Spring 5-13-2016

Working Memory Impairments in Chromosome 22q11.2 Deletion Syndrome: The Roles of Anxiety and Stress Physiology

Ashley F. P. Sanders
University of New Orleans, afsande2@uno.edu

Recommended Citation

Working Memory Impairments in Chromosome 22q11.2 Deletion Syndrome: The Roles of
Anxiety and Stress Physiology

A Thesis

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Master of Science
in
Psychology
Applied Biopsychology

by

Ashley F.P. Sanders

B.S. Loyola University New Orleans, 2011

May 2016

Acknowledgement

I would like to express my sincere gratitude to Dr. Elliott A. Beaton for his guidance and support throughout my study and research. Without his direction, this project would have not been possible. I would like to thank my committee members, Dr. Connie Lamm and Dr. Deidre Devier, for their invaluable feedback and encouragement. I feel very lucky to have had the opportunity to work with them. I extend my deepest appreciation to Dr. Robert Laird and David Stephenson for lending their statistical expertise and further enhancing my learning experience. Finally, I would like to thank my friends and family for their continuous support and reassurance.

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Abbreviations

Adrenocorticotropic Hormone ....ACTH
Attention Deficity Hyperactivity Disorder .... ADHD
Chromosome 22q11.2 Deletion Syndrome... 22q11.2DS
Corticotropin-Releasing Factor...CRF
Electrocardiograph ....ECG
Enzyme-Linked Immunosorbent Assay... ELISA
Full-Scale IQ ....FSIQ
Heart Rate Variability ....HRV
Hypothalamic-Pituitary-Adrenal...HPA
Interleukin 6 .... IL-6
Multidimensional Anxiety Scale for Children Second Edition: Parent ....MASC 2-P
Nonverbal Learning Disability .... NVLD
Parasympathetic Nervous System.. PNS
Respiratory Sinus Arrhythmia ....RSA
Swanson, Nolan, and Pelham Questionnaire ....SNAP-IV
Sympathetic Nervous System .... SNS
Wechsler Intelligence Scale for Children IV ....WISC-IV

Abstract

Stress and anxiety negatively impact the working memory system by competing for executive resources. Broad memory deficits have been reported in individuals with chromosome 22q11.2 deletion syndrome (22q11.2DS). We investigated anxiety and physiological stress reactivity in relation to visuospatial working memory impairments in 20 children with 22q11.2DS and 32 typically developing children ($M = 11.10$ years, $SD = 2.95$). Results indicate reduced post-stress RSA recovery and overall increased levels of cortisol in children with 22q11.2DS. Additionally, anxiety mediated the relationship between 22q11.2DS and visuospatial working memory impairment. However, there was no indication that stress response physiology mediated this association. Results suggest that anxiety exacerbates impaired working memory in children with 22q11.2DS. Thus, treatment and intervention methods for children with 22q11.2DS should address anxiety related symptomology.

Introduction

Working Memory

The working memory system temporarily stores information in a limited capacity, allowing it to be easily retrieved and manipulated (Braver, 2006). It is necessary for complex, higher-order thinking and is controlled by attentional processes (Henry, 2012). The Baddeley model of working memory consists of four parts: the phonological loop, the visuospatial sketchpad, the central executive, and the episodic buffer. The principal component of this paradigm is the central executive which ensures that cognitive resources are being allocated appropriately without interference. This system manages and integrates both the phonological loop and visuospatial sketchpad. The central executive is widely considered core to the working memory system (Baddeley, 2000, 2003; Baddeley & Hitch, 1974).

The most studied component of the working memory system is the phonological loop, which stores speech-based information. Two subcomponents comprise this system: the phonological store and the articulatory rehearsal mechanism. The phonological store is time-sensitive and passively holds auditory information, while the auditory rehearsal mechanism is used to internally recite verbal information in order to prevent decay (Henry, 2012). While the phonological store can only hold information for a few seconds, auditory rehearsal actively refreshes the information in order for it to be maintained in the phonological store. This loop allows one to maintain verbal information (Braver, 2006).

In addition to recitation, the auditory rehearsal mechanism converts visual information to speech. This is referred to as phonological/verbal recoding (Henry, 2012). In the developing child, visuospatial working memory performance improves with age. This is likely due to children's increased ability in converting visual information into a phonological code, which

translates to better maintenance of information using multiple representations. Ultimately, recoding permits visual information to enter the phonological store (Pickering, 2001).

The second component of the working memory system is the visuospatial sketchpad, and like the phonological loop, it also has limited information capacity. It is responsible for mentally manipulating and navigating through a visual mental image (Braver, 2006). The visuospatial sketchpad maintains details regarding 'what' the visual characteristics of a given stimuli are and 'where' it is located in space relative to the observer and relative to other objects (Henry, 2012). Just as verbal information is rehearsed, implicit eye movements to selective locations are believed to aid in attention-based rehearsal (Awh & Jonides, 2001). Logie (1995) describes a passive 'visual cache' that stores visual information and an active 'inner scribe' that rehearses a series of movements through space.

To consciously comprehend and incorporate new cognitive information, these short-term memory subsystems must be able to interact not only with one another but also with long-term memory. This is accomplished through the episodic buffer where information from past experiences, the phonological loop, and the visuospatial sketchpad is combined (Henry, 2012). Though the episodic buffer is also limited in its capacity, it subserves the integration of information in a multi-component fashion. For example, this system incorporates verbal and spatial material that may be temporally separated in order to create a meaningful concept. This binding of information allows for the tracking and placement of experiences into long-term memory in context which in turn facilitates learning and problem solving (Baddeley, 2000).

In developing children, these systems become more efficient over time. However, in children with neurodevelopmental disorders, atypical brain development can impede gains in efficiency and integration of memory subsystems. Furthermore, developmental challenges in

complex syndromes that are ancillary to memory in the medical, cognitive, and socioemotional domains may further influence efficient development and functioning of working memory.

Chromosome 22q11.2 Deletion Syndrome

Chromosome 22q11.2 deletion syndrome, also known as velocardiofacial or DiGeorge syndrome, is a neurodevelopmental disorder that arises from by a 1.5 to 3 megabase microdeletion on the long arm of chromosome 22. Prevalence rates range from 1:2000 and 1:4000 live births (Howley, Prasad, Pender, & Murphy, 2012). With most studies reporting an increased rate of depression, anxiety disorders, and ADHD, 22q11.2DS is also associated with high incidence of psychiatric disorders. Mortality rates for individuals with 22q11.2DS are higher than those seen in typically developing populations, ranging from 8% in infancy to 11.8% in young adulthood (Bassett et al., 2009). Kyburz and colleagues (2008) reported an overall mortality rate of 22.4% in children with both the deletion and a congenital heart defect.

Chromosome 22q11.2 deletion syndrome is associated with a broad psychiatric phenotype. However, the neurocognitive impairments in individuals with the deletion are more consistent, having a mean IQ of 75 and a diagnosis of intellectual disability around 50% (Fabbro et al., 2012; Shashi et al., 2012). Social and communication deficits are often seen in children with 22q11.2DS. Niklasson and colleagues (2001) reported high rates of social impairment symptoms of autism in children with the deletion. These deficits become more obvious as the child ages, leading them to become increasingly anxious and socially withdrawn (Swillen, Devriendt, Ghesquière, & Fryns, 2000). The presence of high anxiety has also been found to predict poorer adaptive function in children with 22q11.2DS (Angkustsiri et al., 2014). Beaton and Simon (2011) suggest that children with 22q11.2DS experience an increased occurrence of

stressors (e.g. cardiac and palatal surgeries, as well as other medical complications) during the course of their lives. These negative life events are believed to influence the commonality of anxiety and mood disorders present in children with the deletion and may contribute to an elevated risk of schizophrenia in adulthood in this population (Schneider et al., 2014; Stephenson, Beaton, Weems, Angkustsiri, & Simon, 2015).

The presence of psychotic symptoms in childhood and adolescence are believed to have prognostic significance for the development of schizophrenia-related psychopathology later in life. The presence of a chromosome 22q11 deletion is the third highest risk factor for developing schizophrenia, trailing only individuals with two schizophrenic parents or an identical twin with a schizophrenia diagnosis (Debbané, Glaser, David, Feinstein, & Eliez, 2006). In a study conducted by Baker and Skuse (2005), over half of the individuals with 22q11.2DS reported positive symptoms of schizotypy or other psychotic experiences. Also of great interest is the presence and severity of psychotic symptoms in the prodromal period in children and adolescents with the deletion. Comparable to individuals diagnosed with schizotypal personality disorder, adolescents with 22q11.2DS report elevated positive, negative, disorganized, and general prodromal symptoms, in relation to controls (Shapiro, Cubells, Ousley, Rockers, & Walker, 2011). Efficient and accurate working and long-term memory allows for mental representation and perception of experiences in the context of past, present, and future. The breakdown of systems (including working memory) that underpin this autonoetic consciousness are likely part of the etiopathology of schizophrenia (Sonntag et al., 2003; Wheeler, Stuss, & Tulving, 1997)

Cognitive and Working Memory Impairments in 22q11.2DS

Children and adolescents with 22q11.2DS display average full-scale IQ scores ranging from moderately deficient to average, with verbal IQ in the low average range (Moss et al., 1999). Approximately 60% of these individuals have a nonverbal learning disability (NVLD), as demonstrated by the significant difference in verbal and performance IQ, with a relative strength in verbal IQ (McDonald-McGinn & Sullivan, 2011). Specific deficits are seen in visual-spatial memory and complex forms of verbal recall (Woodin et al., 2001). The disparity between visuospatial and verbal memory abilities in children with 22q11.2DS do not appear to be related to IQ, suggesting that general intellectual ability is not a feasible explanation (Bearden et al., 2001). Neuroanatomical differences have also been investigated in order to explain these deficits in intellectual functioning. DeBoer and colleagues (2007) found significant correlations between reduced hippocampal volume and IQ in children with 22q11.2DS. Others have suggested reduced functional integrity of white matter as a possible explanation for these neuropsychological shortfalls in NVLD (Fuerst, Dool, & Rourke, 1995). Simon et al., (2005) concluded that deficits in visuospatial and numerical cognitive processes are largely due to a dysfunction of the posterior parietal lobe. Furthermore, anxiety has been shown to be more predictive than general intellectual function, as measured by FISQ, of age-appropriate daily living skills in children with 22q11.2DS (Angkustsiri et al., 2014; Stephenson et al., 2015). Thus, while impairments in general intellectual functioning might be expected to explain these deficits at least in-part, this is not a foregone conclusion given the probable contributing role of anxiety and stress.

While a number of studies report working memory discrepancies in children and adolescents with 22q11.2DS compared to their typically developing peers (Bearden et al., 2001;

Kates et al., 2007; Lajiness-O'Neill1 et al., 2005; Montojo et al., 2014; Simon et al., 2005), these

impairments have not been looked at in connection with their affective profile. Eysenck and

Calvo (1992) posit a theory that anxiety exhausts cognitive properties, ultimately having

deleterious effects on performance and processing efficiency. Alternatively, attentional control

theory states that anxiety disturbs the goal-driven attentional system, while amplifying the

stimulus-driven attentional system (Derakshan & Eysenck, 2009). The former refers to top-

down control of attention, while the latter refers to bottom-up processes that favor behaviorally

relevant and salient stimuli (Corbetta & Shulman, 2002).

Working memory relies on the ability to efficiently update and manipulate task-relevant

information, as opposed to passively storing (Miyake et al., 2000). Inhibition, shifting, and

updating, all which are executive functions associated with working memory, are negatively

effected the presence of anxiety (Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011). As

proposed by attentional control theory, anxiety reduces these top-down mechanisms, thereby

resulting in less attentional control. Inhibition allows one to allocate their attentional resources

to the task at hand, while ignoring task-irrelevant stimuli. However, individuals who are anxious

have a higher probability of diverting these resources to extraneous stimuli. These distractors

can either be external or internal (e.g. worry), which ultimately degrades processing efficiency

(Eysenck, Derakshan, Santos, & Calvo, 2007). Therefore, tasks that involve greater attentional

discipline also require individuals with high trait anxiety to employ more cognitive resources

(Wright, Dobson, & Sears, 2014).

Anxiety and stress have an impact on cognitive performance and memory performance in

a variety of human and animal model studies (Contarino et al., 1999; Dalgleish et al., 2003;

Harrison, Hosseini, & McDonald, 2009; Robert & Hockey, 1997; Roozendaal, 2002), and

anxiety and memory impairments are well documented in people with 22q11.2DS. Given the heterogeneous, complex, and sometimes unpredictable course of 22q11.2DS, stress likely arises from and contributes to symptomology and impairments in this population. Nevertheless, there has been little attention on the role of anxiety and stress on cognitive function in people with 22q11.2DS.

Effects of Chronic Stress on Health

Chronic stress is considered a biobehavioral catalyst for illness and overall health deficits. Consistent exposure to stressful stimuli leads to increased blood pressure and heart rate will later lead to heart disease, hypertension, and a weakened immune system, among other outcomes (Baum & Posluszny, 1999; McEwen, 2003). Cognitively, increased allostatic load is associated with synaptic and dendritic changes and suppressed neurogenesis, which results in a weakened ability for the body to properly respond to stressors (Arnsten, 2009; Brown, Rush, & McEwen, 1999; Juster, McEwen, & Lupien, 2010). Interleukin 6 (IL-6), a pro-inflammatory cytokine, acts to incite immune response after trauma. It plays a crucial role in preparing the body to react to illness as it mediates fever by increasing the body's temperature. In response to chronic stress exposure, though, the body overproduces IL-6. As an individual increases in age, this exaggerated production is associated with osteoporosis, arthritis, type 2 diabetes, and certain cancers (Kiecolt-Glaser et al., 2003). Inflammation is seen in a variety of patient populations including schizophrenia, autism spectrum disorder, Alzheimer's disease, and in those with chronic anxiety, depression, and stress (de Pablos et al., 2006; Maes et al., 1998; Rojo, Fernández, Maccioni, Jimenez, & Maccioni; Roy-Byrne et al., 2008; Saetre et al., 2007; Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Not only does stress increase the risk of

psychiatric symptoms, but increased exposure to stress can lead to serious, life-threatening effects.   Moreover, memory impairment reduces coping capacity and may contribute to anxiety and stress in a reciprocal way.

Biomarkers of Stress Reactivity and Chronic Stress Exposure

Autonomic Nervous System Function

In addition to the psychological effects, physiological responses are triggered in the presence of a stressor. The autonomic nervous system regulates homeostatic and acute stress functions and is comprised of two subdivisions: the parasympathetic (PNS) and the sympathetic nervous system (SNS). The sympathetic division controls metabolic and muscular output in response to the internal and external environment, among other functions. Referred to as the fight-or-flight response, this neuroendocrine system reacts to threatening or stressful situations by increasing heart rate and blood pressure, tensing muscles, and decreasing nonessential functions, such as digestion (Berntson, Cacioppo, & Quigley, 1993). This rapid mobilization of physiological resources and suppression of bodily function such as growth not immediately necessary for survival is a coping response to the stressor. Upon resolution of the stressor, the parasympathetic nervous system enables digestion and conserves energy when the body is at rest (Berntson & Cacioppo, 2007).

Electrical impulses generated by a subset cardiomyocytes (so-called 'pacemaker' myocytes) that spontaneously depolarize are regulated by sympathetic and parasympathetic innervations on the sinoatrial node of the heart. Heart rate variability (HRV) refers to the variation in beat-to-beat intervals. These intervals correspond to the time between R peaks (R-R) in the QRS complex of an electrocardiograph (ECG) waveform. When the PNS is active in a

healthy individual, variability tends to be higher than during sympathetic control (Michels et al., 2013). HRV has been continuously linked to stress and emotion regulation (Berntson et al., 1997; Hjortskov et al., 2004; McCraty, Atkinson, Tiller, Rein, & Watkins, 1995; Porges, 1995; Salahuddin et al., 2007; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Notwithstanding, power in the high frequency band (0.15 to 0.4 Hz) corresponds to parasympathetic activity and is associated with respiratory sinus arrhythmia (RSA). RSA refers to the oscillations in heart periods that occur in conjunction with a breathing cycle (Berntson et al., 1993)

RSA is a widely used measure of cardiac vagal control. The vagus nerve (i.e. the tenth cranial nerve) is controlled by the PNS and inhibits sympathetic upregulation of heart contraction (Rottenberg, Wilhelm, Gross, & Gotlib, 2002). In situations perceived as stressful or threatening, sympathetic upregulation of heart contractions is due to a vagal withdrawal. With the resolution of the stressor, sympathetic influences decrease by vagal induction and the organism returns back to a state of rest. This "vagal brake" allows mammals to quickly respond to their environment and return to a state of homeostasis (Scott & Weems, 2014)

According to the three circuit hierarchy of the polyvagal theory, phylogenetically older neural circuits promote active avoidance (e.g. fight-or-flight) while newer subsystems allow for social communication and engagement (Porges, 2007). These high-order adaptive behavior strategies allow mammals to successfully engage with complex and potentially stressful situations. However, poor RSA modulation can result in a reversion to phylogenetically older neural circuits associated with fear responses that result in a lack of homeostasis and heightened avoidance (Porges, 2001, 2007). Studies have consistently linked lower RSA to poor social and emotional regulation, including social anxiety and depression (Friedman & Thayer, 1998;

McLaughlin, Rith-Najarian, Dirks, & Sheridan, 2015; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996; Rottenberg, Salomon, Gross, & Gotlib, 2005)

Neuroendocrine Responses to Stress

Chronic stress is also reflected in major biochemical pathways that regulate metabolic processes. The hypothalamic-pituitary-adrenal (HPA) axis refers a collection of structures, which include the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland (Smith & Vale, 2006). Corticotropin-releasing factor (CRF) is the primary regulator of the HPA Axis. The secretion of CRF, which is synthesized and released from neurons in the paraventricular nucleus, follows a circadian pattern. CRF stimulates the corticotropic cells of the anterior pituitary, which ultimately synthesizes and releases adrenocorticotropic hormone (ACTH). Finally, ACTH stimulates the adrenal cortex and releases glucocorticoids, such as cortisol (Kandel, Shwartz, & Jessell, 2000). Through a negative feedback loop, cortisol levels are regulated to maintain homeostasis. CRF has been associated with learning and memory, feeding, reproduction, and regulation of the autonomic nervous system (Smith & Vale, 2006).

Upregulation of the HPA axis promotes increased secretion of glucocorticoids, which in turn activates glucose in the muscles and reduces sympathetically-mediated processes in an effort to conserve energy (Sotnikov et al., 2014). These stress-coping systems evolved because organisms that prioritized physiological responses that increased the likelihood of immediate survival lived to reproduce. Nevertheless, alterations in HPA functioning can follow chronic and/or extreme exposure to stress. These maladaptive changes in HPA axis functioning appear to result in two paradoxical outcomes: hypercortisolism and hypocortisolism (Heim, Ehlert, &

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Hellhammer, 2000). Miller and colleagues (2007) suggest that the HPA axis is initially activated in the presence of a stressor, resulting in increased levels of cortisol. As time since the onset of a stressor increases, there is a pattern of hypocortisolism, where cortisol levels decline below normal concentrations. Additionally, they noted that the nature of the stressor results in distinct hormonal profiles. When a stressor was more likely to cause physical harm, participants secreted higher cortisol levels throughout the day, with the exception of morning concentrations.

There appears to be significant variability in the stress-response system as a function of underlying psychopathology. Increased basal cortisol levels have been noted in youth at ultra-high risk for psychosis, while cortisol response to acute stress is blunted compared to healthy controls (Chaumette et al., 2016; Pruessner et al., 2013).

In children with anxiety and depression, there have been conflicting reports regarding HPA function. While some studies report lower basal HPA axis functioning in children experiencing internalizing symptoms, others suggest increased cortisol levels are associated with these problems (c.f. Bae et al., 2015; Dietrich et al., 2013; Granger, 1998). Longitudinal studies indicate a non-monotonic relationship between age and cortisol secretion in response to chronic stress. Children with internalizing behaviors first show a pattern of hypercortisolism after exposure to stress. However, as they age into adolescence and experience prolonged stress exposure, the HPA axis appears dysregulated, resulting in hypocortisolism (Ruttle et al., 2011). Regardless of the heterogeneous findings reported in the literature, there is ample evidence that chronic exposure to stress results in its maladaptive functioning (McEwen, 1998b).

The Current Study

Working memory impairments are well-characterized in children with 22q11.2DS (Bearden et al., 2001; Lajiness-O'Neill1 et al., 2005; Montojo et al., 2014; Simon et al., 2005). While these studies have largely focused on neuroanatomical differences, no research has investigated the roles of anxiety and stress as possible exacerbtaing factors. As outlined by Eysenck and Derakshan (2009), anxiety has deliterious effects on on the goal-driven attentional system of working memory. This ultimately breaks down the central executive system, thereby making it difficult to ignore irrelevant stimuli. Additionally, cortisol activity interacts with brain regions that are relevant to memory function. The hippocampus, which plays a crucial role in feedback regulation of cortisol release, shows an increased rate of cell death and blunted cell development in the presence of cortisol (Al'Absi, Hugdahl, & Lovallo, 2002). These compounding elements are, therefore, necessary to investigate as possible factors resulting in poor working memory in children with 22q11.2DS.

Anxiety disorders and ADHD are two of the most common diagnoses in children with 22q11.2DS, occuring in approximately 35.6% and 37% of these youth, respectively (Schneider et al., 2014). A comorbid diagnosis is not uncommon in the general population, with the Multimodal Treatment Study of Children with ADHD (1999) reporting a co-occurance at 33.5%. Children with ADHD commonly show working memory deficits, as attentional processes are degraded (Barkley, 2014). Yet, as mentioned, theory suggests that anxiety interrupts goal-driven attentional systems (Eysenck & Derakshan, 2011). As ADHD is expected to be a source of homogenous variance, we decided to use it as a covariate in our analyses in order to directly asses the heterogeneous sources of variance in the relationship between group, anxiety, stress physiology, and working memory impairment.

The overarching aim of the current study was to investigate the roles of anxiety and stress on working memory function in children with 22q11.2DS. As discussed, research shows that these children have higher levels of anxiety and a lower working memory capacity. Yet, can anxiety and stress partially explain working memroy deficits in children with 22q11.2DS? While anxiety is considered a cognitive component of worry and threat, examining stress physiology allows us to corraborate evidence suggesting that these children experience a significantly greater amount of stress and gives us potential insight into glucocorticoid mechanisms in this population.

Aim 1: To characterize the proposed relationship between psychological and behavioral symptoms.

Hypothesis 1

22q11.2DS will be positively associated with symptoms of anxiety and ADHD, and negatively associated with full scale IQ scores and working memory capacity.

Aim 2: To measure physiological indices of stress responsivity and recovery.

Hypothesis 2a

Children with 22q11.2DS will have lower baseline levels of respiratory sinus arrhythmia and higher baseline levels of cortisol.

Hypothesis 2b

Children with 22q11.2DS will show blunted cortisol reactivity and recovery compared to controls.

Hypothesis 2c

Children with 22q11.2DS will show blunted RSA reactivity and recovery compared to controls.

Aim 3: Given that children with 22q11.2DS have working memory impairments compared to typically-developing children that have not been explored in relation to anxiety, the role of anxiety and physiological indicators of stress (i.e. cortisol and RSA) will be characterized.

Hypothesis 3a

Anxiety symptoms will mediate the association between group and working memory capacity, controlling for age, sex, and ADHD symptomology.

Hypothesis 3b

Latent physiology (composed of cortisol and RSA reactivity) will mediate the association between group and working memory capacity, controlling for age, sex, and ADHD symptomology.

Method

Participants

Participants were children aged 7 to 16 years ($M = 11.4$, $SD = 2.52$) with ($n = 20$, 10 females) and without ($n = 32$, 13 female) 22q11.2DS and their parents. The majority of participants were Caucasian (82%), while the remainder were identified by their parents as Creole (7%), Hispanic (7%) and African American (4%). The presence of a 22q11.2 deletion was confirmed by fluorescence in situ hybridization. Groups did not differ based on sex composition, $X^2(1, N = 52) = 0.44$, $p = 0.51$ or age, $t(50) = 0.12$, $p = 0.09$. Participants were excluded if they head injury, central nervous system infection, and other focal neurologic abnormality. Exclusion criteria limited to typically developing participants includes a known genetic disorder, learning disorder and behavioral or other known psychiatric Disorder. Table 1 demographic characteristics of the sample.

Table 1

Demographic Characteristics and IQ Scores of the Sample

	Typically Developing	22q11.2 Deletion Syndrome
	($n = 32$)	($n = 20$)
Mean Age in Years (SD)	10.9 (2.5)	12.2 (2.4)
Gender		
% Female	41	50
Ethnicity %		
Caucasian	74.1	94.7
Creole	11.1	0
African American	7.4	0
Hispanic	7.1	5.3
Mean FSIQ (SD)	107.1 (13.4)	72.2 (9.2)

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Procedure

As part of a larger ongoing study, families were recruited via the Louisiana 22q Support Network, social media (e.g. Twitter and Facebook), fliers posted around the New Orleans area, and word-of-mouth. Families spent two and a half days participating in the research activities. Upon arrival, families were briefed on all tasks and procedures to be conducted and gave informed consent. Children signed assent forms to indicate that they understood and wanted to continue with the study. The visit consisted of parents and children filling out questionnaires and completing computer-based tasks. All children completed the Wechsler Intelligence Scale for Children IV (WISC-IV).

Measures

Physiological measures

Cardiac and hemodynamic measures were continuously collected during task participation with Biopac MP150 hardware and Acq*Knowledge* 4 (BIOPAC Systems, Inc., Goleta, CA) software and was sampled at 1000 Hz. Electrocardiogram (ECG) recordings were collected using a Lead II configuration (right clavicle, left clavicle, and left lower torso) and three pre-gelled disposable Ag/AgCl electrodes. A respiration belt transducer was strapped around the abdomen of the participant in order to obtain a respiration signal. Temperature readings were be collected using a Biopac TSD202B temperature probe adhered to the participant's non-dominant hand. Respiratory sinus arrhythmia was calculated with Acq*Knowledge* 4 software using the time-domain peak-and-valley method. A band pass filter between 0.5 and 35 Hz, using 8000 coefficients was applied to the ECG waveform.

Hormone measures

Five saliva samples were collected 1) prior to beginning the tasks, 2) prior to beginning the Math Countdown Task, 3) after the Math Countdown Task/prior to the Math Problems Task, 4) after the Math Problems Task, and 5) after a 15 minute calming period. Participants deposited saliva in 2 mL microcentrifuge tubes. Samples were be frozen immediately at -80 °C. Saliva was assayed for cortisol using Salimetrics enzyme-linked immunosorbent assay (ELISA) kits and were run in duplicate.

Math Stress Computer Task

The Math Task was divided into two parts: the *Math Countdown Task* and the *Math Problems Task*. Each section began with a practice trial before continuing to the real task. The *Math Countdown Task* required the participant to begin at 300 and mentally subtract 7 from each correct answer given. Three possible answers were displayed and a countdown clock ranging from 30 to 15 seconds was shown at the bottom of the screen. If the participant selected an incorrect answer or went over time, they were required to return to the beginning of the task and start again. This section lasted 8 minutes. During the *Math Problems Task*, the participant completed a series of math problems ranging from simple addition and subtraction to geometry and trigonometry. As with the *Math Countdown Task*, three possible answer choices were given, with a countdown clock ranging from 15 to 30 seconds displayed at the bottom. This section was dynamically adjusted for performance and lasted a total of 8 minutes. For this study, physiological and hormone measures taken during the task were used as an indicator of stress response and recovery.

Shapes Working Memory Computer Task

The *Shapes Working Memory Task* presented the participant with eight empty squares surrounding a central focus ("+") (See Figure 1). Different geometric shapes appeared in one of the eight squares for a total of 2000 ms. After the presentations, one shape was displayed at the central focus location. The participant was instructed to tap the empty square where that same shape was previously presented. The practice round consisted of two shapes and two trials. The real task began with two shapes and displayed a maximum of eight shapes. There were four trials per level. Each level was dynamically adjusted for performance. If the participant chose correctly at least 65% of the time, they continued onto the next level. If they chose correctly less than 65% of the time, the task discontinued. For this study, scores in the format of *Level Reached.Percent Accuracy* (i.e. 5.75) were used as a measure of working memory capacity.

Figure 1
Shapes Task Diagram
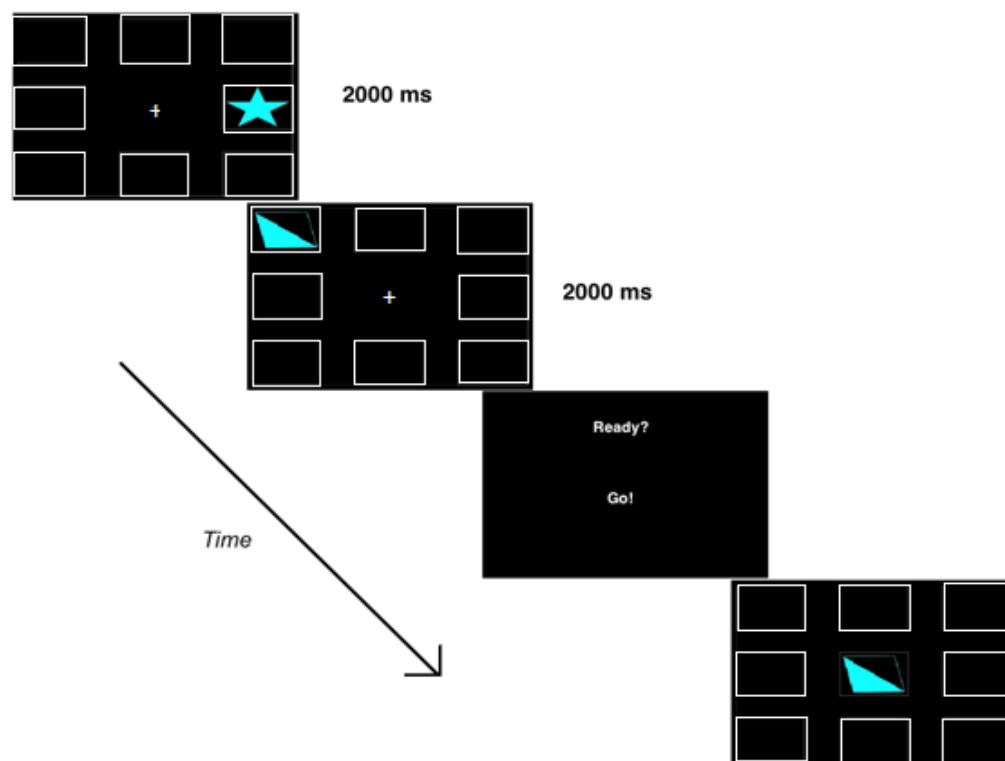
Baseline Motor Task

The *Baseline Motor Task* presented participants with six landscapes. Birds appeared at random locations on a screen. The participant was instructed to press a green button whenever they saw a bird. Bush and colleagues (2011) indicated that "stress reactivity" adjusted for psychomotor activity was incongruent with traditional, resting reactivity. The stress task in this study required the subject to elicit a motor response (i.e. pressing a button). Therefore, this study implemented the baseline motor task instead of a resting baseline in order to account for the possible confound of psychomotor activity.

Stress Recovery Period

The *stress recovery period* consisted of a 15-minute resting state. Participants remained seated while watching a calming video of underwater scenes.

Multidimensional Anxiety Scale for Children Second Edition: Parent (MASC 2-P)

The MASC 2-P (March, 2012) is a 50-item parent report questionnaire that assesses the presence of anxiety-related symptoms in children aged 8 to 19 using a four-point scale (0 = *never* to 3 = *often*). The form yields a total score, an anxiety probability score, and scales for problems including: *Separation Anxiety/Phobias, GAD Index, Social Anxiety, Obsessions & Compulsions, Physical Symptoms, and Harm Avoidance*. The parent scale reports good internal consistency (α = 0.89) and good test-retest reliability (α = 0.80 to 0.93). Total T-scores were used as an indicator of anxiety-related symptoms.

Swanson, Nolan, and Pelham Questionnaire (SNAP-IV)

The SNAP-IV Rating Scale (Swanson et al., 1983) is a parent-report questionnaire which contains items from the DSM-IV criteria for Attention Deficit/Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD). Statements are rated on a four-point scale (0 = *not at*

all to 3 = *very much*). The *SNAP-IV* also contains items from other *DSM-IV* disorders which may overlap with or masquerade as symptoms of ADHD, such as conduct disorder, Tourette's, OCD, anxiety disorders, personality disorders, mania, depression, and PTSD (Swanson, 1992). Bussing et al. (2008) reports excellent overall parent rating reliability ($\alpha = .94$). Internal consistency for specific domains range from acceptable to good ($\alpha = 0.88$ to 0.89 for inattentive, $\alpha = 0.76$ to 0.80 for hyperactive/impulsive, and $\alpha = 0.87$ to 0.90 for ODD). For this study, the sum of inattentive and hyperactive/impulsive scores were used as an indicator of ADHD-like symptoms.

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)

The *WISC-IV* (Wechsler, 2003) is a cognitive ability assessment of verbal comprehension, perceptual reasoning, working memory, and processing speed. Composite scores are reported to have good internal consistency ($\alpha = 0.88$) and good test-retest reliability ($\alpha = 0.80$). Inter-rater reliability is excellent ($\alpha = 0.98$). The WISC-IV was used to assess general intellectual functioning in this study.
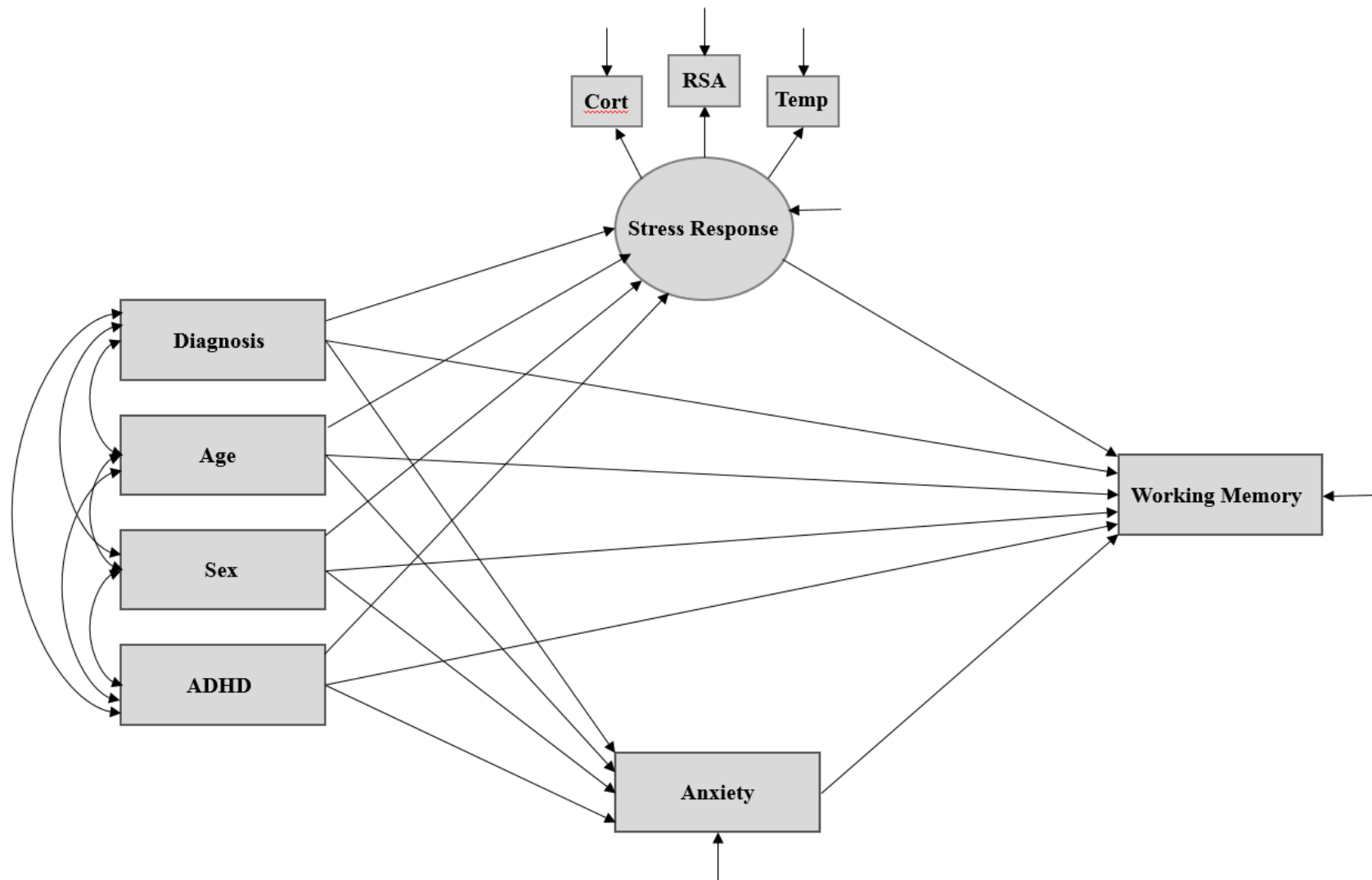

Statistical Analyses

Prior to analysis, the variables: anxiety, ADHD, IQ, working memory capacity, RSA, and cortisol were screened for missing data, normality of distribution, univariate outliers, and multivariate outliers. A series of independent samples t-test were conducted to examine whether children with 22q11.2DS differed from typical controls on levels of anxiety, ADHD, FSIQ, working memory capacity, baseline RSA, and baseline cortisol using IBM SPSS Statistics version 23. In order to test the hypothesis children with 22q11.2DS will show blunted cortisol reactivity and recovery compared to typically developing children, a 2 (group) by 3 (time)

repeated measures analysis of variance (ANOVA) was conducted. To test the hypothesis that

children with 22q11.2DS will show blunted RSA reactivity and recovery compared to controls, a

second 2 (group) by 3 (time) repeated measures ANOVA was conducted.

A mixed variable structural equation model was created in *Mplus* (v. 1.4, Muthen &

Muthen) to test the mediating roles of anxiety and physiology in the association between group

and working memory impairment (see Figure 2). The three observed variables of cortisol, RSA,

and temperature reactivity were used to create the latent variable of Stress Response, while the

MASC 2-P Total T-score as used as the observed variable of Anxiety. Sex, Age, and ADHD

symptoms were entered as covariates in the model. Parameter estimation was assessed through

maximum likelihood, and overall fit of the model was measured by examining various fit

indices, including Chi-square, comparative fit index (CFI), the root mean square of

approximation (RMSEA) and 90% confidence intervals. In order to test the indirect effect, a

95% bootstrap confidence interval was utilized. Bootstrapping is a non-parametric technique

that employs resampling and replacement 1000 times, in the current study (Bollen & Stine, 1990;

Shrout & Bolger, 2002).

Figure 2
Mixed Variable SEM Model

Results

Prior to analysis, the variables: anxiety, ADHD, IQ, working memory capacity, RSA, and cortisol were screened for missing data, normality of distribution, univariate outliers, and multivariate outliers. Analysis of cases with missing data indicated that the missing data appeared to be random, as the missing values were not related to other variable scores. To inspect normality and identify outliers, analysis of univariate distribution was performed. Results indicated that the distribution of baseline cortisol concentration values were positively skewed. To account for the substantial skew, a log transformation was applied. Additionally, one extreme outlier was identified for the anxiety score distribution. This value was removed, as it did not appear to be representative of the sample. Finally, the Mahalanobis distance test, using $p < 0.001$, (*i.e.* Chi-square (6) = 22.5) was conducted to test for multivariate outliers among the scales. No multivariate outliers were identified.

To test the hypothesis that 22q11.2DS will be positively associated with symptoms of anxiety and ADHD and negatively associated with FSIQ and working memory capacity, a series of independent samples t-tests were conducted. To correct for multiple comparisons, a bonferroni correction was applied ($p < 0.008$). Parents of children with 22q11.2DS reported significantly greater levels of anxiety and ADHD symptomology in their children compared to parents of typically developing children. Additionally, children with 22q11.2DS scored significantly lower on the *WISC-IV* FSIQ and shapes working memory task. To test the hypothesis that children with 22q11.2DS will have lower baseline levels of RSA and higher baseline levels of cortisol compared to typically developing controls, bivariate correlations were conducted. Consistent with the hypothesis, children with 22q11.2DS had significantly higher levels of baseline cortisol compared to controls. Yet, there was no significant difference in baseline levels of RSA between the two groups (see Table 2).

Table 2

Independent samples t-test comparing variable means between groups

|	Typically Developing		22q11.2 Deletion Syndrome				
	Mean	SD	Mean	SD	*t*	*df*	*p*
ADHD	8.24	7.15	26.28	10.3	-6.43	37	.000
FSIQ	107.07	13.42	72.21	9.24	9.92	47	.000
Anxiety	49.18	10.68	64.95	10.89	-5.00	46	.000
Working Memory Score	4.26	1.50	2.97	1.10	3.43	45.38	.001
Baseline Cortisol	-1.07	0.19	-0.90	0.25	-2.85	49	.006
Baseline RSA	3.96	0.45	3.85	0.90	0.49	22.15	.631

Note: RSA and cortisol values were log transformed. *p < 0.008.*

To test the hypothesis that children with 22q11.2DS will show blunted cortisol reactivity and recovery compared to typically developing children, a 2 (group) by 3 (time) repeated measures analysis of variance (ANOVA) was conducted. Table 3 presents the means across the assessment points for both groups. Mauchly's test indicated that sphericity could not be assumed. Therefore, the Greehouse-Geisser procedure was used to modify degrees of freedom. Contrary to the hypothesis, results indicated no significant main effect of time, $F(1.53, 73.55) = 0.06$, $p = 0.903$. However, between-subjects results indicated a significant effect of group, $F(1,48) = 14.25$, $p < .001$, with children with 22q11.2DS showing higher overall levels of cortisol concentration at each time point. There was no group by time interaction, $F(1.41,67.78) = 0.17$, $p = 0.77$ (see Figure 3).

Table 3
Means and standard errors of cortisol levels over time

	Baseline			Math Task			Recovery		
	n	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*
TD	31	-1.073	0.038	31	-1.077	0.038	31	-1.080	0.039
22q11.2DS	20	-0.886	0.049	19	-0.876	0.049	20	-0.860	0.050

Figure 3
*Cortisol levels during baseline, math task, and recovery period*
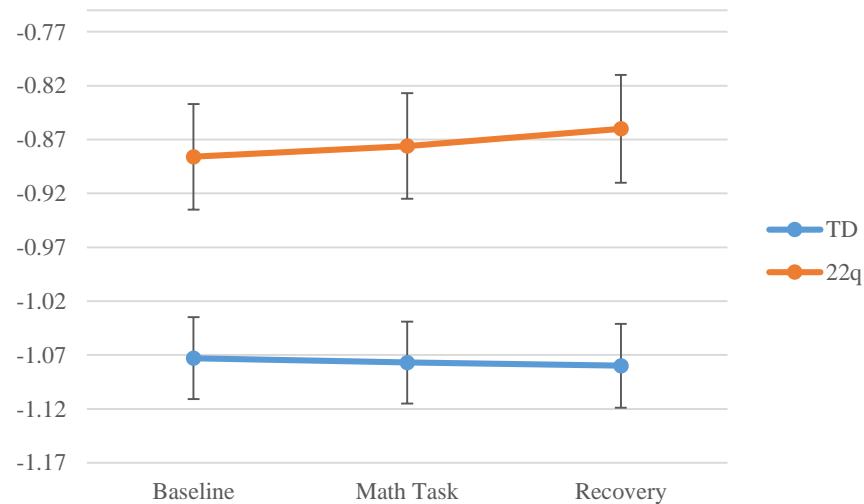
A second 2 (group) by 3 (time) repeated measures ANOVA was performed in order to test the hypothesis that children with 22q11.2DS will show blunted RSA reactivity and recovery compared to controls. Table 4 shows the means across assessment points for both groups. Mauchly's test indicated that sphericity could be assumed. Results indicated a significant main effect of time, $F(2,88) = 7.37$, $p < 0.01$, but no main effect of group, $F(1,44) = 0.23$, $p = 0.88$. Additionally, there was no group by time interaction, $F(2,88) = 0.09$, $p = 0.91$. Follow-up pairwise comparisons indicated a significant RSA recovery for typically developing controls ($p < 0.05$) but not for children with 22q11.2DS ($p = 0.16$) (see Figure 4).

Table 4
Means and standard errors of RSA levels over time

|	Baseline			Math Task			Recovery		
	n	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*
TD	31	4.00	0.11	30	4.04	0.11	30	4.18	0.11
22q11.2DS	18	3.95	0.15	17	4.04	0.15	18	4.16	0.14

Figure 4
RSA levels during baseline, math task, and recovery period
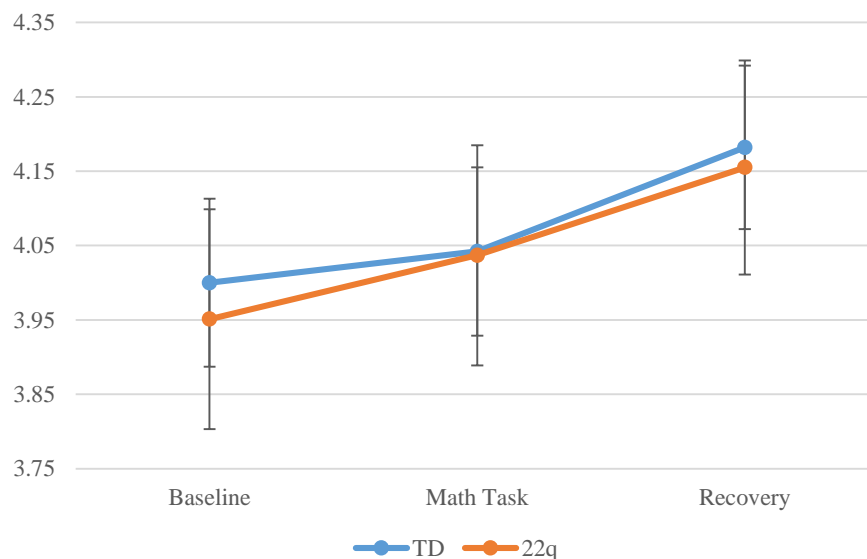
To test the mediating roles of anxiety and latent stress response in the association between group and working memory impairment, a mixed structural equation model was created in Mplus Version 7.4 (Muthen & Muthen). The three observed variables of cortisol reactivity, RSA reactivity, and temperature reactivity were used to create the latent variable of Stress Response, while the MASC 2-P Total T-score was used as the observed variable of Anxiety. Sex, Age, and ADHD symptoms were entered as covariates in the model. Parameter estimation of the model was conducted using Maximum Likelihood (ML) estimates. Overall fit of the model was assessed using the various fit indices, $X^2(12) = 15.08$; $p = 0.24$; RMSEA = 0.082; CFI = 0.93; SRMR = 0.09. These values indicate good fit of the model.

The total effect of group on working memory capacity, controlling for age, sex, and ADHD symptomology, was not significant, $\beta = -1.15$, $p = 0.09$. Kenny and Judd (2013) indicate that since c (i.e. the total effect) and c' (i.e. the direct effect) have relatively low power compared to the indirect effect, it is highly possible that c will not be statistically significant. The direct effect of group on working memory capacity was also not significant, $\beta = -0.24$, $p = 0.78$. However, the specific indirect effect of group on working memory capacity via anxiety was significant, $\beta = -1.15$, $p = 0.04$, with a 95% bootstrapped confidence interval (CI) -2.05 to -0.23. The specific indirect effect of group on working memory capacity via stress response, however, was not significant, $\beta = 0.24$, $p = 0.60$, with a 95% bootstrapped CI -0.20 to 1.21. Results indicate that, contrary to the hypothesis, latent stress response did not mediate the relationship between group and working memory capacity. However, complete mediation through anxiety was demonstrated (see Figure 5).

Figure 5
Mixed Variable SEM with standardized coefficients
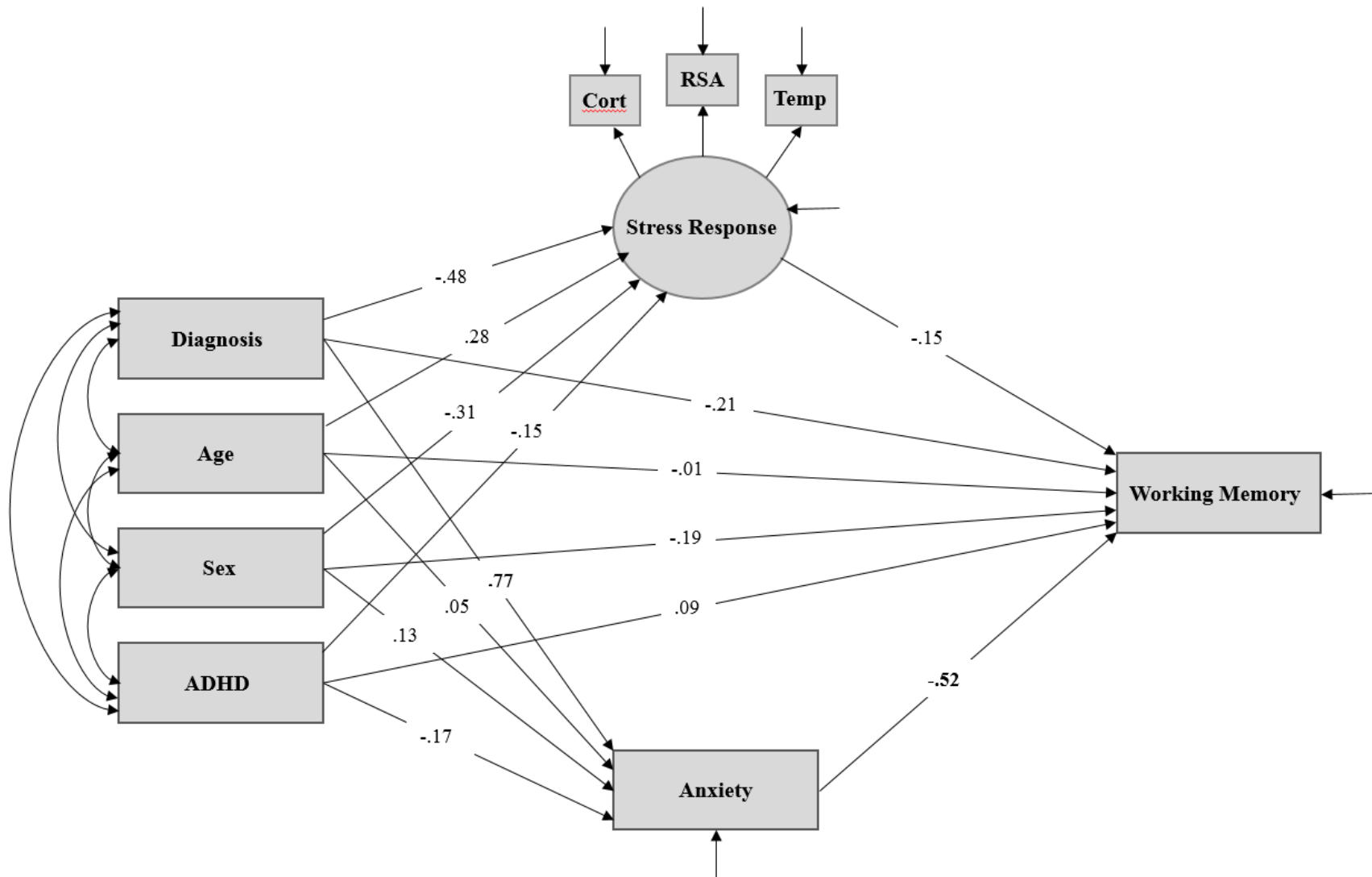
Discussion

This study was designed to address gaps in the existing research investigating associations among anxiety, physiology, and working memory capacity in children with 22q11.2DS. Consistent with hypotheses, parents of children with 22q11.2DS reported significantly higher levels of anxiety and ADHD symptomology in their children compared the control group and those parents' perceptions of their typically developing children.   These findings are in accordance with past studies that report a heightened rate of anxiety disorders and ADHD in individuals with 22q11.2DS (Angkustsiri et al., 2012; Antshel et al., 2010; Gothelf et al., 2013; Green et al., 2009; Hooper et al., 2013; Niklasson, Rasmussen, Óskarsdóttir, & Gillberg, 2009; Philip & Bassett, 2011; Schneider et al., 2014). As noted previously, the commonality of anxiety disorders in children with 22q11.2DS has been linked to stressors associated with early traumatic exposure, difficulties in social assimilation, and differential genetic and neural profiles (Beaton & Simon, 2011). Candidate genes and neurological abnormalities, such as COMT Val/Met variations and patterns of reduced white matter integrity in the frontal and parietal lobes, have also been associated with the increased prevalence of ADHD in this population (Gothelf et al., 2007; Simon et al., 2008).

Children with 22q11.2DS also scored significantly lower on FSIQ and the shapes working memory task, consistent with previous research (Kates et al., 2007; Lajiness-O'Neill1 et al., 2005; McDonald-McGinn & Sullivan, 2011; Moss et al., 1999; Simon et al., 2005; Woodin et al., 2001). The neuropsychological profile of children with 22q11.2DS is markedly varied. While gross intelligence scores range from moderately deficient to average, verbal IQ scores are significantly higher than performance IQ scores (Simon et al., 2002; Sobin et al., 2005; Swillen et al., 1997; Woodin et al., 2001). This pattern is echoed by documented visuospatial working memory deficits. Campbell and colleagues (2010) reported that, compared to FSIQ scores,

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children with 22q11.2DS scored significantly lower than expected on visual but not verbal memory tasks. To date, research has primarily focused on altered brain networks as the possible cause of memory deficits in this population, while little attention has been paid to the potential exacerbating roles of anxiety and stress.

A particularly novel aspect of this study is the characterization of physiological and hormonal profiles in children with 22q11.2DS. While the findings did show significantly higher baseline cortisol levels in these children, baseline RSA values did not differ from controls. Additionally, we found no significant changes in either RSA or cortisol reactivity, or cortisol recovery in the two groups. Nevertheless, the data indicates that RSA recovery from the math stressor task was only significant for typical controls, but not for children with 22q11.2DS. Typically, when a stressful situation is resolved, parasympathetic activation takes over to return the body back to homeostasis. This quick return to baseline is indicative of a flexible and efficient stress recovery system. However, an inability to return to homeostasis is suggestive of allostatic load, which results from a persistently overactive or underactive stress response system (McEwen, 1998a) Additionally, reduced cardiovascular recovery is associated with negative affect and chronic stress and anxiety (Chida & Hamer, 2008).

Though no differences in cortisol reactivity and recovery in relation to the tasks were found, the overall increase in salivary cortisol levels at all three time points suggests potentially abnormal HPA axis functioning. Cognitive deficits, such as selective attention and memory impairment, have repeatedly been associated with corticosteroids (Lupien et al., 1994; Lupien et al., 1998; Starkman, Gebarski, Berent, & Schteingart, 1992; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). While varying causes have been linked to elevated cortisol levels, a variety of studies indicate that chronic stress exposure and anxiety lead to HPA axis

dysregulation (Boudarene, Legros, & Timsit-Berthier, 2001; Ruttle et al., 2011; Takahashi et al., 2005; van Eck, Berkhof, Nicolson, & Sulon, 1996).   The present salivary cortisol findings are thus likely biomarkers of allostatic load in children with 22q11.2DS. While short-term release of cortisol is beneficial in response to stress, chronic excess leads to a compromised immune system and hippocampal dysfunction (McEwen, 1998a). Additionally, increased basal cortisol levels contribute to a persistent state of hypervigilance, where the individual is on constant alert to detect danger. Ultimately, this may inhibit the ability to discern between threatening and non-threatening stimuli (Sapolsky, 1990).

Finally, we investigated the mediating roles of anxiety and stress reactivity in the relationship between 22q11.2DS and impaired working memory. Physiological stress reactivity did not mediate 22q11.2DS and working memory capacity. However, our results suggest that anxiety does mediate this relationship. These findings are congruent with existing theories which suggest that anxiety has deleterious effects on attentional control and processing efficiency (Derakshan & Eysenck, 2009; Eysenck & Calvo, 1992). Anxious individuals show difficulties in attending to task-relevant stimuli. A lack of inhibition results in extraneous stimuli, whether it be internal or external, having greater salience (Eysenck et al., 2007). Shackman and colleagues (2006) suggest that anxious arousal uniquely disturbs visuospatial working memory, as both compete for resources in the right prefrontal cortex and posterior parietal cortex. This effect may be further intensified, as reductions in gray matter volume have been noted in regions of the posterior parietal lobes and prefrontal cortex in children with 22q11.2DS (Gothelf et al., 2011; Shapiro, Takarae, Harvey, Cabaral, & Simon, 2012).

Limitations and Future Directions

Results of this study should be interpreted within the context of known limitations. First, the relatively small and unequal sample sizes may have negatively impacted the ability to detect significant differences both between and within groups. However, this constraint is not uncommon, as recruitment of participants with a relatively rare syndrome (1 in 4000 to 6000 live births) poses significant challenges. Second, we used parental report measures, instead of self-report. Since our sample consisted of a wide age range (7-16 years), we felt that parent-report may give a more reliable account of the child's behavior. However, this data is subject to potential bias, and the inclusion of a secondary reporter (e.g. teacher) could provide additional information. Additionally, future research comparing self- and parent-report data may provide insight into differences of self and observer recognition in children with 22q11.2DS.

Third, as noted previously, our sample consisted of a wide age range. With the vast developmental changes that occur between this period of time, future investigation should attempt to age-match participants and controls in order to efficiently account for these variations. Lastly, using a motor-matched baseline may have activated sympathetically-mediated processes that are not reflective of a true pre-stress state. As shown in our results (see Table 2), RSA values for both children with 22q11.2DS and typically developing controls during baseline were lower than during the math task. This outcome may have been due to the effect of attentional demand, as Porges and Raskin (1969) reported reduced heart rate variability during tasks requiring continued attention. Therefore, our results may have not been truly indicative of a physiological stress response in the absence of a true resting baseline rather than the non-stressful motor baseline task used in the present study. Also, the task may not have been that stressful compared to other unaccounted for stressors resulting in a ceiling effect in the salivary cortisol measures. Finally, the lack of clear differences in physiological stress reactivity in the

context of higher levels of anxiety may indicate that the physiological costs of higher anxiety are not yet evident in these children as a group.

Implications

Though limitations are present, our findings still have important implications for future research and translational work. While impaired memory has been well documented in children with 22q11.2DS (Bearden et al., 2001; Kates et al., 2007; Lajiness-O'Neill1 et al., 2005; Montojo et al., 2014; Simon et al., 2005; Woodin et al., 2001), our study is unique in identifying the potential exacerbating effect of anxiety. The importance of an efficient working memory system cannot be overstated. Its effects permeate every aspect of our lives, and it is, therefore, crucial to identify factors that are both deleterious and beneficial to its operation. A meta-analysis conducted by Fusar-Poli and colleagues (2012) found that, while individuals at ultra-high risk (UHR) for psychosis had significant impairments in working memory compared to healthy controls, those UHR individuals who later transitioned into psychosis displayed an even more diminished working memory capacity than UHR individuals who did not. Given the 25- to 30-fold increased risk for schizophrenia in individuals with 22q11.2DS, the identification of mediating factors that are amenable to treatment, such as anxiety, is particularly significant. These findings have great potential to inform clinical research into interventions and intervention efficacy that specifically target anxiety in children with 22q11.DS and other neurodevelopmental disorders.

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Vita

Ashley Sanders graduated from Loyola University New Orleans (2011) with her B.S. in Biological Sciences. She was accepted into the graduate program at the University of New Orleans in 2014 where she is currently pursuing her Ph.D. in Applied Biopsychology under Dr. Elliott Beaton. There, Ashley is examining the effects of stress and anxiety in children with Chromosome 22q11.2 Deletion Syndrome. Specifically, she is interested in the physiological and hormonal biomarkers of allostatic load in children at ultra-high risk for psychosis.