - 89.63
LF n.u	57	59.79 (20.33)	12.16 - 96.23	23	64.36 (17.56)	28.17 - 87.00	32	68.82 (21.62)	10.32 - 91.60
Social									
HF log	57	5.85 (1.35)	3.24 - 9.16	21	6.19 (1.37)	2.55 - 8.46	31	5.85 (1.51)	1.02 - 8.72
LF log	57	6.39 (0.88)	4.80 - 8.25	21	6.60 (1.19)	3.02 - 8.88	31	6.55 (1.13)	4.06 - 8.63
HF n.u.	57	38.47 (19.26)	7.55 - 88.63	21	41.56 (17.09)	7.39 - 71.98	31	35.12 (15.87)	4.59 - 71.67
LF n.u	57	61.45 (19.31)	11.26 - 92.44	21	58.31 (17.09)	27.98 - 92.53	31	64.79 (15.86)	28.26 - 95.39

Note: HF log and LF log refer to log-transformed values of high frequency and low frequency absolute power; HF n.u. and LF n.u. refer to high frequency and low frequency normalized units

An exploratory repeated measures ANOVA was fit, whereby three categories of AS served as the between-subjects factor and HF log as the within-subjects factor. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of HF log, $X^2(5) = 27.28$, $p = .000$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .82$). Findings, summarized in Table 13, revealed a significant main effect, F (2.47, 234.89) = 5.48, $p = .002$, indicating that HF log differed significantly between tasks. Contrasts revealed significant decreases in HF log, relative to baseline, during cognitive, $F(1,95) = 25.06$, $p = .00$, and social, $F(1,95) = 6.45$, $p = .01$, challenges. Since the interaction effect was not significant, simple contrasts were not examined to determine where groups differences may have emerged.

Table 13

ANOVA Summary Evaluating HF Log Across Challenges in Three AS Categories

Effect	*MS*	*df*	*F*	*p*	Partial η^2
HF log	2.72	2.47	5.48	.002	.06
HF log*AS	0.70	4.95	1.40	.224	.03
Error	0.50	234.89			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Inspection of the interaction graph for other non-significant trends revealed that "sometimes normative AS" and "always normative AS" participants evidenced decreased HF log during all challenges, relative to baseline, as shown in Figure 8. "Never normative" AS participants evidenced decreased HF log during cognitive and social tasks, and increased HF log during the physical task, relative to baseline.

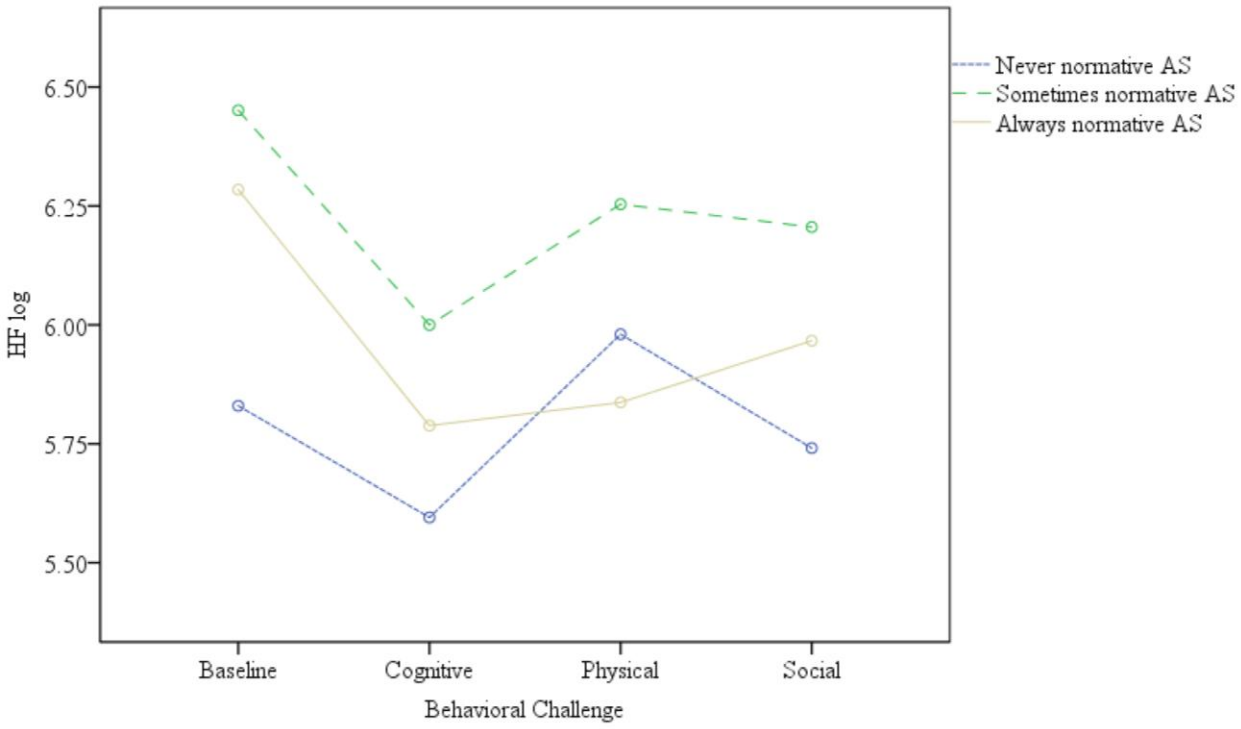

Figure 8. HF-HRV log-transformed absolute power (HF log) at baseline and during each behavioral challenge for "never normative," "sometimes normative," and "always normative" AS participants.

Secondary Hypothesis: Group Differences in Subjective Distress Change

Planned analysis: SUDS differences between two AS groups. A repeated measures ANOVA, with AS group serving as the between-subjects factor and SUDS serving as the within-subjects factor, was utilized in order to explore the secondary hypothesis, whereby high AS participants were predicted to exhibit significantly greater SUDS increases, relative to baseline, than normative AS participants. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of SUDS, $X^2(5) = 16.81$, $p = .005$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .90$). Results, as summarized in Table 14, revealed a significant main effect, F (2.71, 186.16) = 44.67, $p = .00$ as well as an interaction effect, F (2.71, 186.16) = 8.35, $p = .00$. Contrasts, summarized in Table 15, revealed significant differences between normative and high AS participant groups during all

behavioral challenges, relative to baseline. Inspection of the interaction graph, shown in Figure 9, revealed that SUDS increased for both groups during each challenge, relative to baseline. Results from an independent samples t-test indicated that high AS participants reported significantly higher SUDS at baseline than normative AS participants $t(94) = -4.94$, $p = .00$.

Table 14

ANOVA Summary Evaluating SUDS Across Challenges

Effect	*MS*	*df*	*F*	*p*	Partial η^2
SUDS	8314.88	2.71	44.67	0.00	0.32
SUDS*AS	1554.84	2.71	8.35	0.00	0.08
Error	0.50	186.16			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Table 15

Summary of Within-Subjects Contrasts for SUDS

				MS	*df*	*F*	*p*	*Partial* η^2
SUDS	Baseline	vs.	Cognitive	39691.35	1	128.08	.00	0.58
	Baseline	vs.	Physical	15597.05	1	47.99	.00	0.34
	Baseline	vs.	Social	26641.64	1	123.39	.00	0.57
SUDS* AS	Baseline	vs.	Cognitive	7403.85	1	23.89	.00	0.20
	Baseline	vs.	Physical	2184.55	1	6.72	.01	0.07
	Baseline	vs.	Social	4935.39	1	22.86	.00	0.20
Error	Baseline	vs.	Cognitive	309.908	94			
	Baseline	vs.	Physical	324.99	94			
	Baseline	vs.	Social	215.91	94			

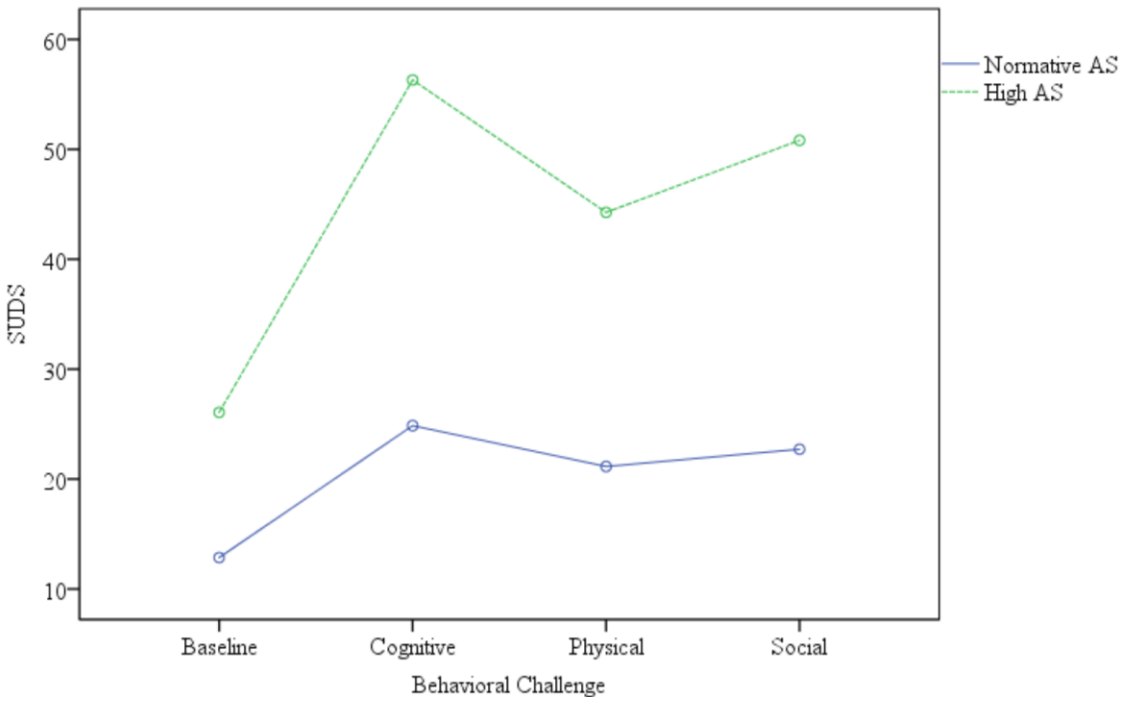

Figure 9. Subjective units of distress (SUDS) at baseline and during each behavioral challenge for normative and high AS participants.

Exploratory analysis: SUDS change between three AS groups. In order to further explore significant main and interaction effects, AS as a three-category variable was again considered. Descriptive statistics for SUDS scores in three categories are presented in Table 16 below.

Table 16

SUDS at Baseline and Post-Behavioral Challenges for Three AS Categories

	Never normative (n = 60)		Sometimes normative (n = 25)		Always normative (n = 35)	
	M (SD)	Range	*M (SD)*	Range	*M (SD)*	Range
Baseline	26.33 (14.12)	0 - 60	20.00 (14.14)	0 - 60	12.86 (8.94)	0 - 30
Post-cognitive	54.67 (19.87)	10 - 90	52.40 (17.80)	10 - 80	24.86 (16.52)	0 - 70
Post-physical	43.50 (23.28)	0 - 90	33.60 (19.34)	0 - 70	21.14 (16.76)	0 - 70
Post-social	49.83 (20.69)	0 - 90	41.00 (20.51)	0 - 80	22.71 (14.16)	0 - 60

An exploratory repeated measures ANOVA was fit, with AS group (i.e., "always normative," "sometimes normative," or "never normative) serving as the between-subjects factor and SUDS serving as the within-subjects factor. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of SUDS, $X^2(5) = 12.77$, $p = .000$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .94$). Findings, summarized in Table 17, revealed a significant main effect, F (2.80, 328.06) = 67.15, p = .00, as well as a significant interaction effect, F (5.61, 328.06) = 4.79, p = .00. Contrasts for the main effect revealed significant increases in SUDS following each challenge, relative to baseline: (cognitive, $F(1,117) = 211.40$, p = .00; physical, $F(1,117) = 55.91$, p = .00; social, $F(1,117) = 140.15$, p = .00. Contrasts for the interaction effect revealed significant differences between those in the "never normative" and "always normative" group categories, whereby, relative to baseline, SUDS were significantly higher following cognitive, $F(1,117) = 20.09$, p = .00, Partial η^2= 0.15, physical, $F(1,117) = 5.45$, p = .02, Partial η^2=0.04, and social, $F(1,117)$ = 16.63, p = .00, Partial η^2= 0.12, challenges. Additionally, significant differences emerged between those in the "sometimes normative" and "always normative" group categories, whereby, relative to baseline, SUDS were significantly higher following cognitive, $F(1,117) = 20.70$, p = .00, Partial η^2= 0.15, and social, $F(1,117) = 7.32$, p = .01, Partial η^2= 0.06, challenges. Although "sometimes normative" and "always normative" groups both evidenced increased SUDS post-physical challenge, relative to baseline, the difference was not statistically significant. Inspection of the interaction graph, shown in Figure 10, revealed that relative to baseline, SUDS increased at each behavioral challenge for all groups.

Table 17

ANOVA Summary Evaluating SUDS Across Challenges in Three AS Categories

Effect	*MS*	*df*	*F*	*p*	Partial η^2
SUDS	12,004.23	2.80	67.15	.00	0.37
SUDS*AS	856.14	5.61	4.79	.00	0.08
Error	178.78	328.06			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

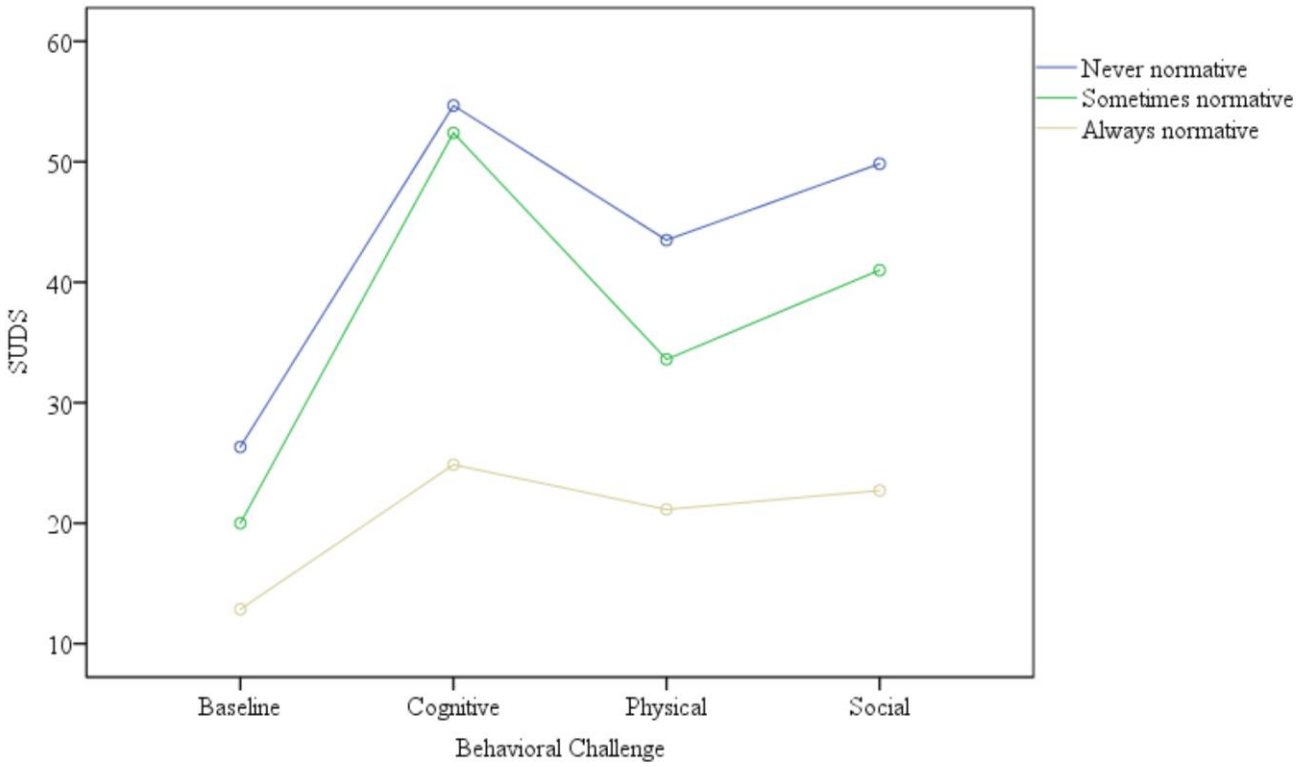

Figure 10. Subjective units of distress (SUDS) at baseline and during each behavioral challenge for "never normative," "sometimes normative," and "always normative" AS participants.

Correlational Analyses

Correlations between ASI-3 total and subscale scores, HRV, SUDS and measures of depression and anxiety were examined for patterns. A number of study psychosocial variables

were significantly correlated at the $p \leq .001$ level, as shown in Table 18. Contrary to expectations, the ASI-3 (at screening and in person) only evidenced a significant correlation with LF-HRV; the relationship was negative, in the opposite direction than would be expected. As would be expected, measures of HF-HRV were significantly correlated ($r = .67$) at the $\leq .001$ level. Measures of LF-HRV, however, were not. A significant negative relationship between HF-HRV and the PROMIS depression measure emerged ($r = 25$, $p < .01$), yielding a small-medium effect in the opposite direction than expected. Participant-reported SUDS at baseline were significantly correlated with PROMIS measures of anxiety ($r = .43$) and depression ($r = .38$), demonstrating a medium-large effect.

Table 18

Correlation Matrix of Screening and Baseline Measures

	ASI-3 Screening Total	ASI-3 Screening Cognitive Subscale	ASI-3 Screening Physical Subscale	ASI-3 Screening Social Subscale	ASI-3 In-Person Total	ASI-3 In-person Cognitive Subscale	ASI-3 In-person Physical Subscale	ASI-3 In-person Social Subscale	PROMIS-Anxiety	PROMIS-Depression	HF-HRV n.u.	HF-HRV log	LF-HRV n.u.	LF-HRV log	SUDS
ASI-3 Screening	1.00														
ASI-3 Screening Cognitive Subscale	0.91 **	1.00													
ASI-3 Screening Physical Subscale	0.89 **	0.77 **	1.00												
ASI-3 Screening Social Subscale	0.87 **	0.67 **	0.64 **	1.00											
ASI-3 In-Person Total	0.86 **	0.78 **	0.72 **	0.79 **	1.00										
In-person Cognitive Subscale	0.75 **	0.81 **	0.58 **	0.60 **	0.88 **	1.00									
In-person Physical Subscale	0.77 **	0.66 **	0.82 **	0.60 **	0.85 **	0.67 **	1.00								
In-person Social Subscale	0.72 **	0.56 **	0.50 **	0.84 **	0.86 **	0.61 **	0.57 **	1.00							
PROMIS-Anxiety	0.69 **	0.65 **	0.58 **	0.62 **	0.76 **	0.69 **	0.62 **	0.65 **	1.00						
PROMIS-Depression	0.52 **	0.52 **	0.40 **	0.46 **	0.57 **	0.59 **	0.39 **	0.48 **	0.75 **	1.00					
HF-HRV n.u.	0.00	-0.05	-0.02	0.06	0.09	0.06	0.07	0.11	0.13	0.25 **	1.00				
HF-HRV log	-0.14	-0.14	-0.13	-0.11	-0.10	-0.10	-0.05	-0.11	-0.02	0.07	0.67 **	1.00			
LF-HRV n.u.	0.00	0.05	0.02	-0.06	-0.09	-0.06	-0.07	-0.11	-0.13	-0.25 **	-1.00 **	-0.67 **	1.00		
LF-HRV log	-0.20 *	-0.16	-0.17	-0.20 *	-0.21 *	-0.18	-0.13	-0.22 *	-0.13	-0.11	0.12	0.81 **	-0.12	1.00	
SUDS	0.42 **	0.42 **	0.34 **	0.37 **	0.51 **	0.42 **	0.43 **	0.46 **	0.43 **	0.38 **	0.04	-0.06	-0.04	-0.11	1.00

Note: **$p \leq .01$; *$p \leq .05$, two-tailed; n.u. = normalized units; log = log transformed absolute power

Exploratory Question: Do Groups Differ in HF-HRV Recorded at Baseline and During Each Behavioral Challenge, After Controlling for Variance Due to Age?

MANCOVA with two AS groups as the independent variable. In exploring sample demographics, a significant difference in age had emerged between high and normative AS groups. Evidence suggests that age may influence HRV (e.g., Anderson, Jönsson, & Sandsten, 2018; Antelmi et al., 2004; Voss, Schroeder, Heitmann, Peters, & Perz, 2015), and therefore, a MANCOVA was fit to further investigate Hypotheses 1-4: whether groups differed in HF log at baseline and behavioral challenges after controlling for variance due to age. AS group served as the independent variable; HF log recorded during baseline and each behavioral challenge served as dependent variables; age was added as a covariate. Before doing so, data scatterplots were visually inspected to ensure that the assumption of linearity was not violated. There was some evidence of nonlinearity, likely due to limited participants of advanced age. Due to limited degrees of freedom, and in order to keep the model parsimonious, the effect was treated as linear. A significant omnibus effect for AS was observed, Pillai's Trace = 0.15, $F(4, 62) = 2.71$, $p = .04$, partial $\eta^2 = 0.15$, indicating that groups differed in HF-HRV (i.e., HF log). After determining that the assumption of homogeneity of variance had not been violated for each dependent variable via Levene's test results, Baseline HF log: $F(1,66) = 0.22$, $p = .64$; Cognitive challenge HF log: $F(1,66) = 0.83$, $p = .05$; Physical challenge HF log: $F(1,66) = 0.04$, $p = .84$, Social challenge HF log: $F(1,66) = 0.13$, $p = .72$, univariate analyses were reviewed to examine between-subjects effects. A Bonferroni correction was applied to results in order to control for Type 1 error. Findings, summarized in Table 19, revealed that after controlling for variance due to age, at baseline and during the social challenge, normative AS participants exhibited significantly higher HF log than high AS participants.

Table 19

Between-Subjects Effects for HF Log After Controlling for Variance Due to Age

Dependent Variable	*F*	*p*	df	df error	Partial η^2	AS Group	*M(SD)*
Baseline HF log (1.61)	6.32	0.01	1	65	0.09	Normative	6.19
						High	5.75 (1.52)
Cognitive HF log	2.67	0.11	1	65	0.04	Normative	5.68 (1.66)
						High	5.59 (1.31)
Physical HF log (1.39)	0.17	0.68	1	65	0.00	Normative	5.73
						High	5.94 (1.29)
Social HF log	5.37	0.02	1	65	0.08	Normative	5.86 (1.65)
						High	5.70 (1.44)

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01−0.06; medium, 0.06−0.13; large, 0.13 and above.

MANCOVA with three AS groups as the independent variable. In order to further explore hypotheses 1-4 through evaluating differences in HF-HRV between groups after controlling for age, another MANCOVA was fit. Three categories of AS (i.e., "always normative," "sometimes normative," "never normative") served as the independent variable, HF log served as the dependent variable, and age was again added into the model as a covariate. Data scatterplots were again visually inspected to ensure that the assumptions of linearity and homoscedastistiy were not violated. Again, there was evidence of nonlinearity. However, due to limited degrees of freedom, and in order to keep the model parsimonious, the effect was treated as linear. A non-significant omnibus effect for AS was observed, Pillai's Trace = 0.12, $F(6, 164)$

= 1.78, p = .11, partial η^2= 0.06, indicating that groups did not significantly differ in HF-HRV (i.e., HF log), after controlling for age.

Exploratory Question: Do Groups Exhibit Differences in HF-HRV Recorded During Challenges, Relative to Baseline, After Controlling for Variance Due to Age?

Repeated measures ANCOVA, with two AS groups as the between-subjects variable. In order to further evaluate Hypotheses 5-7 (i.e., group differences in HF-HRV change between baseline and behavioral challenges), a ANCOVA was fit. Age was added as a covariate, enabling group differences to be explored after controlling for age-related variance. Log-transformed HF-HRV absolute power (i.e., HF log) was selected for inclusion in the analysis, rather than normalized units, as prior findings with HF log yielded more robust results. Before running the analysis, data scatterplots were visually inspected to ensure that the assumptions of linearity were not violated. There was some evidence of non-linearity, however, given limited degrees of freedom, and in order to keep the model parsimonious, the effect was treated as linear. Mauchley's test results were evaluated and indicated that the assumption of sphericity had not been violated, $X^2(5) = 10.14$, p = .07, and thus degrees of freedom were not corrected. ANCOVA results, summarized in Table 20, revealed a significant interaction effect, ($F(3,195) = 4.27$, p = .01, indicating that after controlling for age, significant differences between group HF log change (i.e., between baseline and behavioral challenges) emerged. Contrasts, summarized in Table 21, revealed that groups significantly differed in the magnitude of HF log change: normative AS participants exhibited a decrease in HF log during the physical challenge, relative to baseline, and high AS participants exhibited an increase in HF log during the physical challenge, relative to baseline. Additionally, the interaction plot, shown in Figure

11 was inspected for non-significant trends. This revealed that high AS participants exhibited decreased HF log on cognitive and social challenges, relative to baseline. Normative AS participants exhibited decreased HF log on all challenges, relative to baseline.

Table 20

ANCOVA Summary Evaluating HF Log Across Challenges

	MS	*df*	*F*	*p*	Partial η^2
HF log	0.87	3	2.36	0.07	0.04
HF log*age	0.85	3	2.33	0.08	0.04
HF log.*AS	1.57	3	4.27	0.01	0.06
Error	0.37	195			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Table 21.

Summary of ANCOVA Within-Subjects Contrasts for HF Log

				MS	*Df*	*F*	*p*	Partial η^2
HF log	Baseline	vs.	Cognitive	1.72	1	3.05	0.09	0.05
	Baseline	vs.	Physical	4.09	1	4.71	0.03	0.07
	Baseline	vs.	Social	0.09	1	0.17	0.69	0.00
HF log*age	Baseline	vs.	Cognitive	0.20	1	0.36	0.55	0.01
	Baseline	vs.	Physical	3.12	1	3.60	0.06	0.05
	Baseline	vs.	Social	0.11	1	0.21	0.65	0.00
HF log*AS	Baseline	vs.	Cognitive	1.90	1	3.35	0.07	0.05
	Baseline	vs.	Physical	8.43	1	9.72	0.00	0.13
	Baseline	vs.	Social	0.40	1	0.72	0.40	0.01
Error	Baseline	vs.	Cognitive	0.57	65			
	Baseline	vs.	Physical	0.87	65			
	Baseline	vs.	Social	0.55	65			

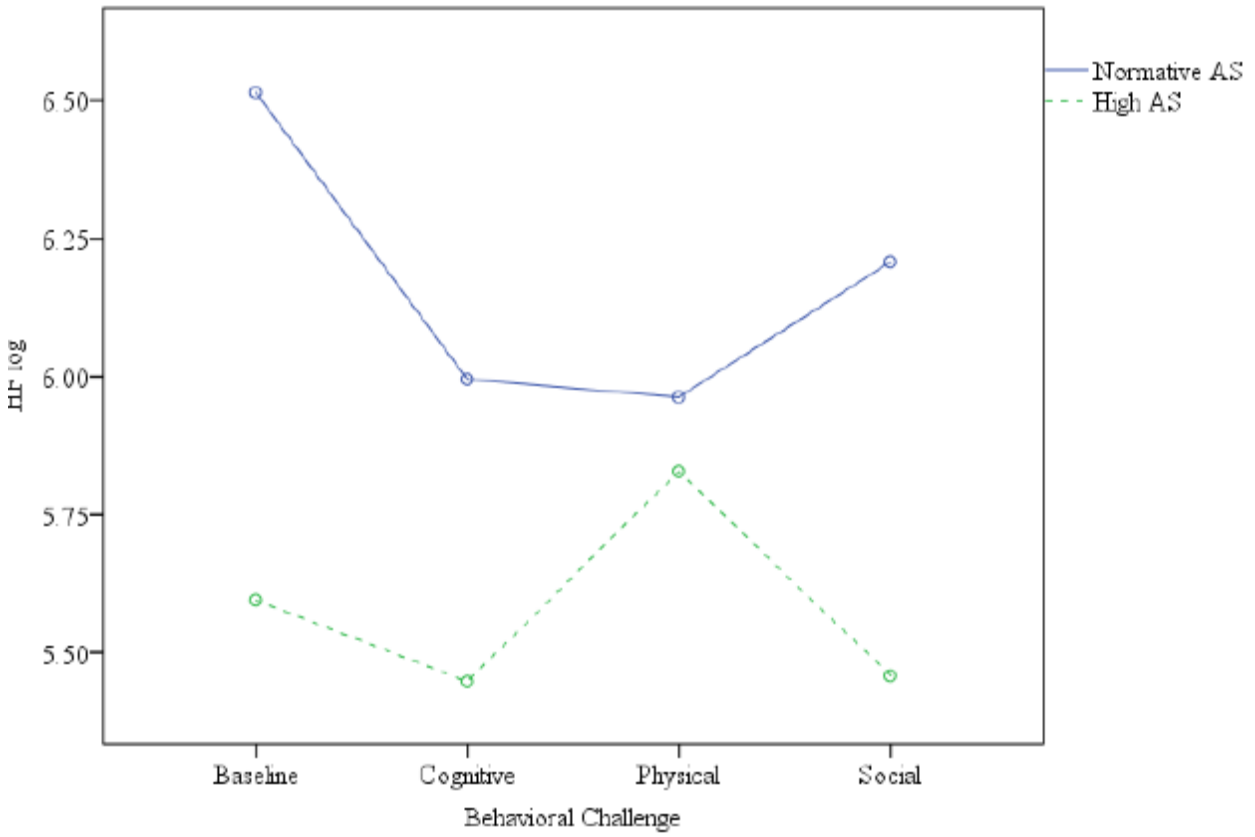

Figure 11. HF-HRV log-transformed absolute power (HF log) after controlling for age-related variance at baseline and during each behavioral challenge for normative and high AS participants

Exploratory Question: Do Groups Differ in LF-HRV Recorded During Each Behavioral Challenge?

MANOVA with two AS groups as the independent variable. In order to investigate whether high and normative participants exhibited differences in LF-HRV during behavioral challenges, an exploratory MANOVA was fit. AS group served as the independent variable; log-transformed values of absolute power (i.e., LF log) recorded during each behavioral challenge (i.e., cognitive, physical, social) served as the dependent variables. A non-significant omnibus effect was observed, Pillai's Trace = 0.04, $F(3,78) = 0.95$, $p = .42$, partial $\eta^2 = 0.04$, indicating that differences in LF log between groups were not significant.

Exploratory Question: Do Groups Differ in LF-HRV Recorded at Baseline and During Each Behavioral Challenge, After Controlling for Variance Due to Age?

MANCOVA with two AS groups as the independent variable. A MANCOVA was performed using log-transformed values of absolute power (i.e., LF log) to investigate whether groups differed in LF-HRV at baseline and during behavioral challenges, after controlling for variance due to age. Before doing so, data scatterplots were visually inspected to ensure that the assumption of linearity was not violated. As with prior analyses, there was some evidence of nonlinearity, however, in order to keep the model parsimonious, it was decided to treat the effect as linear. A significant omnibus effect for AS was observed, Pillai's Trace = 0.22, $F(4, 62) = 4.27$, $p = .00$, partial $\eta^2 = 0.22$, indicating that groups significantly differed in LF log. After determining that the assumption of homogeneity of variance had not been violated for each dependent variable via Levene's test results, Baseline LF log: $F(1,66) = 3.67$, $p = .06$; Cognitive challenge LF log: $F(1,66) = 0.22$, $p = .88$; Physical challenge LF log: $F(1,66) = 0.01$, $p = .94$, Social challenge LF log: $F(1,66) = 0.65$, $p = .43$, univariate analyses were reviewed to examine between-subjects effects. A Bonferroni correction was applied in order to control for Type 1 error. Findings, summarized in Table 22, revealed that after controlling for variance due to age, LF log was significantly higher for normative AS participants at baseline, and during physical and social challenges, than high AS participants.

Table 22.

Between-Subjects Effects for LF Log After Controlling for Variance Due to Age

Dependent Variable	*F*	*p*	df	df error	Partial η^2	AS Group	*M(SD)*
Baseline LF log	13.80	0.00	1	65	0.18	Normative	6.91 (1.30)
						High	6.26 (0.91)
Cognitive LF log	1.09	0.30	1	65	0.02	Normative	6.25 (1.30)
						High	6.26 (1.02)
Physical LF log	4.99	0.03	1	65	0.07	Normative	6.77 (0.86)
						High	6.44 (0.86)
Social LF log	7.02	0.01	1	65	0.10	Normative	6.61 (1.21)
						High	6.40 (0.95)

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

MANCOVA with three AS groups as the independent variable. In order to further explore differences in LF-HRV between groups after controlling for age, another MANCOVA was fit. Three categories of AS (i.e., "always normative," "sometime normative") served as the independent variable, LF log served as the dependent variable, and age was again added into the model as a covariate. A non-significant omnibus effect for AS was observed, Pillai's Trace = 0.11, $F(6, 164) = 1.64$, $p = .14$, partial $\eta^2 = 0.06$, indicating that AS groups did not significantly differ in LF-HRV (i.e., LF log), at any time point, after controlling for age.

Exploratory Question: Do Groups Exhibit Differences in LF-HRV Recorded During Challenges, Relative to Baseline?

Analyses addressing Hypotheses 5-7 focused on group differences in HF-HRV. In order to further explore whether groups differed in LF-HRV change from baseline, a set of exploratory analyses were undertaken using LF log as an outcome variable.

Repeated measures ANOVA, with two AS groups as the between-subjects variable. A repeated measures ANOVA was fit; AS group served as the between-subjects variable, and LF log as the within-subjects variable. Mauchley's test indicated that the assumption of sphericity had not been violated for the main effect of LF log. Results, summarized in Table 23, revealed a significant main effect F (3, 231) = 5.71, p = .001 for LF log, indicating that differences in LF log scores emerged across behavioral challenges. Additionally, results revealed a significant interaction between AS in-person group and LF log, F (3, 231) = 2.74, $p < .05$. Contrast results, summarized in Table 24, revealed that with regards to the main effect, significant differences in LF log, relative to baseline, occurred during cognitive and social tasks. Analysis of interaction effects revealed that normative and high AS participants differed significantly in terms of LF log change between baseline and cognitive tasks. Inspection of the interaction graph (see Figure 12) clarified that normative and high AS participants both evidenced a decrease in LF log during the cognitive challenge, relative to baseline, although the magnitude of this difference was much larger for normative AS participants. Further inspection of plots for information about non-significant trends revealed that normative AS participants also evidenced decreased LF log during physical and social challenges, relative to baseline. High AS participants evidenced an increase in LF log during the physical challenge but virtually no change during the social task, relative to baseline.

Table 23.

ANOVA Summary for AS In-Person Groups, Evaluating LF Log Across Challenges

Effect	*MS*	*df*	*F*	*p*	Partial η^2

LF log	2.18	3	5.71	.001	.07
LF log*AS	1.05	3	2.74	.04	.03
Error	88.08	231			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

Table 24.

Summary of Within-Subjects Contrasts for LF Log

				MS	*df*	*F*	*p*	*Partial* η^2
LF log	Baseline	vs.	Cognitive	10.00	1	15.03	.00	.16
	Baseline	vs.	Physical	0.02	1	0.02	.88	.00
	Baseline	vs.	Social	2.23	1	3.94	.05	.05
LF log* AS	Baseline	vs.	Cognitive	6.25	1	9.40	.00	.11
	Baseline	vs.	Physical	1.37	1	1.86	.18	.02
	Baseline	vs.	Social	1.68	1	2.97	.09	.04
Error	Baseline	vs.	Cognitive	0.67	77			
	Baseline	vs.	Physical	0.73	77			
	Baseline	vs.	Social	0.57	77			

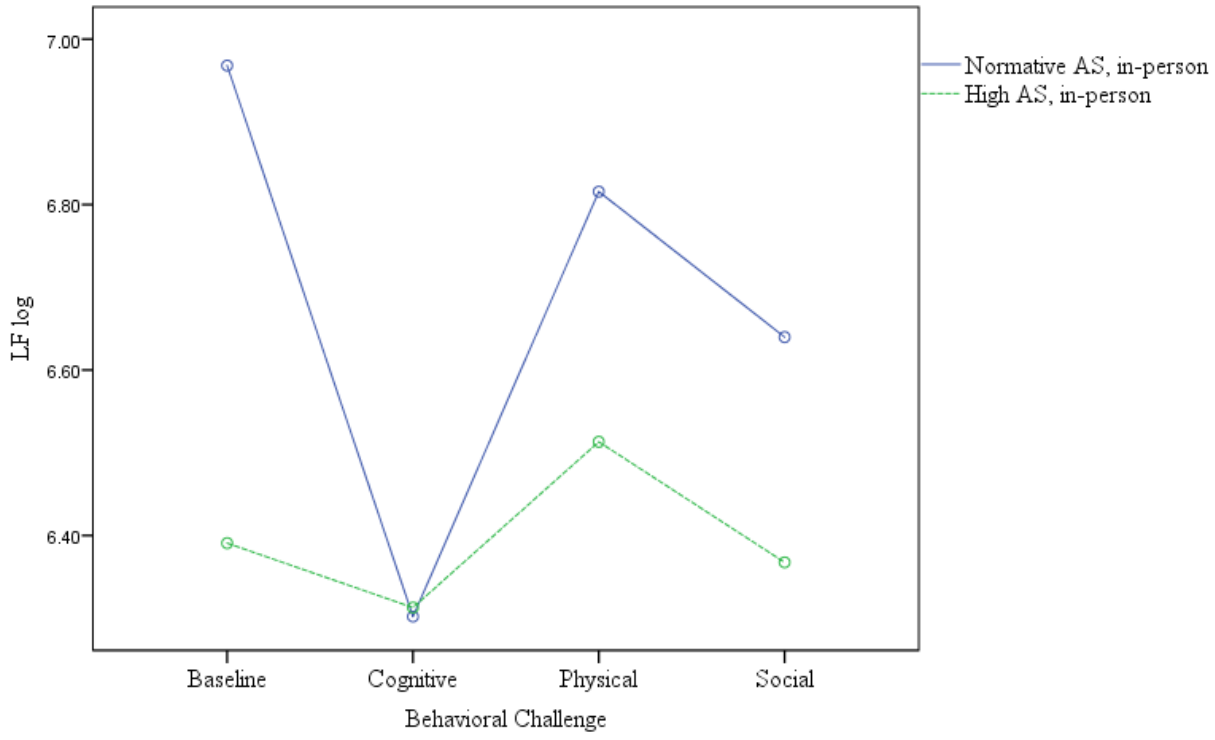

Figure 12. LF-HRV log-transformed absolute power (LF log) at baseline and during each behavioral challenge for normative and high AS participants.

Repeated measures ANOVA, with three AS groups as the between-subjects variable.

In order to further explore differences, a repeated measures ANOVA was fit to evaluate differences in LF log during challenges across three categories of AS: "always normative," "sometimes normative," or "never normative." AS group served as the between-subjects factor and LF log served as the within-subjects factor. Mauchley's test indicated that the assumption of sphericity had been violated for the main effect of LF log, $X^2(5) = 17.38$, $p = .004$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .89$). Findings, summarized in Table 25, revealed a significant main effect for LF log, F (2.66, 252.91) = 8.62, $p = .000$. Contrasts revealed that, relative to baseline, LF log was significantly higher

during baseline and social tasks. Since the interaction effect was not significant, contrasts evaluating differences between groups were not reviewed. The interaction plot was inspected for non-significant trends. As shown in Figure 13, "Always normative" AS participants evidenced decreased LF log across tasks, relative to baseline. "Sometimes normative" and "never normative" AS participants evidenced decreased LF log during cognitive and social challenges, relative to baseline, and increased LF log during the physical challenge.

Table 25

ANOVA Summary Evaluating LF Log Across Challenges in Three AS Categories

Effect	*MS*	*df*	*F*	*p*	Partial η^2
LF log	3.81	2.66	8.62	.00	.08
LF log*AS	0.49	5.32	1.11	.35	.02
Error	0.44	252.91			

Note. Partial η^2 effect size qualitative labels according to Cohen (1988): small, 0.01‑0.06; medium, 0.06‑0.13; large, 0.13 and above.

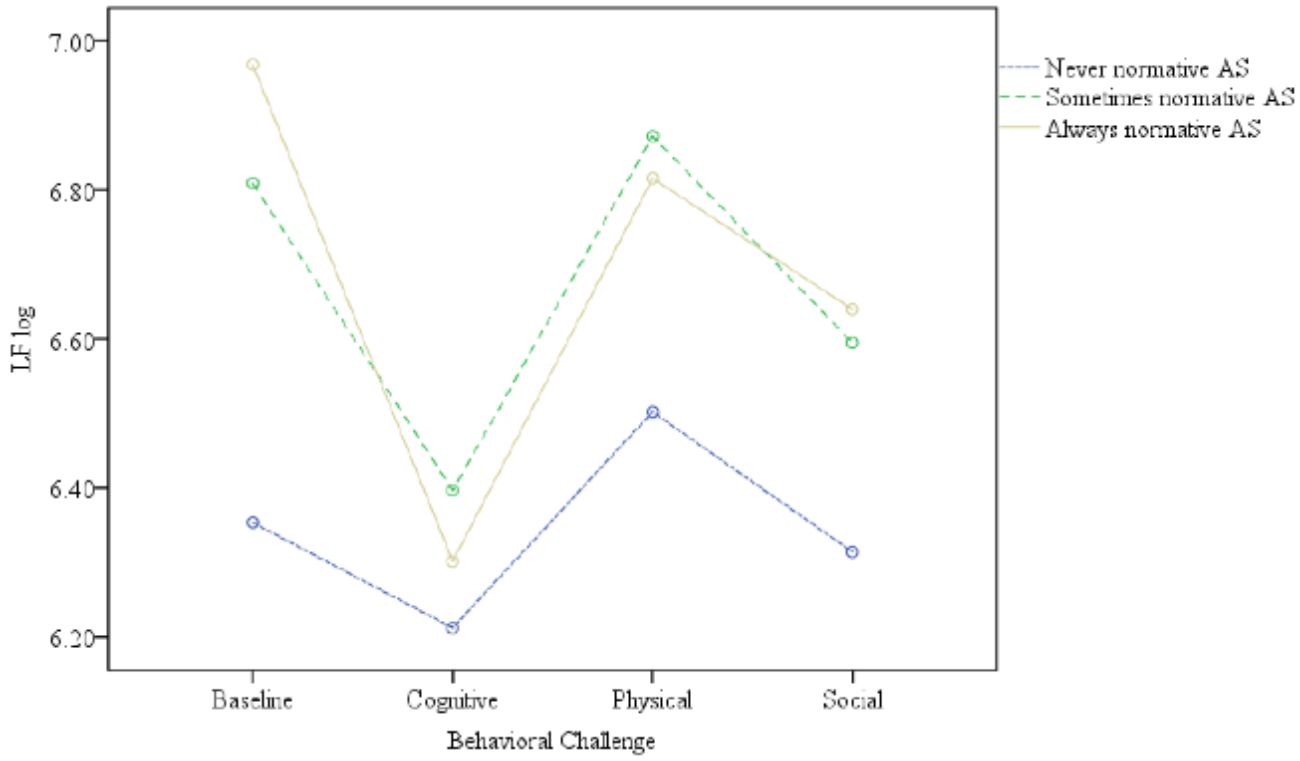

Figure 13. LF-HRV log-transformed absolute power (LF log) at baseline and during each behavioral challenge for three categories of AS participants

Exploratory Question: Do Groups Exhibit Differences in LF-HRV Recorded During Challenges, Relative to Baseline, After Controlling for Variance Due to Age?

An exploratory ANCOVA was then performed in order to explore whether groups differed in magnitude of change, after controlling for age-related variance.

Repeated measures ANCOVA, with two AS groups as the between-subjects variable. In order to investigate whether the magnitude of change between baseline and challenge LF-HRV differed between groups after controlling for age, an exploratory repeated measures ANCOVA was performed. AS group served as the between-subjects variable, LF log served as the within-subjects variable, and age was added as a covariate. Data scatterplots were inspected. Like with HF log, there was some evidence of non-linearity; however, given limited

degrees of freedom, and in order to keep the model parsimonious, the effect was treated as linear. Mauchley's test indicated that the assumption of sphericity had been violated $X^2(5) = 12.72$, $p = .03$. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .88$). ANCOVA results were non-significant, although the interaction effect for group and LF log trended toward significance, F (2.64, 171.50) = 2.68, $p = .06$. Thus, after controlling for age, the significant main effect for LF Log and significant interaction effect for LF log and AS group became non-significant. Inspection of the interaction plot for non-significant trends revealed that normative AS participants exhibited decreased LF log during behavioral challenges, relative to baseline. High AS participants exhibited an increase in LF log during physical and social challenges, relative to baseline (see Figure 14).

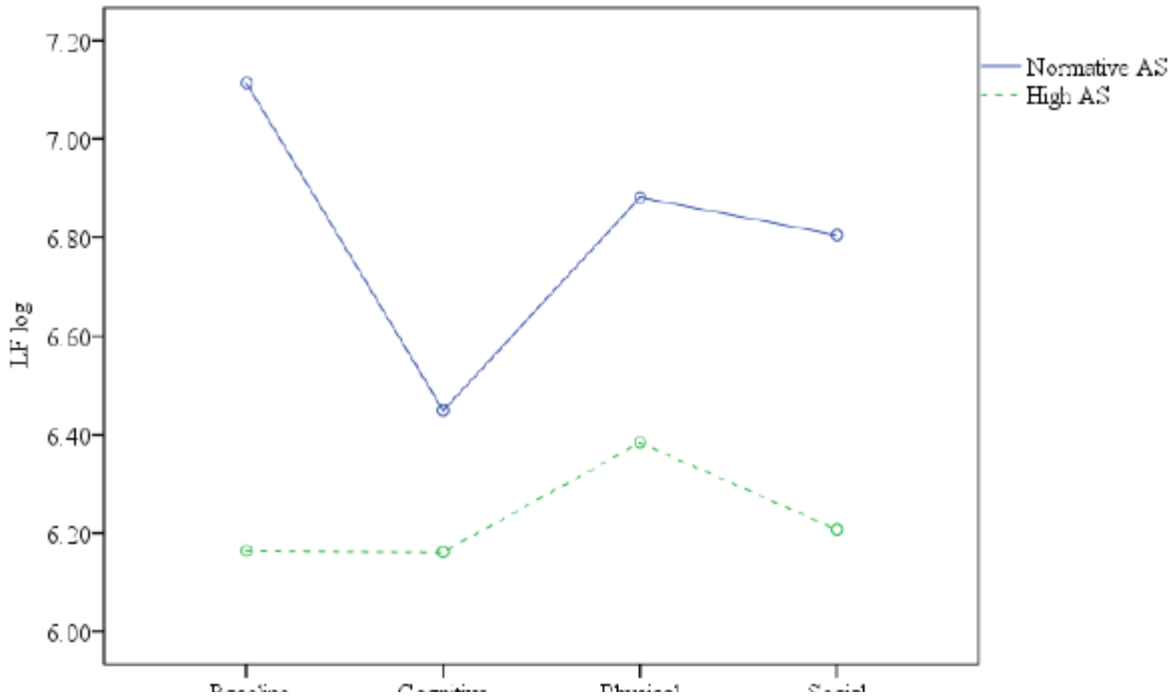

Figure 14. LF-HRV log-transformed absolute power (LF log) at baseline and during each behavioral challenge for normative and high AS participants, after controlling for age-related variance.

Exploratory Question: Subscale Differences

Finally, a series of analyses were undertaken in order to explore whether participants with ASI-3 subscale elevations responded differently to behavioral challenges as compared with participants with normative subscale scores. As previously noted, few participants were "purely" elevated, scoring high on just one scale. Thus, for this series of analyses, participants with an elevation on a subscale were characterized as "high," regardless of whether they were (or were not) also high on other subscales. Descriptive statistics for SUDS scores, categorized for participants "high" and "normative" on ASI-3 subscales, are presented in Table 26.

Table 26

Descriptive Statistics for SUDS, by Subscale Category

	High cognitive subscale		Normative cognitive subscale	
	N	*M (SE)*	*N*	*M (SE)*
Cognitive SUDS	57	56.93 (2.58)	39	29.23 (2.92)
	High physical subscale		Normative physical subscale	
	N	*M (SE)*	*N*	*M (SE)*
Physical SUDS	39	48.46 (3.84)	54	26.85 (2.53)
	High cognitive subscale		Normative cognitive subscale	
	N	*M (SE)*	*N*	*M (SE)*
Social SUDS	60	51.50 (2.62)	25	21.80 (3.33)

Independent samples t-tests were utilized to explore differences between high and normative subscale groups, by "matched" behavioral challenge. Results indicated participants who scored high on the cognitive subscale in person reported significantly higher SUDS following the cognitive challenge (M = 56.93, SE = 2.58) than participants scoring normatively on the cognitive subscale (M = 29.23, SE = 2.92), $t(94) = 7.02$, $p = .000$. Participants who scored

high on the physical subscale reported significantly higher SUDS (M = 48.46, SE = 3.84) than participants who scored in the normative range (M = 26.85, SE = 2.53), $t(91) = 4.89$, $p = .000$. Participants who scored high on the social subscale also reported significantly higher SUDS (M = 51.50, SE = 2.62) than participants who scored in the normative range (M = 21.80, SE = 3.33), $t(83) = 6.46$, $p = .000$.

Discussion

Hypothesis 1: High AS Individuals Will Demonstrate Significantly Lower HF-HRV and a Trend Toward Higher LF-HRV at Rest, Relative to Individuals with Normative AS.

This hypothesis was based on literature demonstrating lower high-frequency heart rate variability (HF-HRV) at rest, relative to healthy controls, among individuals with (a) psychopathology which has shown associations to anxiety sensitivity (AS; e.g., depression, Schiweck, Piette, Berckmans, Claes, & Vrieze, 2019; anxiety disorders, including panic disorder [PD], post-traumatic stress disorder [PTSD], generalized anxiety disorder [GAD], social anxiety disorder [SAD], Pittig et al., 2013) and (b) elevated in traits that, like AS, appear to underlie psychopathology (e.g., perseverative cognitive, worry [Ottaviani et al., 2016; Chalmers et al., 2016; Brosschot et al., 2006]).

Hypothesis 1 was partially supported. Planned analyses revealed that baseline HF-HRV, as indexed by normalized values (i.e., HF n.u.) and log-transformed absolute power (i.e., HF log), did not significantly differ between high AS and normative AS participants. Likewise, groups did not significantly differ on measures of baseline low-frequency heart rate variability (LF-HRV), as indexed by normalized units (i.e., LF n.u.) and log-transformed absolute power (i.e., LF log). However, after controlling for variance due to age, HF-HRV (i.e., HF log) emerged as significantly higher for normative AS participants, relative to high AS participants. After controlling for variance due to age, LF-HRV, indexed by low-transformed absolute power also emerged as significantly higher for normative AS participants, which was in the opposite direction than predicted. Thus, the null hypothesis was rejected.

Hypotheses 2-4: High AS Individuals Will Demonstrate Significantly Lower HF-HRV During Behavioral Challenges, Relative to Individuals with Normative AS.

Hypotheses 2-4 were based on literature which has (a) established AS as a strong predictor of fear response whereby individuals with high AS report increased distress, relative to controls, following experiences of stress evoked during challenge paradigms (e.g., Eke & McNally, 1996; Gonzalez et al., 2011, Richey et al., 2010) and (b) established that HF-HRV decreases during experiences of stress in both healthy controls (e.g., Godfrey et al., 2019, Sheffield et al., 1998) and individuals with psychopathology (e.g., Chalmers et al., 2016; Thayer et al., 2009).

Hypotheses 2: High AS individuals will demonstrate significantly lower HF-HRV during the cognitive challenge (i.e., PASAT-C), relative to individuals with normative AS. Hypothesis 2 was not supported. Results from planned analyses did not evidence significant differences in HF-HRV measured during the cognitive challenge between high and normative AS groups, whether HRV was indexed either via normalized values (i.e., HF n.u.) or log-transformed absolute power (i.e., HF log). Exploratory analyses which accounted for variance due to age also failed to yield evidence for significant differences between groups. Thus, the null hypothesis was accepted.

Related to Hypothesis 2, LF-HRV, as indexed by LF log, was investigated in a series of exploratory analyses to evaluate whether groups differed on this variable during the cognitive challenge. Whether variance due to age was accounted for or not, differences between groups were not significant.

Hypothesis 3: High AS individuals will demonstrate significantly lower HF-HRV during the physical challenge (i.e., hyperventilation), relative to normative AS individuals. Hypothesis 3 was not supported. Results from planned analyses did not evidence group differences in HF-HRV recorded during the physical challenge, whether indexed via normalized values (i.e., HF n.u.) or log-transformed absolute power (i.e., HF log). Exploratory analyses which accounted for variance due to age also failed to yield evidence for significant differences between groups. Thus, the null hypothesis was accepted.

Related to Hypothesis 3, LF-HRV, as indexed by LF log, was investigated in series of exploratory analyses to evaluate whether groups differed on this variable during the physical challenge. After controlling for variance due to age, LF log emerged as significantly higher among normative AS participants than high AS participants during the physical challenge. Differences were non-significant when evaluated across three groups (i.e., "always normative," "sometimes normative," "never normative").

Hypothesis 4: High AS individuals will demonstrate significantly lower HF-HRV during the social challenge (i.e., self-disclosing speech preparation), relative to normative AS individuals. Hypothesis 4 was partially supported. Results from planned analyses revealed that HF-HRV measured during the social challenge, as indexed by normalized values (i.e., HF n.u.) or log-transformed absolute power (i.e., HF log) was not significantly different for high and normative AS participants. However, after accounting for variance due to age, significant differences emerged, whereby HF-HRV, as indexed via HF log, was significantly higher for the normative AS group, than the high AS group, during the social challenge. When this trend was investigated across three AS categories (i.e., "always normative," "sometimes normative,"

"never normative"), group differences were not significant. Thus, the null hypothesis was rejected.

Related to Hypothesis 4, LF log was also investigated in series of exploratory analyses. Findings indicated that groups significantly differed in LF log during the social challenge. LF log emerged as significantly higher among normative AS participants than high AS participants during the social challenge; differences across three groups of AS remained non-significant even after controlling for age-related variance.

Hypotheses 5-7. High AS Individuals Will Demonstrate Greater Decreases in HF-HRV, Relative to Normative AS Individuals, During Behavioral Challenges.

This set of hypotheses was based on literature which demonstrated decreased HRV during behavioral challenges, relative to rest (e.g., Castaldo et al., 2015), among participants with elevated AS (Dodo & Hashimoto, 2017), those with elevated depression scores (Hughes & Stoney, 2000), and anxiety disorders (e.g., Keary et al., 2009; Thayer et al., 1996).

Hypothesis 5: High AS individuals will demonstrate greater decreases in HF-HRV relative to normative AS individuals during the cognitive challenge (i.e., PASAT-C). Hypothesis 5 was not supported. Planned analyses revealed that groups did not significantly differ in the magnitude of HF-HRV change between baseline and cognitive challenge recordings, whether indexed via HF n.u. or HF log. Interestingly, normative participants evidenced an increase in HF n.u. during the cognitive challenge, relative to baseline and high AS participants evidenced a decrease. When HF log was evaluated, as expected, all AS groups evidenced a decreased HF-HRV during the challenge, relative to baseline. After controlling for variance due to age, group differences in HF log decreases evidenced a trend ($p = .07$), whereby normative AS

participants demonstrated greater decreases in HF-HRV than high AS participants, although this difference fell short of significance. Thus, the null hypothesis was accepted.

Related to Hypothesis 5, LF-HRV, as indexed via LF log, was investigated in a series of exploratory analyses evaluating whether the magnitude of change between baseline and cognitive recordings differed between groups. Results revealed that normative AS participants evidenced a significantly greater decrease in LF-HRV during the cognitive challenge than high AS participants, relative to baseline. Interestingly, after controlling for age, the magnitude of this difference between groups became non-significant.

Hypothesis 6: High AS individuals will demonstrate greater decreases in HF-HRV relative to normative AS individuals during the physical challenge (i.e., hyperventilation). Hypothesis 6 was not supported. Planned analyses revealed that while both groups exhibited decreases in HF-HRV (i.e., HF n.u.) during the physical challenge, relative to baseline, the magnitude of HF n.u. change between baseline and physical challenge recordings did not significantly differ between groups. When HF log was evaluated, again, differences were non-significant, although normative AS participants exhibited a decrease in HF log, whereas high AS participants exhibited a slight increase. Across three AS categories, "sometimes normative" and "always normative" participants exhibited a decrease whereas "never normative" participants exhibited an increase, although again, these differences were not significant.

Interestingly, after controlling for variance due to age, significant differences between the groups emerged whereby high AS participants evidenced increased HF log during the physical challenge, relative to baseline, whereas normative AS participants evidence a decrease. Thus, the null hypothesis was rejected.

Related to Hypothesis 6, LF-HRV, as indexed via LF log, was investigated in a series of exploratory analyses evaluating whether the magnitude of change between baseline and physical challenge HRV differed between groups. The magnitude of change in LF-HRV was not significantly different between groups, although notably, high AS participants evidenced an increase in in LF log during the physical challenge, relative to baseline, whereas normative AS participants evidenced a decrease. When non-significant trends were examined across three groups of AS participants, those in the "never" and "sometimes normative" categories evidenced an increase during the physical challenge, relative to baseline, whereas the "always normative" group evidenced a decrease. After controlling for variance due to age, results remained non-significant; high AS participants still evidenced an increase in HF-HRV whereas normative AS participants evidenced a decrease during the physical challenge, relative to baseline.

Hypothesis 7: High AS individuals will demonstrate greater decreases in HF-HRV relative to normative AS individuals during the social challenge (i.e., self-disclosing speech preparation). Hypothesis 7 was not supported. Planned analyses revealed that the magnitude of change between HF-HRV (i.e., HF n.u., and HF log) at baseline and the social challenge was not statistically significant. Notably, when HF-HRV was indexed via HF n.u., high AS participants evidenced a decrease during the social task, relative to baseline, whereas normative AS participants evidenced an increase during the social task, relative to baseline. When HF-HRV was indexed via HF log, both groups evidenced a decrease during the social task, relative to baseline. When trends in change were inspected across three AS categories, all groups exhibited decreased HF log during the social task, relative to baseline. Trends remained non-significant even after accounting for variance due to age.

Related to hypothesis 7, a series of exploratory analyses evaluated whether the magnitude of change between baseline and social challenge in LF-HRV, as indexed via LF log, differed between groups. Results revealed significant differences between groups whereby normative AS participants evidenced a significantly greater decrease in LF-HRV during the social challenge than high AS participants. After controlling for variance due to age, this effect became non-significant.

Secondary Hypothesis. High AS Individuals Will Report Increased Subjective Distress Following Behavioral Challenges, Relative to Normative AS Individuals.

A secondary hypothesis was proposed in order to evaluate the degree to which AS, as measured by the Anxiety Sensitivity Index-3 (ASI-3), is associated with subjective distress. It was hypothesized that high AS individuals would report increased subjective distress following stressful cognitive, social, and physical tasks, relative to low normative AS individuals. This hypothesis was based on literature demonstrating AS to be predictive of subjective distress in response to stressful behavioral challenge paradigms, including cognitively-oriented (e.g., mental arithmetic; Stewart et al., 2001), physically-oriented (e.g., hyperventilation; Brown et al., 2003) and socially oriented (e.g., speech planning; Conrod, 2006) tasks.

This hypothesis was supported; significant differences between groups emerged, whereby high AS participants evidenced greater increases in subjective distress (i.e., SUDS) than normative AS participants following each behavioral challenge, relative to baseline.
When group differences were explored across three categories of AS, the most robust differences emerged between “never normative” and “always normative” AS participants and between “sometimes normative” and “always normative” AS participants. Therefore, those who met

criteria for normative AS at screening but not in-person (i.e., “sometimes normative”) did not differ significantly from those met criteria for normative AS at screening and in-person (i.e., “always normative”) with regards to SUDS change at behavioral challenges, relative to baseline.

Related to this secondary hypothesis, a series of exploratory analyses were undertaken in order to evaluate the degree to which ASI-3 subscale elevations predict distress. Findings indicated that participants categorized with at least one subscale elevation (i.e., cognitive, physical, social) reported significantly higher subjective distress (indexed via SUDS) relative to those scoring in the normative range of that subscale.

Validity of the ASI-3 (Taylor et al., 2007)

Taken together, study results offered solid support for the use of the ASI-3. Findings related to secondary hypotheses supported the predictive utility of AS as indexed via ASI-3, whereby those categorized with high AS evidenced higher subjective distress in response to challenges than low AS. This is consistent with literature evidencing AS to predict self-reported anxiety (e.g., Gregor & Zvolensky, 2008) and anxious responding (e.g., Rapee & Medoro, 1994) in response to behavioral challenges. Correlational analyses demonstrated that ASI-3 total scores [at screening and in-person] were strongly associated with measures of anxiety and depression ($r = 0.57–0.76$), thereby providing evidence of convergent validity, consistent with previous validation efforts (e.g., Kemper et al., 2012). Subscales were likewise strongly intercorrelated as expected and evidenced significant associations with PROMIS measures of emotional distress. Interestingly, of the two PROMIS measures of emotional distress included in the study, all of the ASI-3 subscales were more strongly corelated with PROMIS-Anxiety. This finding is notable, given the well-established association between the AS cognitive subscale and depression

(Zinbarg et al., 2001); a stronger association between the two variables would have been expected. Test-retest validity was strong for both the full scale ASI-3 as well as subscales; on the whole, the measure demonstrated strong internal consistency. Interestingly, internal consistency for screened normative group emerged as much weaker (α = 0.31) than the screened high group (α =0.83).

It is worth noting that despite evidence of strong test-retest reliability, 4/60 participants who met criteria for high AS at screening no longer met criteria during the in-person portion of the study; 25/60 participants who met criteria for normative AS at screening no longer met criteria during the in-person portion of the study. This was unexpected and may have been due in part to low internal consistency demonstrated by the normative group at baseline. It is also possible that AS at low levels may function differently than AS at high levels. Low AS, for example, may function as a malleable *state*, whereas high AS, may be more stable and thus function more as a *trait*. There has been considerable debate in the study of AS surrounding its characterization as a trait or state. Given that traits are generally defined as highly enduring and possibly lifelong (Fridhandler, 1986), early findings illustrating AS stability over time (Maller & Reiss, 1992; Reiss, Peterson, Gursky, & McNally, 1986) supported this contention. Treatment outcome studies for PD evaluating AS as a secondary outcome measure, however, have demonstrated its malleability in response to behavioral interventions (Ehlers, 1995; Otto & Reilly-Harrington, 1999; Schmidt et al., 2007). This controversy has led many to regard AS as a state-like trait. The present study findings may offer new insights into the state-trait debate.

AS and HRV

In general, primary study hypotheses delineating a relationship between AS and HRV were partially somewhat supported. Before controlling for variance due to age, only one significant difference between normative and high AS had emerged: normative AS participants exhibited a significantly greater decrease in LF-HRV during cognitive challenge than high AS participants. Interestingly, significance fell away after controlling for variance due to age.

Numerous significant differences emerged between normative and high AS participants after controlling for variance due to age. These are summarized as follows:

- HF-HRV was significantly higher among normative AS participants at baseline.
- LF-HRV was significantly higher among normative AS participants at baseline.
- HF-HRV was significantly higher for normative AS participants during the social challenge.
- LF-HRV was significantly higher among normative AS participants during the social challenge.
- LF-HRV was significantly higher among normative AS participants during the physical challenge.
- The magnitude of HF-HRV change between baseline and physical challenge differed significantly between groups. High AS participants exhibited an increase in HF log during the physical challenge whereas normative AS participants exhibited a decrease.

Findings demonstrating significantly higher HRV among normative AS participants than high AS participants at baseline and during the social challenge were consistent with predictions. Indeed, decreases in HF-HRV have been described as a displacement of parasympathetic/vago-sympathetic balance, whereby sympathetic activation overcomes parasympathetic inhibition (i.e., the vagal brake; Castaldo et al., 2015; Porges, 2001). Thus, this study finding suggests that parasympathetic activity was higher among normative AS individuals, relative to high AS individuals at rest and during at least one stressful task and is consistent with the literature more broadly. Interestingly, significant differences in HF-HRV did not emerge between groups during cognitive and physical tasks, which is puzzling, since findings indicated that high AS participants demonstrated significantly greater increases in subjective distress, measured via SUDS at each task, than normative AS participants. Other investigations have failed to reveal differences in HRV between clinical groups and controls. Blechert and colleagues (2007), for example, identified only non-significant trends in HRV change among PD patients, PTSD patients, and healthy controls following a behavioral challenge. More recently, Durdu and colleagues (2018) investigating HRV in drug-free PD patients identified only a non-significant trend toward lower HF-HRV (reported as RMSSD and PNN50 values) in PD patients (p = .229, p = .571, respectively).

Findings demonstrating LF-HRV to be higher among normative AS participants than high AS participants at baseline, and during physical and social challenges were also unexpected. It is unclear what might have accounted for this; although it is plausible that the elevation relates to the vago-sympathetic interplay that characterizes LF-HRV output. Other investigations have predominantly demonstrated increased LF-HRV during stress (see Castaldo et al., 2015 for a

review), although some studies have not (e.g., Hjortskov et al., 2004; Taelman, Vandeput, Vlemincx, Spaepen, & Van Huffel, 2011; Tharion, Parthasarathy, & Neelakantan, 2009). As noted by Shaffer and Ginsburg (2017), the relationship between the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) branches should not be described as a "zero sum" system illustrated by a teeter-totter; elevated PNS activity may be associated with a decrease, increase, or no change in SNS activity.

This suggests other factors may have accounted for the unexpected elevations in LF-HRV noted among normative participants and general non-significant differences between groups. Indeed, the finding evidencing significant decrease between baseline and social HRV became non-significant after controlling for variance due to age. Thus, other factors must be considered.

Potential Confounding Variables

Antidepressant use. Participant use of antidepressants was not evaluated as part of screening criteria. Antidepressants have shown associations with increased heart rate and decreased HRV (Kemp et al., 2014), which to some extent, is counter-intuitive since psychopharmacological treatment decreases symptoms of depression. Thus, it would be reasonable to assume that decreased depression, treated with antidepressants or not, is associated with increased HRV. Yet this is not the case. In a large-scale study of anxiety and depression in the Netherlands, Licht, De Geus, Van Dyck, and Penninx (2009) investigated HRV among healthy controls as compared with individuals with current and remitted anxiety disorders (i.e., PD, GAD, and social phobia). Significant differences between groups emerged, whereby those with current and remitted anxiety had significantly lower HF-HRV at rest as compared with

controls. However, after adjusting for antidepressant use, significant associations became non-significant. The authors concluded that the association between diminished HRV and anxiety disorders may be driven by antidepressant use.

Data from the 2000 Medical Expenditure Panel Survey found that 60.8% of individuals with self-reported depression had at least one antidepressant prescription (Eisenberg & Chung, 2012). Since 24.2% of the present study sample met the PROMIS® Emotional Distress cutoff for depression, it is reasonable to assume that at least some of had engaged in pharmacological treatment. Had this been the case, participant use of anti-depressants likely had a substantial impact on study findings. Future studies should consider excluding participants actively utilizing antidepressant medications.

Differential impact of challenges. Although the literature more broadly has demonstrated decreases in HRV during challenge paradigms (Castaldo et al., 2015), there is also literature which suggests that challenge paradigms differentially affect HRV. Recent research by Hu and colleagues (2016) indicated that the type of behavioral challenge may have an impact on HRV response. Authors found that, relative to healthy controls, patients with anxiety and depression exhibited increased HF-HRV (as measured via RMSSD) following an emotionally stressful task, and decreased HF-HRV following a cognitively stressful arithmetic task. They attributed this differential responding to autonomic "hyperreactivity," resulting in a decrease in HF-HRV versus "hyporeactivity," resulting in an increase in HF-HRV.

Hughes and Stoney (2000) found that while participants categorized with high depression elicited significantly greater decreases in HF HRV following a social stressor task, they also elicited significantly lower decreases in HF HRV following a physiological cold pressor task,

relative to those categorized with low depression. Another investigation using a cold-pressor behavioral challenge paradigm evidenced HRV decreases in both low and high AS participants, but noted that diminished HRV sustained longer (i.e., during a post-challenge recovery phase) among high AS participants (Dodo & Hashimoto, 2017). Thus, it is plausible that effects of challenge paradigms used in the present study were more nuanced; further, although participants were allotted a ten-minute rest period between each task, it remains possible that carry-over effects from prior challenges continued to influence HRV.

Respiration. It is also possible that HRV measurement during the study was more generally affected by the physiological task selected. Hyperventilation is commonly used in challenge studies as a means of evoking mild psychological distress and has been extensively used in work investigating the predictive utility of AS (e.g., Holloway & McNally, 1987; Asmundson et al., 1998; Pittig et al., 2013). In the present study, the hyperventilation challenge was selected as a non-invasive, accessible challenge, designed to tap into the physiological subscale of AS. However, in hindsight, the paced breath work involved in the task may have impacted HRV. As previously discussed in detail, HRV is strongly tied to respiration, whereby expiration serves to activate parasympathetic responding (Beauchaine, 2015; Thayer, 2006). Thus, it is plausible that altering respiration through the hyperventilation challenge impacted HRV.

Dodo and Hashimoto (2019) recently concluded that respiration served as a confounding variable in their investigation of HRV. The authors measured HF-HRV at rest and during two speech-related tasks which were designed to induce mild stress: one which required reading aloud and one which required reading silently. Participants evidenced no differences in mood

between tasks, although self-ratings of their performances were significantly lower for the read-aloud task. Thus, investigators interpreted the task to produce greater psychological loading. Interestingly, HF-HRV increased during the "read-aloud" task, in comparison with the "read silently" task. The authors postulated that respiration involved in the "read aloud" task impacted the results. A similar pattern emerged in the present study, whereby despite reporting significant distress, participants failed to exhibit significant decreases in HRV. Notably, another study which utilized hyperventilation as a challenge in the study of HRV still found significant differences between clinical and control groups (Pittig et al., 2013), although these authors noted that gender and age evidenced multiple main effects. However, in hindsight, a more appropriate physiological task would ideally avoid breath work in the investigation of HRV.

The Effect of Age

Taken together, the results of the present study indicate that age accounted for much more variance than was originally anticipated. Participants were not screened to fit into an "age-cohort," as utilized in other investigations (e.g., Agelink et al., 2001; Antelmi et al., 2004) since recruitment targeted a college sample. However, Eastern Michigan University represents a unique, "commuter campus," whereby many students are "non-traditional." As per the university website, 45.4% of currently enrolled students are in the "traditional" undergraduate age range of 18 to 21 bracket, compared to the national average of 60%.

Study Limitations

In addition to aforementioned factors discussed, additional variables may serve to limit study findings.

Unique college sample. Participants were recruited via multiple methods (i.e., fliers, emails, classroom presentations) on the Eastern Michigan University college campus. Eastern Michigan University is a unique, mid-sized "commuter-campus" university. That is, many students do not live on campus and concurrently work while attending school. Initially, this study sought to recruit participants "low" in AS, rather than "normative" in AS. Study criteria was changed early in recruitment efforts after it became apparent that few of those who completed screening measures met criteria for "low" AS whereas recruitment of "high" AS participants was steady.

It is plausible that the Eastern Michigan University campus climate is "higher" in stress and pathology than would be found in the general population. Therefore, recruitment of a high-stress, college sample would limit the generalizability of study findings to the general population. Indeed, 24.2% of the present study sample met PROMIS® Emotional Distress cut-off criteria for depression and 30.0% for anxiety. This is substantially higher than prevalence of anxiety (18.1%) and depression (6.7%) in the U.S., reported by the Anxiety and Depression Association of America.

Sample size. A power analysis using G*Power 3.1 indicated that a sample size of 120, with 60 in each group was adequate to achieve power of .8 with alpha set to .05 (two-tailed) assuming a medium effect size, $d = .5$. Although 120 screened participants completed full study procedures, 24% no longer met ASI-3 cut-point criteria at the time of the study. Therefore, the sample size for proposed analyses was substantially lower, likely resulting in a loss of power. In an effort to examine data from participants whom had to be "cut" from analyses, participants

were re-categorized into three groups in several exploratory analyses, although doing so failed to provide additional information.

Study Strengths

There were several strengths associated with the present study. First and foremost, this work contributed to the AS literature in a meaningful way. The extant literature investigating AS in the context of behavioral challenge paradigms has done so using the original ASI (Peterson & Reiss, 1987), which has evidenced problematic subscale psychometrics. Thus, use of the ASI-3 (Taylor et al., 2007) enabled instrument psychometrics, including construct reliability, convergent validity, and test-retest validity to be further established. This study further contributed to the literature through exploring the responses of individuals with elevated subscale scores. Although AS has been heavily investigated in the context of challenge paradigms, nothing in the literature had investigated whether various challenge paradigms effectively and prompt subjective distress in individuals with subscale elevations. This study represented an initial effort to so, thereby contributing to the behavioral challenge literature broadly.

Future Directions

Clearly, additional work is needed in order to further explore a possible relationship between AS and HRV. Findings from the present investigation underscore important avenues for future research to better delineate how the two constructs may be related. First, future work should systematically control for variables such as age and antidepressant use. To this end, study of AS on a continuum would be beneficial in order to assess mediation and moderation effects of such variables. To date, most studies have utilized AS in a categorical fashion to delineate groups. Further, results suggest that behavioral challenges could potentially have a differential

impact on HRV. It is plausible that the use of hyperventilation to evoke physiological distress may have influenced the study of HRV in this investigation. Thus, future work should aim to both understand the impact of hyperventilation on HRV as well as investigate HRV in the context of physiological challenge which does not involve respiration (e.g., CO2 inhalation, hyperventilation, paced breathing).

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APPENDICES

Appendix A: Human Subjects Committee Approval

RESEARCH @ EMU

UHSRC Determination: **FULL BOARD INITIAL APPROVAL**

DATE: **February 9, 2017**

TO: **Bethany Gourley, M.S.**
Eastern Michigan University

Re: **UHSRC: # 989801-1**
Approval Date: February 9, 2017
Expiration Date: February 8, 2018

Title: **Exploring the Relationship between Anxiety Sensitivity and Heart Rate Variability**

Your research project, entitled **Exploring the Relationship between Anxiety Sensitivity and Heart Rate Variability,** has been approved in accordance with all applicable federal regulations.

This approval includes the following:

1. Enrollment of 120 subjects to participate in the approved protocol.
2. Use of the following study measures: *Subjective Units of Distress Scale (SUDS); Demographics Questionnaire; PROMIS® (Patient-Reported Outcomes Measurement Information System) Emotional Distress- Anxiety; PROMIS® Emotional Distress- Depression; Anxiety Sensitivity Index-3; Screening Questionnaire*
3. Use of the following stamped recruitment materials: *Class announcement; Recruitment flyer*
4. Use of the stamped: *Screening consent form; Informed consent form (main study); Debriefing form*

Renewals: This approval is valid for one year and expires on February 8, 2018. If you plan to continue your study beyond February 8, 2018, you must submit a Continuing Review Form by January 9, 2018 to ensure the approval does not lapse.

Modifications: All changes must be approved prior to implementation. If you plan to make any minor changes, you must submit a **Minor Modification Form.** For any changes that alter study design or any study instruments, you must submit a **Human Subjects Approval Request Form**. These forms are available through IRBNet on the UHSRC website. Please note that major modifications will require Full Board review and should be submitted at least 30 days in advance to allow for the UHSRC monthly meeting schedule.

Problems: All major deviations from the reviewed protocol, unanticipated problems, adverse events, subject complaints, or other problems that may increase the risk to human subjects **or** change the category of review must be reported to the UHSRC via an **Event Report** form, available through IRBNet on the UHSRC website

Follow-up: If your Expedited research project is not completed and closed after **three years,** the UHSRC office requires a new **Human Subjects Approval Request Form** prior to approving a continuation beyond three years.

Please use the UHSRC number listed above on any forms submitted that relate to this project, or on any correspondence with the UHSRC office.

Good luck in your research. If we can be of further assistance, please contact us at 734-487-3090 or via e-mail at human.subjects@emich.edu. Thank you for your cooperation.

Generated on IRBNet

Sincerely,

April M Gravitt, MS
Research Compliance Analyst
University Human Subjects Review Committee

Generated on IRBNet

Appendix B: Recruitment Flier

RESEARCH STUDY IN SEARCH OF VOLUNTEERS!

You may be eligible to take part in a study investigating risk factors for developing anxiety or depression.

If you are 18 or over, complete a brief, two-minute screening survey to find out if you are eligible to participate.

The survey is available at https://emichpsych.co1.qualtrics.com/SE/?SID=SV_4ZQqVdUC7rXBFFb

Participants who complete the entire study will receive a $25 Amazon gift card and one SONA research credit (if applicable).

To find out more, please contact the principal investigator, Bethany Gourley, at bgourley@emich.edu or 734.487.4987.

Approved by the Eastern Michigan University Human Subjects Review Committee
UHSRC Protocol Number: 989801-1
Study Approval Dates: 02/09/17 – 02/08/18

Research Study bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu	**Research Study** bgourley@emich.edu

Appendix C: Recruitment Script

Classroom Recruitment Script

Hi all, I am Beth Gourley-- I am a clinical psychology doctoral student here in the EMU Psychology Department, and I wanted to talk to you briefly about my study which is looking at risk factors for anxiety and depression. The study will take approximately an hour, during which participants will be asked to wear a chest strap to measure heart rate, complete a brief questionnaire (which will take approximately 10 minutes) and then three exercises: a 10-minute computer involving addition, a 2-minute rapid, paced breathing exercise, and a writing exercise during which you will prepare a speech.

We will be looking at your performance on these tasks and your responses to such activities, including changes in your heart rate.

Participants who complete the full study will receive a $25 Amazon Gift Card and if allowed by their instructor, will earn one "research credit in SONA" for participation.

If you are interested in participating, please log on the site listed on this flier to complete a brief screening questionnaire. This questionnaire will take about two minutes to complete and we will use the information to determine if you are eligible to participate in this study. If you meet study eligibility, a research assistant will contact you to set up a time for your participation. If you are not eligible for study participation, your study screening questionnaire will be destroyed.

*** The study investigator will also write the screening study Qualtrics URL on the dry erase board of the room if available. Fliers will be provided to interested students.*

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Appendix D: Screening Questionnaire

1. How old are you? _____
2. Are you
    a. Male
    b. Female
    c. Non-cisgender

    Do you smoke, either occasionally or daily?_____
3. Do you have diabetes?
4. Do you have a history of heart problems or conditions (including a heart murmur or congenital heart disease)?
5. Do you have a history of respiratory problems or conditions (including asthma)?
6. Are you currently taking a beta-blocker, such as Propranolol, Metoprolol, or Bisoprolol?

For the following questions, select a number from the scale that best describes how typical or characteristic each of the 12 items is of ***you***. You should make your ratings in terms of how much you agree or disagree with the statement as a ***general*** description of yourself.

0	1	2	3	4
very little	a little	some	much	very much

1. It is important for me not to appear nervous.
2. When I cannot keep my mind on a task, I worry that I might be going crazy.
3. It scares me when my heart beats rapidly.
4. When my stomach is upset, I worry that I might be seriously ill.
5. It scares me when I am unable to keep my mind on a task.
6. When I tremble in the presence of others, I fear what people might think of me.
7. When my chest feels tight, I get scared that I won't be able to breathe properly.
8. When I feel pain in my chest, I worry that I'm going to have a heart attack.
9. I worry that other people will notice my anxiety.
10. When I feel "spacey" or spaced out I worry that I may be mentally ill.
11. It scares me when I blush in front of people.
12. When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.
13. When I begin to sweat in a social situation, I fear people will think negatively of me.
14. When my thoughts seem to speed up, I worry that I might be going crazy.
15. When my throat feels tight, I worry that I could choke to death.
16. When I have trouble thinking clearly, I worry that there is something wrong with me.
17. I think it would be horrible for me to faint in public.
18. When my mind goes blank, I worry there is something terribly wrong with me.

I am interested in completing an hour-long follow up to this study, whereby I will receive course credit (if applicable) and a $50 Amazon gift card.

_____No
_____Yes; my contact information is as follows. EMAIL, MOBILE PHONE

Appendix E: Screening Consent Form

RESEARCH @ EMU

Informed Consent Form

The person in charge of this study is Bethany Gourley. Bethany Gourley is a student at Eastern Michigan University. Her faculty adviser is Dr. Ellen Koch. Throughout this form, Bethany Gourley will be referred to as the "investigator."

Purpose of the study

The purpose of this research study is to determine your eligibility for participating in a study designed to investigate the relationship between anxiety sensitivity and heart rate variability.

Anxiety sensitivity refers to "fear of fear" or "fear of anxiety." Everyone has some degree of anxiety sensitivity, however, individuals with elevated anxiety tend to detect certain harmless sensations that may arise during stress (e.g. increased heart rate and breath or the feeling of one's mind going blank) or social situations and misinterpret these sensations as dangerous.

Heart rate variability is an index of central nervous system activity that can be measured with a heart rate monitor.

Anxiety sensitivity and heart rate variability are both associated with mental health, although it is not clear as to whether they are related to each other. We are screening individuals who may be eligible to participate in a study which will explore the ways that anxiety sensitivity and heart rate variability may be related.

Blue Cross Blue Shield of Michigan Foundation Student Award Program is paying for this research.

What will happen if I participate in this study?

You will be asked to complete a questionnaire in order to determine your eligibility to participate in a later, one-hour study. If you would like to participate in the later study, by signing this consent form you are giving Bethany Gourley permission to contact you to schedule an in-person follow-up visit.

Completion of the screening questionnaire will take approximately 5 minutes.

What are the anticipated risks for participation?

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There are no anticipated physical or psychological risks to participation, however, it is possible that you will uncomfortable answering questions which are personal in nature.

You do not have to complete any portion of the questionnaire that makes you uncomfortable and you may stop participating at any time.

Additionally, although unlikely, another risk of participation in this study is a potential loss of confidentiality.

Are there any benefits to participating?

You will not directly benefit from participating in this research.

Benefits to society include better understanding of the relationship between anxiety sensitivity and heart rate variability and risk factors for developing psychopathology.

What are the alternatives to participation?

The alternative is not to participate.

How will my information be kept confidential?

We will keep your information confidential by using a code to label data with the code linked to identifiable information in a key stored separately from data. Your information will be stored in a locked filing cabinet. We will make every effort to keep your information confidential, however, we cannot guarantee confidentiality. There may be instances where federal or state law requires disclosure of your records.

Other groups may have access to your research information for quality control or safety purposes. These groups include the University Human Subjects Review Committee, the Office of Research Development, the sponsor of the research, or federal and state agencies that oversee the review of research. The University Human Subjects Review Committee reviews research for the safety and protection of people who participate in research studies.

We may share your information with other researchers outside of Eastern Michigan University. If we share your information, we will remove any and all identifiable information so that you cannot reasonably be identified.

The results of this research may be published, presented at professional conferences, or used for teaching. Identifiable information will not be used for these purposes.

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Storing study information for future use

We would like to store your information from this study for future use related to anxiety sensitivity and heart rate variability. Your information will be labeled with a code and not your name. Your information will be stored in a password-protected or locked file. Your de-identified information may also be shared with researchers outside of Eastern Michigan University. Please initial below whether or not you allow us to store your information:

_____Yes _____No

Are there any costs to participation?

Participation will not cost you anything.

Will I be paid for participation?

You will not be paid or receive course credit for participating in this portion of the study.

Study contact information

If you have any questions about the research, you can contact the Principal Investigator, Bethany Gourley, at bgourley@emich.edu or by phone at 734.487.4987. You can also contact Bethany Gourley's adviser, Dr. Ellen Koch, at ellen.koch@emich.edu or by phone at 734.487.0189.

For questions about your rights as a research subject, contact the Eastern Michigan University Human Subjects Review Committee at human.subjects@emich.edu or by phone at 734-487-3090.

Voluntary participation

Participation in this research study is your choice. You may refuse to participate at any time, even after signing this form, with no penalty or loss of benefits to which you are otherwise entitled. You may choose to leave the study at any time with no loss of benefits to which you are otherwise entitled. If you leave the study, the information you provided will be kept confidential. You may request, in writing, that your identifiable information be destroyed. However, we cannot destroy any information that has already been published.

Statement of Consent

Approved by the Eastern Michigan University Human Subjects Review Committee **UHSRC Protocol Number**: 989801-1 **Study Approval Dates**: 02/09/17 – 02/08/18

I have read this form. I have had an opportunity to ask questions and am satisfied with the answers I received. I give my consent to participate in this research study.

Signatures

_____
Name of Subject

_____ _____
Signature of Subject Date

I have explained the research to the subject and answered all his/her questions. I will give a copy of the signed consent form to the subject.

_____
Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

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Appendix F: In-Person Consent Form

RESEARCH @ EMU

Informed Consent Form

The person in charge of this study is Bethany Gourley. Bethany Gourley is a student at Eastern Michigan University. Her faculty adviser is Dr. Ellen Koch. Throughout this form, Bethany Gourley will be referred to as the "investigator."

Purpose of the study

The purpose of this research study is to investigate the relationship between anxiety sensitivity and heart rate variability.

Anxiety sensitivity refers to "fear of fear" or "fear of anxiety." Everyone has some degree of anxiety sensitivity, however, individuals with elevated anxiety tend to detect certain harmless sensations that may arise during stress (e.g. increased heart rate and breath or the feeling of one's mind going blank) or social situations and misinterpret these sensations as dangerous.

Heart rate variability is an index of central nervous system activity that can be measured with a heart rate monitor.

Anxiety sensitivity and heart rate variability are both associated with mental health, although it is not clear as to whether they are related to each other. This study will explore ways in which anxiety sensitivity and heart rate variability may be related.

Blue Cross Blue Shield of Michigan Foundation Student Award Program is paying for this research.

What will happen if I participate in this study?

Participation in this study will take place on one occasion only, for approximately one-hour total.

If you decide to participate in this study, you will:

- Answer a brief paper and pencil questionnaire about your personal history, including questions about depression, anxiety, and your socioeconomic status
- Wear a chest strap for approximately one hour to monitor your heart rate
- Be asked to complete three behavioral challenge activities. Each activity will take between 2 and 15 minutes to complete. Behavioral challenge activities include: one 10-minute task during which you will be asked to complete mental arithmetic, one 10-15 minute writing exercise during which you will

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be asked to prepare a speech, and a 2-minute, rapid, paced breathing exercise.
- The total time you will spend on behavioral challenge activities is approximately 30 minutes.

What are the anticipated risks for participation?

There are no anticipated physical or psychological risks to participation, however, it is possible that you will feel mildly distressed while taking part in the study. Some survey questions are personal in nature and may make you feel uncomfortable. It is also possible that you may find study tasks to be uncomfortable. For example, some persons with elevations in anxiety sensitivity may experience physical or cognitive sensations during the study tasks which they find to be uncomfortable or which may make them mildly anxious.

You do not have to complete any portion of the study that makes you uncomfortable and you may stop participating at any time.

Additionally, although unlikely, another risk of participation in this study is a potential loss of confidentiality.

Are there any benefits to participating?

You will not directly benefit from participating in this research.

Benefits to society include better understanding of the relationship between anxiety sensitivity and heart rate variability and risk factors for developing psychopathology.

What are the alternatives to participation?

The alternative is not to participate.

You do not have to participate in this research study to earn SONA research credit. If you choose not to participate, your instructor will inform you of alternate ways to obtain research credit in SONA.

How will my information be kept confidential?

We will keep your information confidential by using a code to label data with the code linked to identifiable information in a key stored separately from data. Your information will be stored in a locked filing cabinet. We will make every effort to keep your information confidential, however, we cannot guarantee confidentiality. There may be instances where federal or state law requires disclosure of your records.

Approved by the Eastern Michigan University Human Subjects Review Committee
UHSRC Protocol Number: 989801-1
Study Approval Dates: 02/09/17 – 02/08/18

Other groups may have access to your research information for quality control or safety purposes. These groups include the University Human Subjects Review Committee, the Office of Research Development, the sponsor of the research, or federal and state agencies that oversee the review of research. The University Human Subjects Review Committee reviews research for the safety and protection of people who participate in research studies.

We may share your information with other researchers outside of Eastern Michigan University. If we share your information, we will remove any and all identifiable information so that you cannot reasonably be identified.

The results of this research may be published, presented at professional conferences, or used for teaching. Identifiable information will not be used for these purposes.

Storing study information for future use

We would like to store your information from this study for future use related to anxiety sensitivity and heart rate variability. Your information will be labeled with a code and not your name. Your information will be stored in a password-protected or locked file. Your de-identified information may also be shared with researchers outside of Eastern Michigan University. Please initial below whether or not you allow us to store your information:

_____Yes _____No

Are there any costs to participation?

Participation will not cost you anything.

Will I be paid for participation?

You will be given a $25 Amazon gift card upon completion of this study. Also, if applicable, you will earn one SONA "research credit" following completion of the study.

Study contact information

If you have any questions about the research, you can contact the Principal Investigator, Bethany Gourley, at bgourley@emich.edu or by phone at 734.487.4987. You can also contact Bethany Gourley's adviser, Dr. Ellen Koch, at ellen.koch@emich.edu or by phone at 734.487.0189.

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For questions about your rights as a research subject, contact the Eastern Michigan University Human Subjects Review Committee at human.subjects@emich.edu or by phone at 734-487-3090.

Voluntary participation

Participation in this research study is your choice. You may refuse to participate at any time, even after signing this form, with no penalty or loss of benefits to which you are otherwise entitled. You may choose to leave the study at any time with no loss of benefits to which you are otherwise entitled. If you leave the study, the information you provided will be kept confidential. You may request, in writing, that your identifiable information be destroyed. However, we cannot destroy any information that has already been published.

Statement of Consent

I have read this form. I have had an opportunity to ask questions and am satisfied with the answers I received. I give my consent to participate in this research study.

Signatures

_____
Name of Subject

_____ _____
Signature of Subject Date

I have explained the research to the subject and answered all his/her questions. I will give a copy of the signed consent form to the subject.

_____
Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

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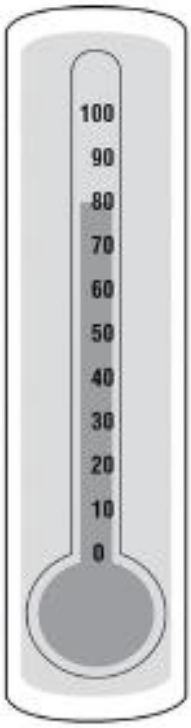
Appendix G: Subjective Units of Distress Scale (SUDS)



100 – Highest anxiety/distress that you have ever felt

90 – Extremely anxious/distressed

80 – Very anxious/distressed; can't concentrate. Physiological signs present.

70 – Quite anxious/distressed; interfering with functioning. Physiological signs may be present

60 – Moderate-to-strong anxiety or distress

50 – Moderate anxiety/distress; uncomfortable, but can continue to function

40 – Mild-to-moderate anxiety or distress

30 – Mild anxiety/distress; no interference with functioning

20 – Minimal anxiety/distress

10 – Alert and awake; concentrating well

0 – No distress; totally relaxed

Appendix H: Demographics Questionnaire

1. Are you a student at Eastern Michigan University?

2. If yes, how many credits are you enrolled in this Semester?

3. If yes, how many college credits have you completed?

4. If no, how did you learn about this study?

5. What is your ethnicity?
    a. Not Hispanic or Latino
    b. Hispanic or Latino

6. Some people identify themselves as belonging to one or more racial groups. Please indicate which of the following groups you belong to. Please check all that apply.
    a. White or Caucasian
    b. Black or African-American
    c. Hispanic or Latino
    d. American Native/American Indian
    e. Alaskan Native
    f. Asian
    g. Pacific Islander
    h. Middle Eastern
    i. Other _____

7. What is the economic status of your family household currently? (Please indicate one.)
    a. We have barely enough to get by
    b. We have enough to get by, but no more
    c. We are solidly middle class
    d. We have plenty of “extras”
    e. We have plenty of “luxuries”
    f. Don’t know/unsure/prefer not to say

Appendix I: Anxiety Sensitivity Index-3 (ASI-3)

Enter the number from the scale below that best describes how typical or characteristic each of the 18 items is of ***you***, putting the number next to the item. You should make your ratings in terms of how much you agree or disagree with the statement as a ***general*** description of yourself.

0	1	2	3	4
very little	a little	some	much	very much

1. It is important for me not to appear nervous.
2. When I cannot keep my mind on a task, I worry that I might be going crazy.
3. It scares me when my heart beats rapidly.
4. When my stomach is upset, I worry that I might be seriously ill.
5. It scares me when I am unable to keep my mind on a task.
6. When I tremble in the presence of others, I fear what people might think of me.
7. When my chest feels tight, I get scared that I won't be able to breathe properly.
8. When I feel pain in my chest, I worry that I'm going to have a heart attack.
9. I worry that other people will notice my anxiety.
10. When I feel "spacey" or spaced out I worry that I may be mentally ill.
11. It scares me when I blush in front of people.
12. When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.
13. When I begin to sweat in a social situation, I fear people will think negatively of me.
14. When my thoughts seem to speed up, I worry that I might be going crazy.
15. When my throat feels tight, I worry that I could choke to death.
16. When I have trouble thinking clearly, I worry that there is something wrong with me.
17. I think it would be horrible for me to faint in public.
18. When my mind goes blank, I worry there is something terribly wrong with me.

Appendix J: PROMIS Health Measures

Please respond to each question or statement by marking one box per row.

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
I felt worthless….....	☐	☐	☐	☐	☐
I felt helpless…….....	☐	☐	☐	☐	☐
I felt depressed……...	☐	☐	☐	☐	☐
I felt hopeless…….....	☐	☐	☐	☐	☐
I felt fearful…….….....	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety…….	☐	☐	☐	☐	☐
My worries overwhelmed me.....	☐	☐	☐	☐	☐
I felt uneasy…….....	☐	☐	☐	☐	☐

Appendix K: Debriefing Sheet

Debriefing Sheet: Exploring the relationship between anxiety sensitivity and heart rate variability

Thank you for participating in our study. The information you have provided is greatly appreciated and will be useful as we strive to learn about the relationship between anxiety sensitivity and heart rate variability.

Anxiety sensitivity refers to a "fear of anxiety" or "fear of fear." Individuals with elevated anxiety sensitivity often find harmless sensations to be uncomfortable. For example, individuals with elevations in anxiety sensitivity might find experiencing a racing heartbeat, rapid breathing (i.e. physiological stress responses), racing thoughts, or the sensation of one's mind "going blank" (i.e. cognitive stress responses), or worrying about embarrassment or feeling judgment (i.e. social concerns) to be distressing.

Anxiety sensitivity has been linked to the development of future anxiety and depression. Researchers are not yet aware, however, of the degree to which anxiety sensitivity may be related to nervous system activity. Heart rate variability, which is a marker of the central nervous system, is being investigated in this study alongside anxiety sensitivity in order to help us understand whether the two are related.

For this study, we selected individuals both high and low in anxiety sensitive to participate. Individuals with elevated anxiety sensitivity may have experienced mild discomfort during study tasks. If you are concerned about the level of distress you experienced during one of these tasks, please let the study investigator know.

If you have general concerns about your mood and would like to pursue treatment, the following local clinics offer free or low-cost therapy options.

Eastern Michigan University Counseling and Psychological Services (CAPS)
313 Snow Health Center
Ypsilanti, MI 48197
734.487.1118
University clinic offering free individual and group therapy to students.

Eastern Michigan University Psychology Clinic
611 W. Cross Street
Ypsilanti, MI 48197
734.487.4987
Community-based clinic offering individual therapy for $10/session.

University of Michigan Psychological Clinic
500 E. Washington Street, Suite 100
Ann Arbor, Michigan 48104
734.469.3391
Community-based clinic offering individual therapy on a sliding scale fee.

Again, we greatly appreciate your participation in our study.

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Appendix L: ASI-3 Items and Corresponding Subscales

Item no.	Item	Cognitive	Physical	Social
1	It is important for me to not appear nervous.			x
2	When I cannot keep my mind on a task, I worry that I might be going crazy.	x		
3	It scares me when my heart beats rapidly		x	
4	When my stomach is upset, I worry that I might be seriously ill.		x	
5	It scares me when I am unable to keep my mind on a task.	x		
6	When I tremble in the presence of others, I fear what people might think of me.			x
7	When my chest feels tight, I get scared that I won't be able to breathe properly.		x	
8	When I feel pain in my chest, I worry that I'm going to have a heart attack.		x	
9	I worry that other people will notice my anxiety.			x
10	When I feel "spacey" or spaced out I worry that I may be mentally ill.	x		
11	It scares me when I blush in front of people.			x
12	When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.		x	
13	When I begin to sweat in a social situation, I fear people will think negatively of me.			x
14	When my thoughts seem to speed up, I worry that I might be going crazy.	x		
15	When my throat feels tight, I worry that I could choke to death.		x	
16	When I have trouble thinking clearly, I worry that there is something wrong with me.	x		
17	I think it would be horrible for me to faint in public.			x
18	When my mind goes blank, I worry there is something terribly wrong with me.	X		

Appendix M: Structure of the SPSS-Readable Batch File

Parameters

`#Detrending`: Detrending method used
`#InterpRate`: Interpolation rate of RR data
`#MinMaxHR`: Nbr of beats averaged for Min/Max HR
`#NNxxThreshold`: Threshold for NNxx and pNNxx in msec
`#VLFband`: VLF frequency band limits in Hz
`#LFband`: LF frequency band limits in Hz
`#HFband`: HF frequency band limits in Hz
`#FreqPoints`: Nbr of points in spectra (points/Hz)
`#FFTorLomb`: FFT (Welch) or Lomb periodogram used
`#WelchWindow`: Window width (overlap) in Welch
`#LombWindow`: Smoothing window width in Lomb periodogram
`#ARspectrum`: Order of AR spectrum (factorisation)
`#Entropy`: Embedding dimension (tolerance)
`#DFAshortterm`: DFA, short-term fluctuations range
`#DFAlongterm`: DFA, long-term fluctuations range
`#RecurrencePlot`: RPA, embedding dimension (threshold)
`#NbrSamples`: Number of analysed samples
`#ArtifactCorrection`: RR artifact correction method

Sample Info

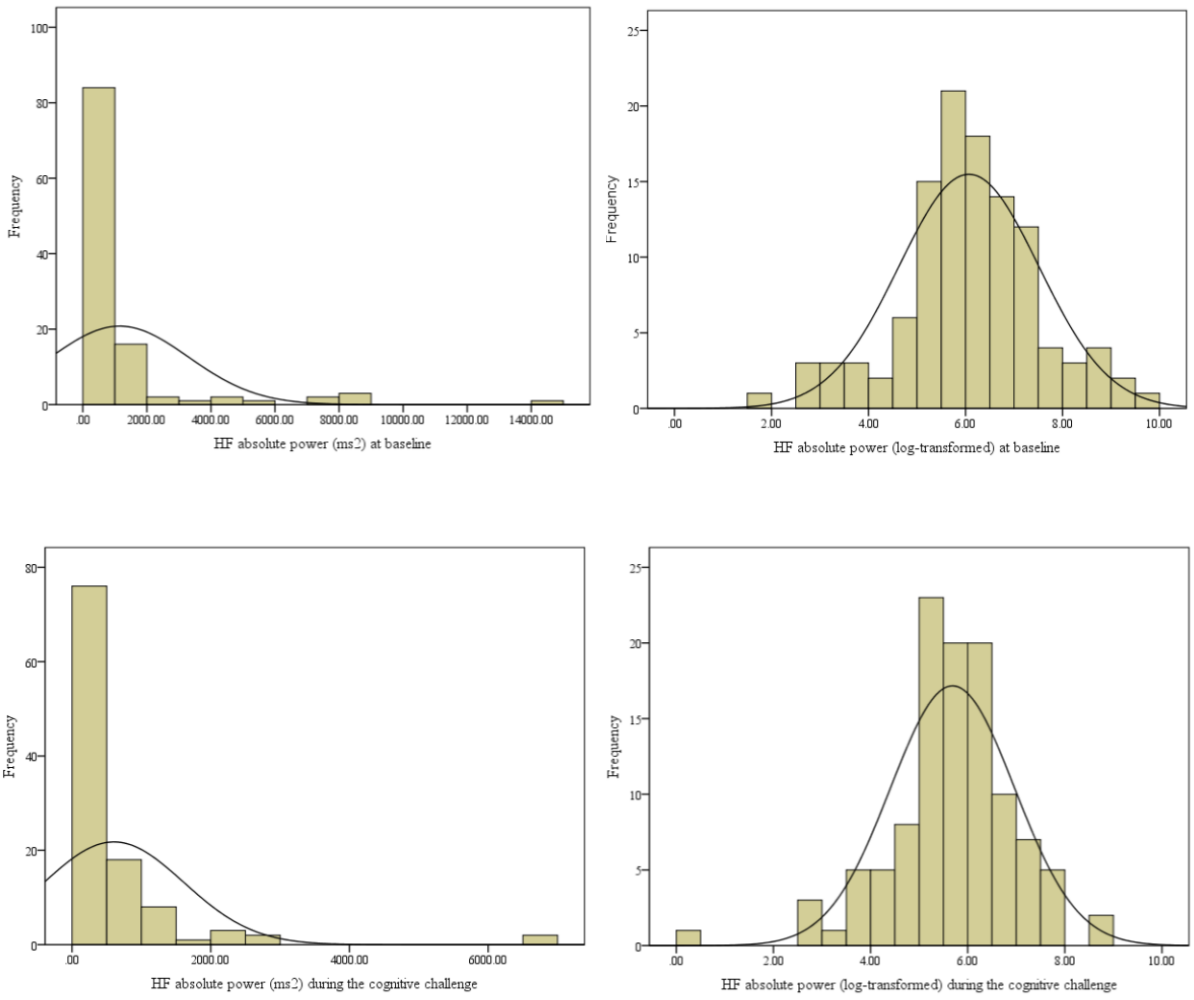
`Onset-Offset`: Sample onset-offset times (hh:mm:ss)
`Artifacts (%)`: Corrected artifacts within the sample

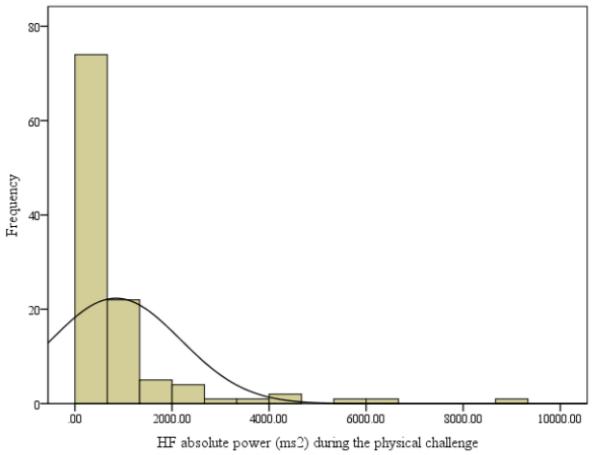
HRV variables

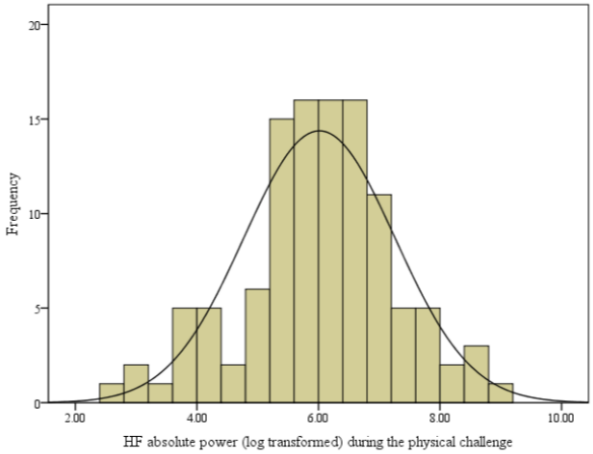
`PNS index`: Parasympathetic nervous system tone index
`SNS index`: Sympathetic nervous system tone index
`Stress index`: Square root of Baevsky's stress index
`Mean RR (ms)`: Mean of RR intervals
`SDNN (ms)`: Standard deviation of RR intervals
`Mean HR (bpm)`: Mean heart rate
`SD HR (bpm)`: Standard deviation of heart rate
`Min HR (bpm)`: Minimum HR using N beat MA
`Max HR (bpm)`: Maximum HR using N beat MA
`RMSSD (ms)`: RMS of successive RR interval differences
`NNxx (beats)`: Nbr or successive RRs > xx ms
`pNNxx (%)`: Percentage of successive RRs > xx ms
`HRV triangular index`: RR histogram area/height
`TINN (ms)`: RR histogram baseline width
`SDANN (ms)`: SD of 5-min RR interval segment means
`SDNNI (ms)`: Mean of 5-min RR interval segment SDs
`VLFpeak_FFT`* `(Hz)`: VLF band peak frequency (FFT)
`LFpeak_FFT (Hz)`: LF band peak frequency (FFT)
`HFpeak_FFT (Hz)`: HF band peak frequency (FFT)
`VLFpow_FFT (ms2)`: Absolute VLF power (FFT)
`LFpow_FFT (ms2)`: Absolute LF power (FFT)
`HFpow_FFT (ms2)`: Absolute HF power (FFT)
`VLFpow_FFT (log)`: Log VLF power (FFT)
`LFpow_FFT (log)`: Log LF power (FFT)
`HFpow_FFT (log)`: Log HF power (FFT)
`VLFpow_FFT (%)`: Relative VLF power (FFT)
`LFpow_FFT (%)`: Relative LF power (FFT)
`HFpow_FFT (%)`: Relative HF power (FFT)
`LFpow_FFT (n.u.)`: Normalised LF power (FFT)
`HFpow_FFT (n.u.)`: Normalised HF power (FFT)
`TOTpow_FFT (ms2)`: Total spectral power (FFT)
`LF_HF_ratio_FFT`: LF/HF power ratio (FFT)
`VLFpeak_AR (Hz)`: VLF band peak frequency (AR spectrum)
`LFpeak_AR (Hz)`: LF band peak frequency (AR spectrum)
`HFpeak_AR (Hz)`: HF band peak frequency (AR spectrum)
`VLFpow_AR (ms2)`: Absolute VLF power (AR spectrum)
`LFpow_AR (ms2)`: Absolute LF power (AR spectrum)
`HFpow_AR (ms2)`: Absolute HF power (AR spectrum)
`VLFpow_AR (log)`: Log VLF power (AR spectrum)
`LFpow_AR (log)`: Log LF power (AR spectrum)
`HFpow_AR (log)`: Log HF power (AR spectrum)
`VLFpow_AR (%)`: Relative VLF power (AR spectrum)
`LFpow_AR (%)`: Relative LF power (AR spectrum)
`HFpow_AR (%)`: Relative VLF power (AR spectrum)
`LFpow_AR (n.u.)`: Normalised LF power (AR spectrum)
`HFpow_AR (n.u.)`: Normalised HF power (AR spectrum)
`TOTpow_AR (ms2)`: Total spectral power (AR spectrum)
`LF_HF_ratio_AR`: LF/HF power ratio (AR spectrum)
`EDR (Hz)`: ECG derived respiration
`SD1 (ms)`: Poincaré plot short term variability
`SD2 (ms)`: Poincaré plot long term variability
`SD2_SD1_ratio`: SD2/SD1 ratio
`ApEn`: Approximate entropy
`SampEn`: Sample entropy
`D2`: Correlation dimension
`DFA1`: DFA, short term fluctuations slope
`DFA2`: DFA, long term fluctuations slope
`RP_Lmean (beats)`: RPA, mean line length
`RP_Lmax (beats)`: RPA, maximum line length
`RP_REC (%)`: RPA, recurrence rate
`RP_DET (%)`: RPA, determinism
`RP_ShanEn`: RPA, Shannon entropy
`MSE_1 …MSE_20`: Multiscale entropy for scales $\tau = 1, \ldots, 20$

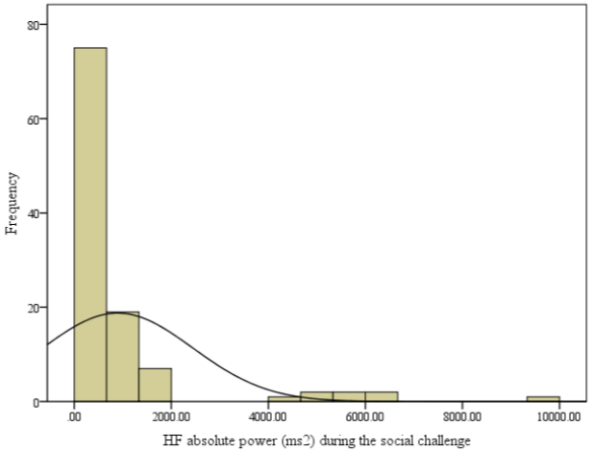
* If Lomb-Scargle periodogram is used instead of Welch's periodogram, `FFT` $\rightarrow$ `Lomb`

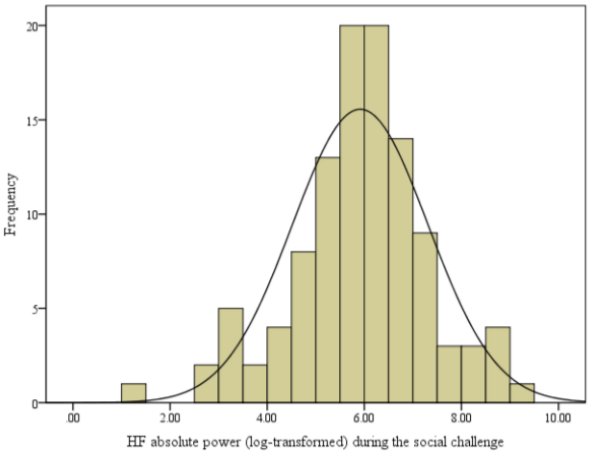
Appendix N: Frequency Histograms for High-Frequency (HF) Absolute Power (ms^2 and Log-Transformed)



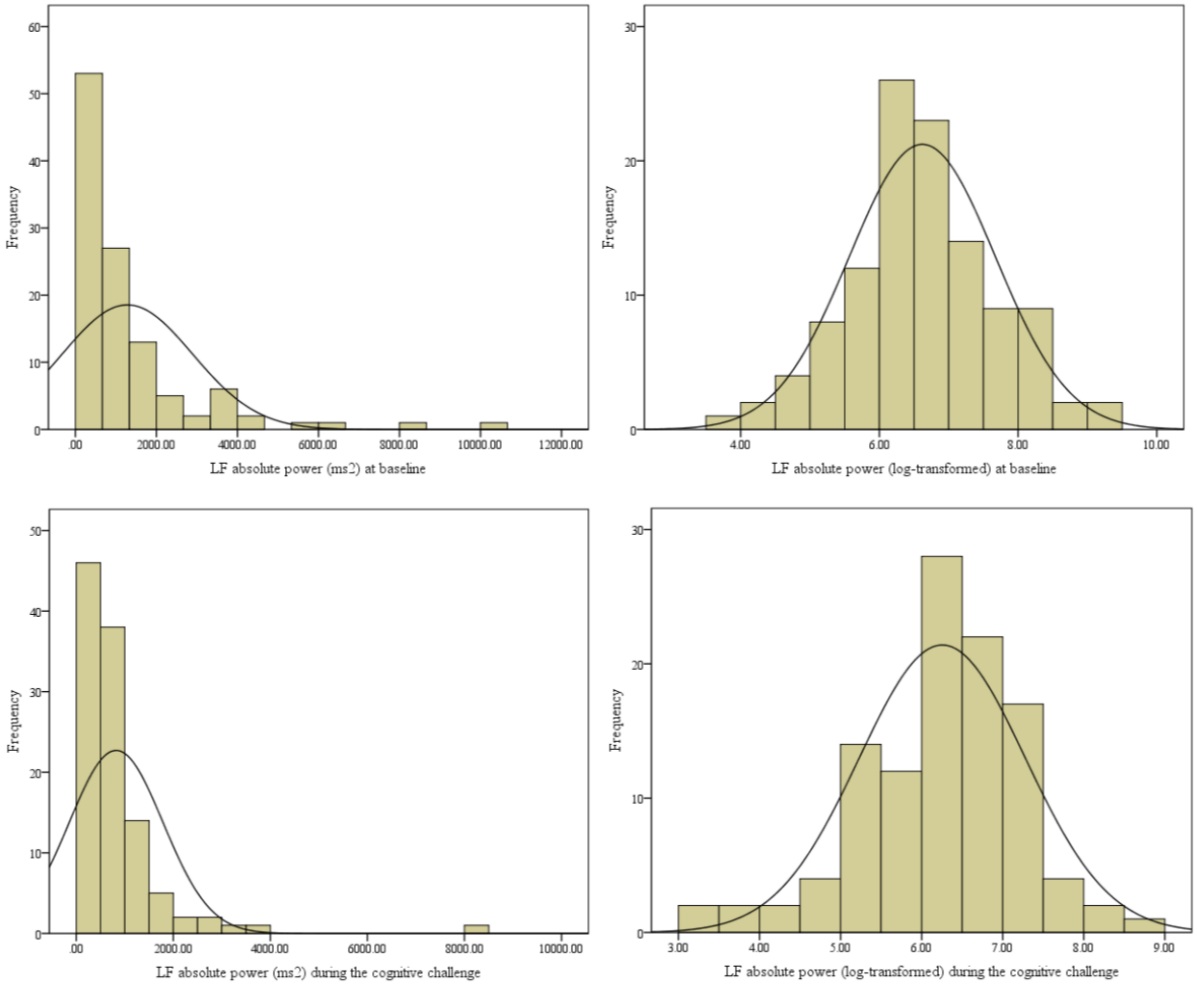

Frequency
80
60
40
20
0
.00
2000.00
4000.00
6000.00
8000.00
10000.00
HF absolute power (ms2) during the physical challenge

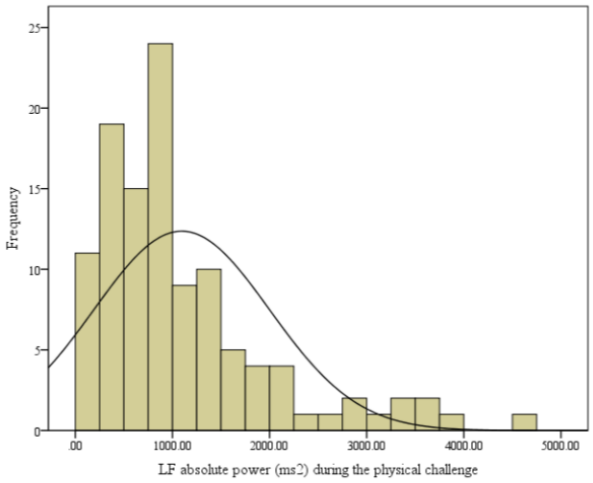

Frequency
20
15
10
5
0
2.00
4.00
6.00
8.00
10.00
HF absolute power (log transformed) during the physical challenge

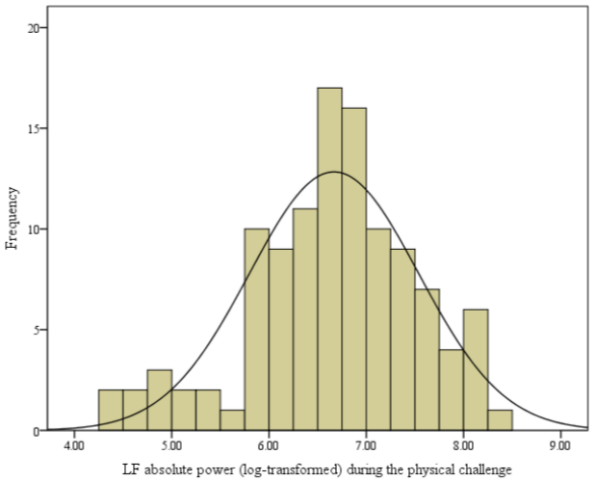

Frequency
80
60
40
20
0
.00
2000.00
4000.00
6000.00
8000.00
10000.00
HF absolute power (ms2) during the social challenge

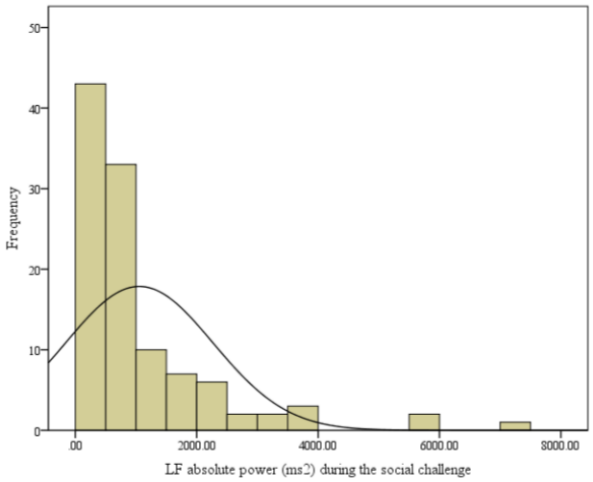

Frequency
20
15
10
5
0
.00
2.00
4.00
6.00
8.00
10.00
HF absolute power (log-transformed) during the social challenge

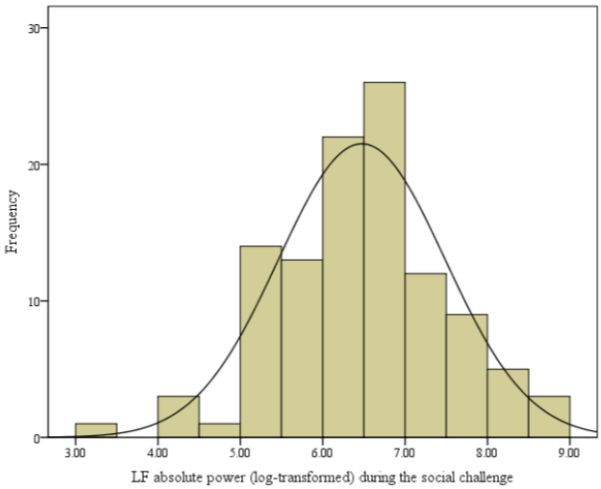
Appendix O: Frequency Histograms for Low Frequency (LF) Absolute Power (ms^2 and Log-Transformed)




Frequency
LF absolute power (ms2) during the physical challenge


Frequency
LF absolute power (log-transformed) during the physical challenge


Frequency
LF absolute power (ms2) during the social challenge


Frequency
LF absolute power (log-transformed) during the social challenge