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Theory of mind in youth and emerging adults with chromosome 22q11.2 deletion syndrome, with and without comorbid mood disorder

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Theory of Mind in Youth and Emerging Adults with Chromosome 22q11.2 Deletion Syndrome, With and Without Comorbid Mood Disorder

by

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Abstract

Mood disorders are some of the most commonly diagnosed psychiatric disorders in childhood and adolescence. Major Depressive Disorder (MDD) and Bipolar Disorder (BPD) have become more widely recognized in children and adolescents in recent years and are especially common in individuals with chromosome 22q11.2 deletion syndrome (22q11.2DS). Disruptions in social functioning are a common feature of mood disorders, including social withdrawal and loss of interest in activities that the individual typically experiences as pleasurable (anhedonia). Studies of individuals with 22q11.2DS also show they experience difficulty with social functioning, as well as social cognition, visuospatial, and executive functioning tasks. Studies of theory of mind (ToM) ability in youth and emerging adults with 22q11.2DS and comorbid mood disorder remain elusive, and a better understanding of whether or not social cognition plays a role in the development of mood disorders may help provide a target area for treatment. This study investigated the social, visuospatial, ToM, and executive functioning abilities of 15 youth and emerging adults with 22q11.2DS who met inclusion criteria for mood disorders and 46 individuals with 22q11.2DS with no mood disorder. These results were compared with the results from 22 unaffected sibling and 26 unaffected community controls.

A multiple mediator model examining the contributions of visuospatial, social, ToM, and executive functioning to a diagnosis of mood disorder indicated that social functioning was the only significant mediator. Youth and emerging adults with 22q11.2DS and a comorbid mood disorder did not demonstrate greater deficits in visuospatial, ToM, or executive functioning skills relative to individuals with 22q11.2DS only. However, youth and emerging adults with 22q11.2DS and comorbid mood disorder did show greater social

deficits on both the SRS and VABS-II Socialization Index. Correlational analyses demonstrated few significant associations between visuospatial and adaptive functioning, while several significant moderate positive associations were found between executive and adaptive functioning, particularly in the group of individuals with 22q11.2DS and no mood disorder. ToM performance was not significantly associated with adaptive functioning measures. Results confirmed that greater deficits in social functioning were associated with mood disorder diagnosis, and highlight the importance of early social skills intervention for individuals with 22q11.2DS.

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Chapter 1: Introduction and Background

Chromosome 22q11.2 deletion syndrome (22q11.2DS), also known as velo-cardio-facial syndrome (VCFS), or DiGeorge syndrome, is a genetic neurodevelopmental disorder that occurs as a result of an interstitial deletion of 40-50 genes on the long arm of chromosome 22 (Ryan et al., 1997). The deletion is associated with a myriad of clinical features, several of which co-occur; however, each individual with 22q11.2DS demonstrates a distinct phenotype likely dependent on the specific genes affected. Chromosome 22q11.2DS affects approximately one in every 5,950 live births (Botto et al., 2003), although more recent research estimates a higher rate (Gothelf, 2007). The deletion can occur in one of two ways. The *de novo*, that is, present for the first time, deletion occurs in most cases of 22q11.2DS, but familial inheritance is responsible for about 15% of 22q11.2DS cases (Swillen et al., 1998). As a result of the deletion, individuals with 22q11.2DS demonstrate various distinctive facial characteristics, palatal abnormalities, and also tend to have a range of cardiac anomalies.

Physical Characteristics Associated with 22q11.2DS

Some of the more common physical characteristics of 22q11.2DS include cardiac and craniofacial anomalies. Cardiac malformations often seen in cases of 22q11.2DS include ventricular septal defect, coarctation of the aorta, and aortic valve anomalies. Craniofacial anomalies include structurally asymmetric faces, microcephaly, cleft palate, and small or congenitally missing teeth (Shprintzen, 2000). Although distinct facial features and cardiac defects are characteristic of the disorder, a diagnosis of 22q11.2DS is not given until confirmed via genetic testing known as fluorescence *in situ* hybridization (FISH; Driscoll, Budarf, & Emanuel, 1992). In this procedure, a fluorescently labeled sequence of DNA nucleotides is examined. This sequence is used as a probe to determine the presence or

absence of a chromosomal deletion in area 22. If two copies of each chromosome are present, two signals appear (as in a typical individual); however, if only one copy of a chromosome is present, fluorescence is seen in only one signal, indicating a chromosomal deletion (Driscoll, Budarf, & Emanuel, 1992). Diagnosis of 22q11.2DS is also being confirmed with Affymetrix GeneChip microarray genotyping technology. Currently in its sixth version (Affy6), this method involves the use of gene chip, which determines whether perfect gene pairs are present or absent (Gautier, Cope, Bolstad, & Irizarry, 2004).

Neuropsychological and Psychiatric Factors Associated with 22q11.2DS

In addition to distinctive physical characteristics, individuals with 22q11.2DS often experience learning difficulties. Many studies of children and adults with 22q11.2DS have shown a distinct neuropsychological profile, consisting of a low average Full Scale IQ (FSIQ) in the preschool years that can decrease to borderline scores in the elementary and secondary school years (Golding-Kushner, Weller, & Shprintzen, 1985; Shprintzen, 2000; Swillen et al., 1997). FSIQ scores are quite variable among the 22q11.2DS population, with up to 45% experiencing mild intellectual disability (Moss et al., 1999; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2002; Swillen et al., 1997). In addition, a significant number of individuals with 22q11.2DS show a discrepancy between verbal comprehension and perceptual reasoning abilities, favoring the verbal domain (De Smedt et al., 2007; Golding-Kushner et al., 1985; Lajiness-O'Neill et al., 2006; Moss et al., 1999; Niklasson et al., 2002; Shprintzen, 2000; Swillen et al., 1997).

Two studies (De Smedt et al., 2007; Swillen et al., 1997) have attempted to explain the variability of FSIQ findings in light of the type of deletion that occurs. Swillen and colleagues (1997) compared IQs of children with *de novo* vs. familial deletions, and

discovered a higher incidence of familial deletions in a group of children with intellectual disability, i.e., lower IQ. When parental educational level (mother and father) was included in an analysis of covariance examining the relationship of child IQ with parental educational level, the mean FSIQ of familial cases was not significantly lower than the mean for *de novo* cases; however, when corrected for the educational level of the father only, the mean FSIQ of the cases with familial deletions was significantly lower than the mean FSIQ of the *de novo* cases (Swillen et al., 1997). De Smedt and colleagues (2007) added 66 individuals with 22q11.2DS to the previous study, in an effort to further explore the *de novo* versus familial deletion differences. The authors described similar results, in that children with a familial deletion had significantly lower FSIQ scores than children with a *de novo* deletion, which they attributed to higher educational levels, and therefore greater intellectual ability, in the parents of children with *de novo* deletions (De Smedt et al., 2007).

Research into the neuropsychological profile associated 22q11.2DS has also shown that many of the phenotypic variations of 22q11.2DS involve a psychiatric component (Niklasson & Gillberg, 2010; Shprintzen, 2000; Simon et al., 2002; Swillen et al., 1997). As such, individuals with 22q11.2DS experience high rates of psychiatric disorders. For example, Major Depressive Disorder (MDD) and Dysthymia are common in late childhood and adolescence, with rates ranging from 12-64% in the 22q11.2DS population (Antshel et al., 2010; Arnold, Siegel-Bartelt, Cytyrnbaum, Teshima, & Schachar, 2001; Baker & Skuse, 2005; Jolin, Weller, & Weller, 2012). Bipolar Disorder (BPD) was originally believed to be more common in adolescents and emerging adults with 22q11.2DS (Papolos et al., 1996); however, a follow up studies have questioned this result due to the difficulty that has been encountered distinguishing manic symptoms from those of Attention Deficit/Hyperactivity

Disorder (ADHD) (Aneja et al., 2006; Shprintzen, 2000). Rates of anxiety disorders, particularly specific phobias, have been found in 34-62% of 22q11.2DS cohorts (Antshel et al., 2006; Baker & Skuse, 2005; Fabbro, Rizzi, Schneider, Debanne, & Eliez, 2012; Shprintzen, 2000; Tang et al., 2013). Rates of Autism Spectrum Disorder (ASD) are quite variable, ranging between five and 20% of the 22q11.2DS population (Antshel et al., 2007; Niklasson & Gillberg, 2010), and rates of ADHD range between 35-55% (Antshel et al., 2006; Baker & Skuse, 2005; Jolin, Weller, & Weller, 2012; Tang et al., 2013). Finally, at least 25% of individuals with 22q11.2DS go on to develop psychotic disorders, including schizophrenia, in young adulthood (Murphy, Jones, & Owen, 1999; Schneider et al., 2014), making the syndrome the most common genetic basis for schizophrenia next to being born to two parents with schizophrenia. Due to the high rates of psychiatric disorders present in the 22q11.2DS population, it serves as a genetic model for studying these disorders and the variety of associated impairments (Niarchou et al., 2014).

Children with 22q11.2DS are also known to have social impairments, although studies demonstrating difficulties with social cognition, particularly theory of mind (ToM), are few, and results are mixed (Bearden et al., 2005; Campbell et al., 2010; Ho et al., 2012; Jalbrzikowski et al., 2012; Kiley-Brabeck & Sobin, 2006; Shashi et al., 2012; Woodin et al., 2001). Although researchers have found that individuals with 22q11.2DS do have difficulty with visuospatial functioning and social reasoning difficulties, which are associated with impairments in reading facial expressions (Andersson et al., 2008; Campbell et al., 2010; van Amelsvoort et al., 2006), the literature is sparse with respect to understanding whether or not psychiatric comorbidities play a role in ToM skills. Only one study to date has attempted to understand the relationship between social cognition difficulties and mood disorders in

children with 22q11.2DS (Campbell et al., 2011). Although the authors found an association between social cognition and mood problems in children with 22q11.2DS, the study did not include a formal diagnostic assessment of mood disorder, nor did the study explore differences between children with 22q11.2DS and mood disorder and children with 22q11.2DS and no mood disorder. Intriguingly, Antshel and colleagues (2010) found that WISC-III Processing Speed and a backward visual span task at Time 1 of a longitudinal study predicted a diagnosis of MDD in individuals with 22q11.2DS, but not their typically developing siblings, at Time 2, three years later. Similarly, Time 1 scores on the Behavioral Assessment System for Children, Second Edition (BASC-2) Withdrawal and Social Skills scales predicted a diagnosis of MDD at Time 2 (Antshel et al., 2010). This finding points to the possibility of impaired social and visual processing skills as a precursor to the development of mood disorder in individuals with 22q11.2DS.

Executive functioning is another domain of interest in the neuropsychological profile of individuals with 22q11.2DS. Executive function is a term for a group of higher-order cognitive processes, such as initiation of activity, decision making, judgment, planning, and cognitive flexibility (Spreen & Strauss, 1998). Research into the executive function abilities of children and adolescents with 22q11.2DS has shown poorer performance in both parent report and objective tests (Kiley-Brabeck & Sobin, 2006; Lajiness-O'Neill et al., 2006). In addition, Antshel and colleagues (2006) found that children and adolescents with 22q11.2DS and comorbid MDD demonstrated more executive dysfunction on a parent report of executive functioning. However, whether or not executive function difficulties play a role in the development of mood disorder among individuals with 22q11.2DS remains to be seen.

Individuals with 22q11.2DS therefore experience a range of difficulties, including emotion recognition impairments and a cognitive profile with nonverbal learning difficulties. In addition, many individuals with 22q11.2DS develop co-occurring psychiatric disorders, including mood disorders. However, there is a gap in the extant literature with respect to the effects of comorbid mood disorders on social functioning in individuals with 22q11.2DS; at present, it remains to be seen whether a co-occurring mood disorder contributes an additive effect to the ToM impairment that can occur in 22q11.2DS. The extant literature on depression in children and adolescents with 22q11.2DS is also lacking on how MDD presents in this population. Therefore, the next sections will address the epidemiology and characteristics of pediatric major depressive disorder, as well as biopsychosocial factors associated with pediatric MDD.

Major Depressive Disorder

Epidemiology of MDD in children and adolescents. Mood disorders are among the most frequently diagnosed mental disorders in the general pediatric population, especially among adolescents. In particular, MDD is the most prevalent mood disorder among adolescents (Lewinsohn, Rohde, & Seeley, 1998a). MDD not only affects the cognitive and affective lives of youth; it can also have a profound effect on social functioning. This is often demonstrated by social withdrawal and a loss of interest in activities that usually bring the individual pleasure. A decreased ability in social cognition, or understanding others' thoughts and feelings, may make it even more difficult for children to successfully engage with others, causing them increased social distress.

Major Depressive Disorder is less common in young children, but it is one of the more common psychiatric diagnoses among adolescents; it is estimated that about 28% of

adolescents will experience a major depressive episode by the time they reach age 19 (Klein, Dougherty & Olino, 2005; Lewinsohn, Rohde, & Seeley, 1998a). Rates of MDD are associated with gender and puberty, thus rates increase as children grow older. Children with MDD demonstrate equal gender representation, but postpubertal adolescents show higher rates of depression in females than males. Female adolescents are two times more likely to be depressed than males, the same ratio found for adult MDD (Chrisman, Egger, Compton, Curry, & Goldston, 2006). Rates of MDD in children and adolescents with 22q11.2DS are also quite high, ranging from 12-64% (Antshel et al., 2010; Antshel et al., 2006; Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Baker & Skuse, 2005; Fabbro et al., 2012; Green et al., 2009; Jolin et al., 2009; Jolin, Weller, & Weller, 2012; Tang et al., 2014). A similar gender difference has been noted among 22q11.2DS individuals diagnosed with MDD, with female overrepresentation particularly present in adulthood (Schneider et al., 2014). Other non-22q11.2DS longitudinal studies have shown that MDD in adolescence is often predictive of depression in adulthood, indicating the need for early and effective interventions (Aalto-Setala, Marttunen, Tuulio-Henriksson, Poikolainen, & Lonnqvist, 2002; Lewinsohn, Rohde, & Seeley, 1998b; Pelkonen, Marttunen, Kaprio, Huurre, & Aro, 2008).

Characteristics of pediatric MDD. Pediatric diagnosis of MDD is currently based on the standard adult diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5; American Psychiatric Association, 2013). The criteria for MDD include the presence of one or more major depressive episodes. A major depressive episode is characterized by five or more of the following symptoms nearly every day during a two-week period: depressed mood – which often manifests as irritable mood in children – or loss of interest or pleasure in activities (anhedonia); significant weight loss not related to

dieting, or weight gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness; decreased ability to concentrate or make decisions; and recurrent thoughts of death or suicidal ideation (APA, 2013). In addition, these symptoms must cause significant impairment in social or school functioning. In children, social impairment may involve withdrawing from peers due to increased self-consciousness and low feelings of social competence (Lewinsohn, Rohde, & Seeley, 1998a). Several disorders often co-occur in children with MDD, including anxiety disorders, disruptive behavior disorders such as ADHD, and substance abuse disorders (Chrisman et al., 2006; Kovacs, 2001; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000).

Biological factors involved in pediatric mood disorders. There has been much research into a possible biological cause of depression, yet the exact cause remains unknown (Nemeroff & Vale, 2005). Neuroendocrine studies have received substantial attention, particularly those involving the hypothalamic-pituitary-adrenal (HPA) axis. Studies have repeatedly shown that individuals who are depressed show hyperactivity in the HPA axis, which secretes the stress hormone cortisol (Nemeroff, 1996). Elevated cortisol levels are hypothesized to be associated with damage to the hippocampus, leading to reduced hippocampal volume in individuals who are depressed (Brown, Varghese, & McEwen, 2004; Lee, Ogle, & Sapolsky, 2002; Masi & Brovedani, 2011; Sapolsky, 2001). The hippocampus plays an essential role in learning and memory, and hippocampal volume reduction in individuals who are depressed helps to explain some of the cognitive difficulties associated with the disorder. A Magnetic Resonance Imaging (MRI) study by Bremner and colleagues (2000) examined 16 patients with major depressive disorder in remission compared to 16 matched non-depressed subjects. The study found a statistically significant smaller left

hippocampal volume in patients than in the comparison subjects, while other areas of interest (amygdala, caudate, frontal lobe, and temporal lobe) showed no differences. The question still remains whether reduced hippocampal volumes are the result of major depression, or whether individuals are predisposed to major depression due to having smaller hippocampi (Bremner et al., 2000; Masi & Brovedani, 2011).

Abnormal functioning in prefrontal cortical brain regions is also hypothesized to contribute to depression, including the dorsolateral prefrontal cortex (DLPFC), involved in working memory; the medial prefrontal cortex (mPFC), involved in mediating emotions; and the anterior prefrontal cortex (Bremner et al., 1997; George, Ketter, & Post, 1994). Further examination of brain structures in depressed individuals have indicated decreased regional homogeneity in the insula, an area believed to be involved in mood regulation, and the cerebellum (Liu et al., 2010). Regional homogeneity refers to the amount of regional blood oxygen level-dependent (BOLD) signal observed in imaging studies, and is used to explore specific neural activity patterns during resting state. Previous studies have demonstrated decreased regional homogeneity in the same brain regions in individuals with schizophrenia and ADHD, indicating a possible common abnormality in neural circuitry among the three disorders (Liu et al., 2010).

Since the late 1960s, neurochemical systems have received a great deal of attention for their roles in depression, particularly the serotonergic and noradrenergic systems. These neurotransmitter systems appear to modulate the symptoms of depression, evidenced by the fact that treatment with selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs), which keep more of the neurotransmitters available in the brain's synaptic spaces, help to alleviate symptoms of the disorder (Bremner et al., 2003). Although

research has shown a consistent relationship between the effects of drugs on neurotransmitters and affective states, it is not clear whether serotonin and norepinephrine pose separate etiologies for depression, or whether the two systems act on common brain regions in order to mediate depressive symptoms (Bremner et al., 2003; Schildkraut & Kety, 1967). Most studies support a combination of genetic/biological factors and early childhood experiences as the best explanatory model for the development of depression (Bremner et al., 2000; Nemeroff & Vale, 2005; Nemeroff, 1996; Schildkraut & Kety, 1967; Shyn & Hamilton, 2010).

Genetic studies have also indicated a possible link between BPD and 22q11.2DS. One study (Papolos et al., 1996) indicated that 17 of 25 children diagnosed with 22q11.2DS also met Diagnostic and Statistical Manual for Mental Disorders, Fourth edition (DSM-IV; APA, 2000) criteria for a form of BPD. The children exhibited rapid mood swings, which then developed into manic or hypomanic episodes. These episodes later came to be recognized as the same pattern of symptoms manifested by children with BPD, thereby leading the authors to question whether the deletion on chromosome 22 also contributes to BPD (Papolos et al., 1996). Other studies have provided different results, including a link between BPD and a deletion on the short arm of chromosome 11, as well as linkage to chromosome 18; however, these results have not been replicated. Since more recent research has not shown increased rates of BPD among individuals with 22q11.2DS, it appears instead that BPD is more of a polygenic disorder, or perhaps a disorder with a single genetic mutation that is modified by the environment as well as other variations in genetic makeup (Aneja et al., 2007; Papolos & Papolos, 1999; Schneider et al., 2014).

Neuroimaging studies have provided some insight into brain structure abnormalities associated with BPD. These studies have provided a wealth of information related to biological differences in individuals with BPD, particularly with respect to emotional regulation difficulties. A functional MRI study involving children with BPD examined neural activation with attention directed to emotional aspects of faces as compared to nonemotional aspects. Rich et al. (2006) found that when compared to typical controls, children with BPD perceived greater hostility and reported greater fear when exposed to neutral faces. When asked to rate hostility, the children with BPD showed greater activation in the limbic system, particularly the left amygdala, left nucleus accumbens, left putamen, and left ventral prefrontal cortex. The children with BPD also showed greater bilateral activation in the nucleus accumbens when asked to rate their fear of the face. The authors conclude that the amygdala hyperactivation seen in BPD children may be a result of dysregulation in limbic system, indicative of the deficient emotion-attention interaction seen in these children (Rich et al., 2006).

As an extension of similar findings in adults with BPD, a study by Kaur et al. (2005) examined the cingulate cortex in children with BPD. The authors posited that due to its location in the limbic system, the cingulate may be a key structure in helping to modulate mood (Kaur et al., 2005). The authors studied 16 children with BPD, and results indicated significantly smaller left anterior and bilateral posterior cingulate cortices in subjects with BPD as compared to healthy controls. These findings were consistent with results found in adults with BPD, indicating that cortical abnormalities in BPD are present at a young age (Kaur et al., 2005). Volumetric abnormalities, including a smaller anterior cingulate and amygdala, have also been reported in many other psychiatric disorders, including autism

(Kaur et al, 2005; Monk et al., 2010), indicating a possible common biological marker for psychiatric problems.

Cognitive and behavioral factors involved in MDD. The cognitive theory of depression based on the work of Beck posits that a "cognitive triad" of negative thoughts and views of the self, others, and the future is responsible for depression (Rulcovius & Reinhard, 1990; Young, Rygh, Weinberger, & Beck, 2008). These cognitive distortions lead the individual with depression to erroneously attribute minor disappointments into opportunities for self-blame and failure, and they therefore maintain their negative views. Research has demonstrated cognitive distortions such as those initially suggested by Beck occur in children who are depressed, and they show a tendency to catastrophize, overgeneralize, personalize, and selectively attend to negative situations (Wicks-Nelson & Israel, 2003).

Cognitive attributions, or attributional style, can also play a role in the Learned Helplessness theory of depression. Peterson and Seligman (1984) explained depression as a result of an individual coming to perceive oneself as having little control over one's environment as a result of learning history (Peterson & Seligman, 1984). In depression, the authors posit that one takes on an attributional or explanatory style in which oneself is blamed for negative events, views the cause as stable over time, and generalizable across situations (Peterson & Seligman, 1984). Although mainly researched in adults, a study by Seligman and colleagues (1984) examined attributional style and depressive symptoms in children. The authors found a strong correlation between the child's attributional style and depressive symptoms, and that attributional style for bad events was predictive of future depressive symptoms (Seligman et al., 1984). A longitudinal investigation also demonstrated that children with a maladaptive explanatory style showed more depression and achievement

problems than children with a different explanatory style; the children who attributed bad events to internal, stable, and global causes and good events to external, unstable, and specific causes showed more difficulty with achievement and reported more depression (Nolen-Hoeksema, Girgus, & Seligman, 1986). These studies provided some support for the Learned Helplessness theory of depression in children, but the authors proposed the need for a clearer explanation of the relationship between attributional style and life events.

Social factors involved in MDD. Other explanations for depression include social theories, mainly factors related to parental attachment and object relations. Bowlby initially described attachment as a child's fundamental need with a biological basis; the goal of the child's attachment is to stay close to a preferred individual as way of maintaining a sense of security (Davies, 2004). This sense of security can be seen as a feeling of protection for young children, and when the child is distressed, he or she does what is needed to restore the sense of security. Based on Bowlby's work, Mary Ainsworth began to study the dynamics involved in attachment. Through her "Strange Situation" procedure, Ainsworth was able to delineate three types of attachment based on an infant's reaction to a stressful situation; a secure attachment style, and two insecure styles (Davies, 2004). Securely attached children feel that their attachment figures are consistently available, sensitive, and responsive to their needs. They feel soothed by their attachment figures and are able to use their caregiver as a secure base of exploration. Ambivalently attached children show fearful attachment behavior, and demonstrated an increased dependence on the attachment figure. Children who show an avoidant attachment pattern have a tendency to hide negative feelings, and they have difficulty engaging in neutral interactions with their attachment figure, thereby leading to a minimization of the caregiver's importance as a source of comfort (Davies, 2004). Further

research has since identified an additional type of insecure attachment called disorganized attachment (Hesse & Main, 2000). Children with this attachment style have difficulty coping with stress when their caregiver is present; they do not have a coherent or organized means of coping with the distress and tend to show bizarre or contradictory behavior when experiencing a difficult situation (Brumariu & Kerns, 2010; Hesse & Main, 2000).

Attachment theory arose out of the psychoanalytic object relations theory. Object relations theory posits that depression is a result of a continuous pattern of poor attachment, which begins in childhood and continues into adulthood. The child fears or feels he or she will lose an important loved object. This object loss can involve a wide range of situations, including physical separation, death, or divorce, as well as other situations, which can lead to the unavailability of a caregiver. Bowlby postulated that such an uncontrollable loss, whether it is perceived or actually true, increases one's vulnerability to depression (Bowlby, 1980, as cited in Brumariu & Kerns, 2010). Studies have indicated that attachment insecurity – particularly avoidant and ambivalent styles – is related to the development of anxiety and depression among children and adolescents (Brumariu & Kerns, 2010; Herbert, McCormack, & Callahan, 2010; Vivona, 2000).

Social impairment in mood disorders. In order to meet criteria for a diagnosis of MDD or BPD, the symptoms might manifest in impairment in social functioning (APA, 2013). Although once questioned, research has demonstrated social impairment in children with MDD (Lack & Green, 2009; Levendosky, Okun, & Parker, 1995; Rockhill, Fan, Katon, McCauley, Crick, & Pleck, 2007; Rudolph, Hammen, & Burge, 1994). In addition to demonstrating social isolation and withdrawal in children with MDD, studies have shown that children with MDD also experience deficits in social cognitive and social problem-

solving skills (Kovacs & Goldston, 1991; Levendosky, Okun, & Parker, 1995). Whether social impairment precedes a MDD diagnosis remains a viable question, as research has demonstrated continued social impairment in peer relationships after recovery from depressive episodes (Puig-Antich, et al., 1985). Studies of social impairment in children with BPD are scarcer, in part due to the diagnostic questions associated with the disorder. However, common social problems seen in children with BPD include difficulty with peer and family interactions, play and recreation, and social withdrawal (Lack & Green, 2009). Such social problems may be related to social cognitive impairment, which will be discussed next.

Social Cognition

Social cognition has been defined as "the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others" (Green et al., 2008, p. 1211). It is a term that has been used to refer to various domains related to how one thinks, feels, and responds to others (Thirion-Marissiaux & Nader-Grosbois, 2008a,b). These different aspects of social cognition include theory of mind (ToM), attributional style, social perception, and emotional processing (Green et al., 2008; Pinkham et al., 2013). Theory of mind, also known as mentalizing, refers to the ability to infer the intentions or beliefs of others. First order, or affective ToM abilities, involve an individual's ability to understand what another individual is thinking or feeling, whereas more cognitively related, or second order ToM abilities are concerned with the ability to accurately predict another's intent (Happé, 1994). ToM is widely known to be a key deficit in schizophrenia spectrum disorders and ASD (Baron-Cohen, Leslie, & Frith, 1985; Colle, Baron-Cohen, & Hill, 2007; Green et al., 2008; White,

Hill, Happé, & Frith, 2009). Attributional style refers to the way individuals explain or make sense of social interactions and events. Social perception is a component of social cognition that refers to how one decodes and interprets social cues in others. It involves knowing social rules, roles, and goals (social knowledge), as well as how to use those rules, roles, and goals, and understand how they influence others (Green et al., 2008; Pinkham et al., 2013). Finally, emotion processing involves how one perceives and uses emotions, including identifying/recognizing facial emotion and tone of voice, as well as understanding and managing emotions.

Although many of these social cognitive abilities interact with one another, each one plays a special role in the development of social competence, and several measures have been developed to measure these different constructs (Table 1). Tasks related to ToM, which measure one's understanding of others' emotional states and points of view, are particularly important, as this is an essential part in predicting how others will feel and act in various situations. Correct identification of others' thoughts and feelings is essential for knowing how to respond appropriately to another individual. Therefore, social impairment may result if individuals have difficulty identifying the emotions and intent of others.

Research has shown that many social cognitive abilities are first noticed at about age 18 months, and most become developed between the ages of four and six years (Frith & Frith, 2003). For example, the capacity for theory of mind begins to develop in infancy, and reaches full development by age four or five (Adolphs, 2001; Choudhury, Blakemore, & Charman, 2006). Emotion processing abilities, specifically emotion recognition abilities, are also first noticed in infancy. By one year of age, infants are able to recognize several

emotional expressions (Bornstein & Arterberry, 2003; Nelson, 2001), and these abilities are considered to be fully developed by about age seven (Bruce et al., 2000).

Table 1

Social Cognition Components and Related Measures

Social Cognition Component	Description	Measures
Theory of Mind (ToM)	Ability to understand others' mental states, infer their thoughts, feelings, beliefs.	Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001); Silent Animations/Triangles (Abell, Happe, & Frith, 2000)
Attributional Style	How individuals explain causes/make sense of social events/interactions.	Ambiguous Intentions and Hostility Questionnaire (AIHQ; Combs, Penn, Wicher, & Waldheter, 2007); Internal, Personal, and Situational Attributions Questionnaire (IPSAQ; Kinderman & Bentall, 1996)
Social Perception	How one decodes, interprets others' social cues.	Interpersonal Perception Task (IPT-15; Costanzo & Archer, 1989)
Emotion Processing	How one perceives, uses emotion. Includes emotion recognition, understanding emotion, managing emotion.	Diagnostic Test of Nonverbal Accuracy 2 (DANVA2; Nowicki & Duke, 1994); Penn Emotion Recognition Test (ER-40; Kohler et al., 2003)

Note. Adapted from Green et al., 2008 and Pinkham et al., 2013.

Biological factors involved in social cognition. Research into the neural mechanisms involved in social cognition has identified several regions of interest (ROIs) in the brain. A review by Cusi, Nazarov, Holshausen, MacQueen, and McKinnon (2012) noted that these areas include prefrontal regions such as the ventromedial prefrontal cortex and dorsolateral prefrontal cortex, previously implicated in the biology of major depressive disorder. Other regions of interest include the anterior cingulate cortex, which is involved in conflict monitoring and integrating information to motivate behavior; the amygdala; the ventral striatum, which plays a role in motivational and emotional aspects of behavior, and the temporoparietal junction, which is involved in perspective-taking (Adolphs, 2001; Cusi, Nazarov, Holshausen, MacQueen, & McKinnon, 2012).

As previously discussed, abnormal functioning in prefrontal cortical regions have been implicated in depressed individuals, particularly the DLPFC and mPFC. Studies in individuals with mood disorders demonstrate reduced activation in these and other regions of interest during facial emotion processing tasks (Cusi et al., 2012). More specifically, mood disorders are associated with increased activity (hyperactivity) in the inferior frontal gyrus, fusiform gyrus, and left amygdala, and decreased activity (hypoactivity) in the DLPFC. In addition, a negative processing bias has been noted in individuals with MDD, wherein they demonstrate enhanced attention to negatively valenced (e.g., sad, angry) faces (Cusi et al., 2012). Other studies have demonstrated that the fusiform gyrus plays an important role for the general recognition of faces (i.e., eyes, nose, mouth), but the superior temporal sulcus (STS) is important for the recognition of facial emotion (Adolphs, 2001; Glaser et al., 2010), and that individuals with 22q11.2DS show an atypical processing network in response to faces (Andersson et al., 2008; Campbell et al., 2010).

A volumetric magnetic resonance imaging (MRI) study has also revealed amygdala volume reduction and amygdala hyperactivation during face processing tasks in children with BPD, in addition to demonstrating reduced connectivity between the amygdala and temporal association cortical regions (Rich, Fromm, et al., 2008). These facial emotion labeling deficits and the accompanying structural and functional abnormalities may therefore be an indicator of BPD in children (Brotman et al., 2008).

Social cognitive impairment. Research on social cognition impairment began in the schizophrenia spectrum disorder population, based on Frith's (1992, as cited in Brüne & Brüne-Cohrs, 2006) suggestion that psychotic symptoms found in schizophrenia could indicate social cognitive impairment. Individuals with schizophrenia spectrum disorders can have difficulty experiencing their behavior as a result of their own intentions, thus they may therefore see their own actions as being under another's control (Brüne & Brüne-Cohrs, 2006). Frith has argued that impaired social cognition in schizophrenia may help explain negative and disorganized symptoms of the disorder, delusions of being under another's control, and delusions of reference or persecution (Frith, 1992, as cited by Brüne & Brüne-Cohrs, 2006). Studies have shown that patients with schizophrenia, a common differential diagnosis for adults with BPD, do in fact have particular social cognitive deficits. A meta-analysis by Sprong, Schothorst, Vos, Hox, and vanEngeland (2007) examined 29 studies of social cognition in schizophrenia published between January 1993 and May 2006. The authors estimated effect sizes, based on the difference between the mean scores of the schizophrenia group and the mean scores of the control group, divided by the pooled standard deviation. The authors found an overall effect size of -1.1255, demonstrating that on average, the social cognitive performance of patients with schizophrenia was more than

one standard deviation below that of healthy controls (Sprong, Schothorst, Vos, Hox, & VanEngeland, 2007).

Another study examining social cognition in schizophrenia compared ToM in first-episode schizophrenia to community, university, and depressed controls (Kettle, O-Brien-Simpson, & Allen, 2008). The authors found that the schizophrenia group demonstrated significant social cognition impairments compared to non-psychiatric control groups. Although comparison did not demonstrate a significant difference between individuals with schizophrenia and those with depression, results did show overall accuracy on the social cognition task was lower in the schizophrenia group compared to a control group of university students ($p < .001$) and a community control group ($p = .033$). This led the authors to posit a hierarchical finding among the groups, with the schizophrenia group being the most impaired, followed by the depression group, then community control, and finally the university group with the least amount of social cognitive impairment (Kettle, O'Brien-Simpson, & Allen, 2008). In addition, the results indicated the possibility for ToM impairment among individuals with mood disorders. Given the high rate of schizophrenia spectrum disorders among adults with 22q11.2DS, it seems prudent to examine where these difficulties in ToM first appear, as well as whether or not they are related to a prior diagnosis of mood disorder, in order to identify a potential "stepping stone" on the path to psychosis among individuals with 22q11.2DS. In other words, is ToM impairment in individuals with 22q11.2DS a way to distinguish those who go on to develop mood disorders or more severe psychiatric disorders such as psychosis from those who do not?

ToM impairment has been noted in adults with mood disorders, particularly during mood episodes. Kerr, Dunbar, and Bentall (2003) found impaired performance on social

cognition tasks in both bipolar depressed and bipolar manic patients as compared to bipolar remitted individuals and typical controls. The study further demonstrated similarity in cognitive deficits between patients with BPD and patients with schizophrenia (Kerr, Dunbar, & Bentall, 2003). Inoue, Tonooka, Yamada, and Kanba (2004) examined 34 patients with unipolar depression and 16 affected with bipolar disorder. The authors assessed ToM using a sequenced cartoon picture story, and asked patients different questions based on the story. Results indicated impairment on the more cognitively-based second order false belief question and a reality question; 62% in the mood disorder group answered correctly, compared to 96% in the control group, a significant difference at $p < .0001$ (Inoue, Tonooka, Yamada, & Kanba, 2004).

A follow-up study by Inoue, Yamada, and Kanba (2006) found that 58% of the patients with ToM deficits had relapsed and experienced a major depressive episode within one year. The authors also mentioned that poor performance on a false belief question was associated with poorer social adjustment, as evidenced by Global Assessment of Functioning (GAF), Social and Occupational Functioning Assessment Scale (SOFAS) and the Global Assessment of Relational Functioning (GARF) scores from the DSM-IV (Inoue, Yamada, & Kanba, 2006). The authors concluded that social cognition deficits after symptom remission in mood disordered patients helped to predict a high relapse rate.

Wang, Wang, Chen, Zhu, and Wang (2008) examined social cognitive ability in adults with major depression with and without psychotic symptoms. They found that psychotic depressed patients performed worse than typical controls and nonpsychotic depressed patients on a social cognitive task related to social slips, and both depressed groups performed worse on a ToM task (mind reading; Wang, Wang, Chen, Zhu, & Wang, 2008).

Similarly, Lee, Harkness, Sabbagh, and Jacobson (2005) discovered poorer ability to identify others' mental states among a sample of women with depression, which provides evidence of affective ToM deficits among adults with MDD. Finally, studies by Uekermann et al. (2008) and Zobel et al. (2010) demonstrated similar deficits of ToM coupled with poorer executive functioning in adults with chronic depression, linking social cognition to cognitive deficits associated with depression.

Social cognitive impairment in pediatric mood disorders. Following a natural progression in the hopes of better understanding the developmental trajectory of social cognition impairments, studies of social cognition in children with BPD have increased recently; however, studies of social cognition in children with MDD remain scarce. Social cognition research in children with BPD has focused on facial emotion discrimination and emotion processing. Similar to findings with adults, these studies have indicated children with or at risk for BPD have more difficulty identifying and processing emotions correctly, and they also require significantly more intense facial emotion before they can correctly label the emotion being expressed (Guyer et al., 2007; Rich, Grimley, et al., 2008; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). A recent study by Schenkel, Marlow-O'Connor, Moss, Sweeney, and Pavuluri (2008) was the first to examine more cognitively related ToM skills, using a verbal false belief task in BPD children. Results were consistent with previous adult findings, in that children with BPD performed more poorly than controls on ToM tasks (Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008).

Rationale for Studying Theory of Mind in Youth and Emerging Adults with 22q11.2DS and Comorbid Mood Disorder

As previously discussed, 22q11.2DS is a genetic and therefore biologically determined developmental disability that has a high rate of co-occurring psychiatric diagnoses, including mood disorders (Aneja et al., 2007; Antshel et al., 2006; Baker & Skuse, 2005; Fabbro et al., 2012; Murphy, Jones, & Owen, 1999; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001; Schneider et al., 2014; Shprintzen, 2000). Most clinicians agree that biological, psychological, and social factors all play a role in the development of major depressive disorder. The question of nature (genes) versus nurture (environment) with respect to depression is no longer a debate between one versus the other. Rather, it appears that both biological explanations and the environment interact with each other and result in depressive symptomatology.

Studies in adults with mood disorders have led researchers to think about similar considerations in the pediatric population, but many questions remain. Limitations in current pediatric research demonstrate room for improvement in mood disorder diagnosis among children and adolescents, as many current studies rely on parent report. In addition, studies also show a need for the assessment of ToM as related to possible comorbidity with pediatric mood disorders and social skills deficits. Diagnosis of specific pediatric mood disorders still relies on adult DSM-5 criteria, when it has been clearly demonstrated that these disorders do not always present in the same manner seen in adults. A better understanding of pediatric MDD is especially needed, as several studies show different phenomenology and outcomes. In order to enhance our understanding of the pediatric mood disorder research, a common understanding of the disorder is necessary. The DSM-5 Work Group has taken steps to make

differentiation of mood problems in children more feasible with the diagnosis of Disruptive Mood Dysregulation Disorder (DMDD); however, this diagnosis is not a replacement for MDD or BPD. In addition, studies exploring the social cognitive skills of children with 22q11.2DS and comorbid mood disorders (a genetic model of MDD and BPD) have focused mainly on the presence of social cognitive deficits, with no attempts to understand mechanisms for the development of MDD. For example, it is possible that the social cognitive, executive functioning, and visual perceptual deficits seen in the 22q11.2DS population play a role in the development of MDD. Taken together, these studies indicate the need for more research that studies skills such as ToM in individuals with 22q11.2DS, as well as individuals with 22q11.2DS who experience mood disorders, particularly since our current understanding of ToM difficulties in youth and emerging adults with MDD is limited.

In addition, the social impairment that can occur with mood disorders can potentially be severe, resulting in withdrawal, limited opportunities for reinforcement, and lack of social support. Without good peer relationships, which are crucial for healthy psychosocial development, children may miss out on important developmental experiences. Based on the biological and social similarities among children with 22q11.2DS and mood disorders, a better understanding of the social impairment associated with mood disorders seems crucial. This is particularly true with respect to the possible contribution that ToM and social difficulties may add towards the development of mood disorder; the current literature supports the need to explore the path along which these problems may develop. As mentioned previously, individuals with MDD have shown anomalies in the medial prefrontal cortex, an area associated with emotion processing, as well as a negative cognitive attributional style (Bremner et al., 1997; George, Ketter, & Post, 1994; Peterson & Seligman,

1984; Rulcovius & Reinhard, 1990; Young, Rygh, Weinberger, & Beck, 2008). In addition, children with MDD also tend to have an avoidant attachment style, in which they have difficulty engaging in affectively neutral situations, or an ambivalent style where they depend on the attachment figure for help in identifying others' mood states (Brumariu & Kerns, 2010; Davies, 2004). Given this combination of factors, it is plausible that much like adults, youth and emerging adults with mood disorders experience difficulty with ToM, making it more difficult for them to function in a socially appropriate or effective manner. Further examination of these areas could help illuminate areas for intervention in these individuals.

Given the prevalence of mood disorders and social difficulties in the 22q11.2DS population, this study explored possible differences in ToM between youth and emerging adults with 22q11.2DS and comorbid mood disorder (22q11.2DS+MD), 22q11.2DS alone (22q11.2DS-MD), and unaffected sibling and community controls. This study also investigated whether childhood visuospatial skill deficits, ToM impairment, executive functioning deficits, and social impairment were predictors of MDD in the late adolescent/emerging adult 22q11.2DS population.

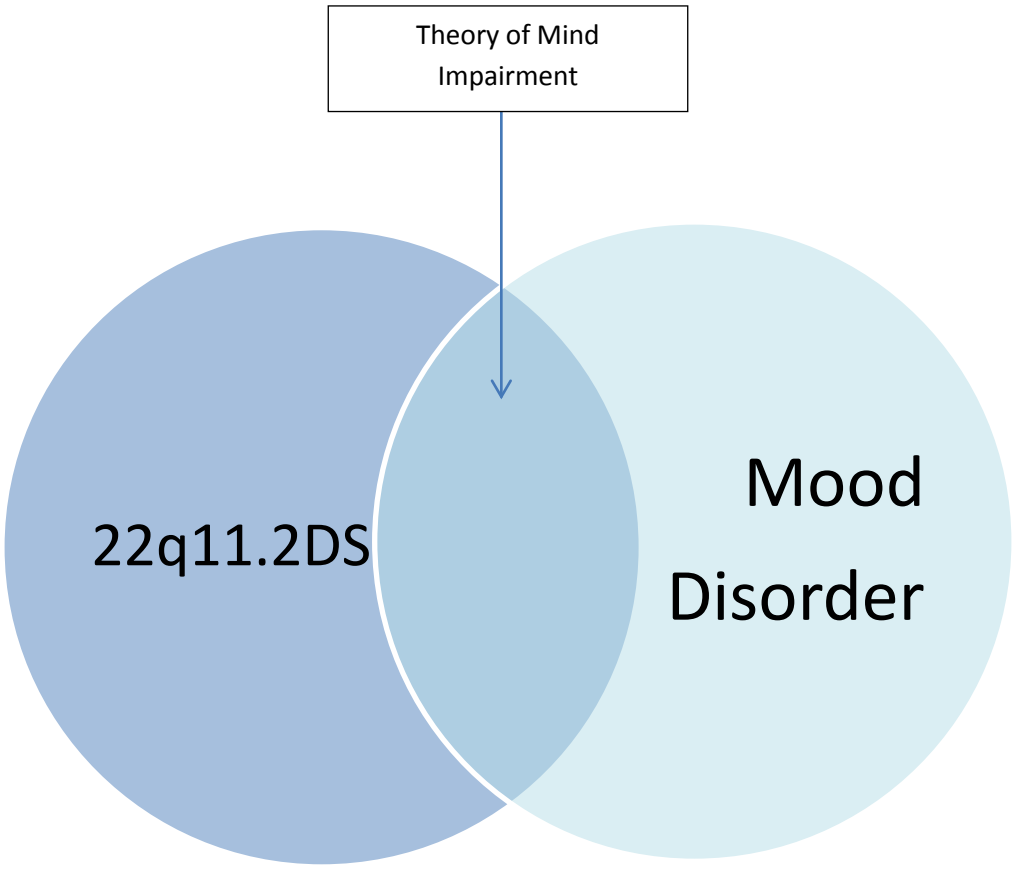

Figure 1. Possible overlap between 22q11.2DS and mood disorder. 22q11.2DS = 22q11.2 Deletion Syndrome.

Specific Aims and Hypotheses

Specific Aim 1

To replicate past research by demonstrating greater problems in the social, perceptual, and executive functioning domains in youth and emerging adults with 22q11.2DS as compared to unaffected typically developing (TD) controls.

Hypothesis 1. Individuals with 22q11.2DS+MD will show greater impairment in social functioning than individuals with 22q11.2DS-MD, who will show a moderate level of impairment (as demonstrated by effect size) in social functioning as compared to TD controls as evidenced by lower scores as measured by the Socialization scale of the VABS-II and higher scores measured by the Total score on the SRS.

Hypothesis 2. Individuals with 22q11.2DS+MD will show greater impairment (lower scores) in visuospatial skills as measured by the WISC-III or WAIS-III Block Design subtest scaled scores as compared to individuals with 22q11.2DS-MD. In turn, individuals with 22q11.2DS-MD will show a moderate level (as demonstrated by effect size) of impairment in visuospatial skills as compared to TD controls.

Hypothesis 3. Individuals with 22q11.2DS+MD will show greater impairment (lower scores) in executive functioning skills as measured by the Wisconsin Card Sorting Test (WCST) Total Correct raw score, number of categories completed, and Perseverative Error standard scores. Individuals with 22q11.2-MD will show a moderate level (as demonstrated by effect size) of impairment in executive functioning skills as compared to TD controls.

Specific Aim 2

To compare performance on a task of ToM, the Triangles Test, in children and adolescents with 22q11.2DS+MD and 22q11.2DS-MD to typically developing controls.

Hypothesis 1. Individuals with 22q11.2DS+MD will score lower on a measure of ToM as measured by the Triangles Test compared to 22q11.2DS-MD. Individuals with 22q11.2DS-MD will show moderately reduced scores (based on effect size) on the Triangles Test compared to the TD groups.

Specific Aim 3

To compare performance in adaptive functioning as measured by scores on the VABS-II in youth and emerging adults with 22q11.2DS+MD and youth and emerging adults with 22q11.2DS-MD to typically developing controls.

Hypothesis 1. Individuals with 22q11.2DS+MD will show poorer functional outcomes (lower scores on the Daily Living Skills, Socialization, Communication, and Adaptive Composite scales of the VABS-II) compared to individuals with 22q11.2-DS. Individuals with 22q11.2-MD will show a moderate degree of functional outcome impairment (as determined by effect size) compared to the TD groups.

Specific Aim 4

To examine whether performance on measures of social, perceptual, and executive functioning (as measured by the SRS, WISC-III/WAIS-III Block Design scaled score, and WCST) are related to functional outcome as measured by the VABS-II in all groups.

Hypothesis 1. Scores on the Total scale on the SRS will be negatively correlated with functional outcomes as measured by the Socialization, of Daily Living Skills, Communication, and Adaptive Composite scales of the VABS-II.

Hypothesis 2. Scaled scores on the WISC-III/WAIS-III Block Design will be positively correlated with functional outcomes as measured by the Daily Living Skills, Socialization, Communication, and Adaptive Composite scales of the VABS-II.

Hypothesis 3. Scores on the WCST (Total Correct raw score, categories completed, Perseverative Error standard score) will be positively correlated with functional outcome as measured by the Daily Living Skills, Socialization, Communication, and Adaptive Composite scales of the VABS-II.

Specific Aim 5

To examine the relationship between ToM (as measured by the Triangles Test) and functional outcomes in individuals with 22q11.2DS+MD, individuals with 22q11.2DS-MD, and neurotypical youth and emerging adults, as measured by the VABS-II.

Hypothesis 1. Scores on the Triangles Test will be positively correlated with functional outcomes as measured by the Daily Living Skills, Socialization, Communication, and Adaptive Composite scales of the VABS-II in all groups.

Specific Aim 6

To examine the relative contributions of visuospatial, social, executive, and ToM functioning as potential mediators of mood disorder diagnosis among individuals with 22q11.2DS (Figure 2).

Hypothesis 1. Lower visuospatial functioning performance (as measured by the WISC-III or WAIS-III Block Design scaled score), lower social functioning performance (as measured by the VABS-II Socialization scale), lower executive functioning performance (as measured by the WCST Perseverative Error Standard Score) and lower ToM performance (as

measured by the Triangles Test Mentalization score) will lead to greater likelihood of a mood disorder diagnosis (as determined by the K-SADS) in individuals with 22q11.2DS.

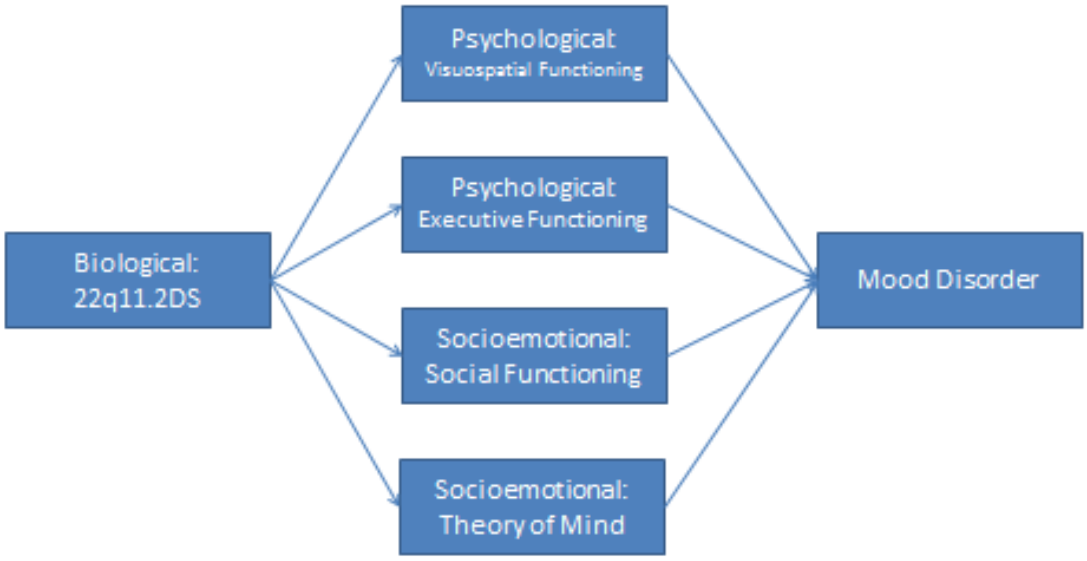

Figure 2. Proposed biopsychosocial model for predictors of mood disorder in 22q11.2DS. 22q11.2DS = 22q11.2 Deletion Syndrome.

Chapter 2: Method

Participants

The current project examined data that was collected as part of a longitudinal study for risk factors for psychosis in 22q11.2DS under Principal Investigator Wendy R. Kates, Ph.D. As described in previous studies (Aneja et al., 2007; Antshel et al., 2010; Antshel et al., 2007; Antshel et al., 2006), participants were enrolled in a longitudinal study of risk factors for psychosis in 22q11.2DS. In addition to the 22q11.2DS group, sibling control and community control cohorts were included. Participants with 22q11.2DS and their siblings were recruited from a large academic medical center in the Northeastern United States.

At the time point examined in this study (Time 3), 77 individuals with 22q11.2DS (mean age = 18.08 years, SD = 2.17), 26 siblings of individuals with 22q11.2DS (mean age = 18.51 years, SD = 1.73) and 30 community controls (mean age = 17.64 years, SD = 1.38) participated in the study. No age, F (2, 120) = 0.44, p = .673, η^2 = .01, or gender differences, χ^2 (df = 2) = 0.91, p = .686, existed between the groups. A sample size of at least 45 per group, for a total sample size of 180, was recommended for optimal power (1-β = 0.80) with a medium effect size (f^2V = 0.20), while a sample size of 19 per group, for a total sample size of 76, was recommended for optimal power with a large effect size (f^2V = 0.40) in the statistical analyses that will be conducted (Erdfelder, Faul, & Buchner, 1996).

Inclusion/exclusion criteria. Only children with fluorescence *in situ* hybridization (FISH) confirmed deletion in the q11.2 region of chromosome 22 were included in the sample. The community control group was recruited from local public schools. Mood disorder was diagnosed by a diagnostic psychiatric interview with the KSADS-PL. For the purposes of this study, inclusion criteria for individuals with 22q11.2DS + mood disorder

group were based on KSADS-PL diagnosis of MDD, BPD, Dysthymic Disorder, and Depressive Disorder Not Otherwise Specified (Table 2). Children diagnosed with BPD were not excluded if they had reported comorbid diagnoses of Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, or Conduct Disorder, as these are common conditions known to coexist with pediatric BPD/DMDD (Geller et al., 2000; Papolos & Papolos, 1999; Tillman et al., 2003). Exclusionary criteria for individuals with 22q11.2DS + mood disorder included traumatic brain injury (TBI), other neurological disorders, autism spectrum disorders (ASD), and comorbid diagnosis of social anxiety disorder in order to ensure that participants were not intentionally refraining from meaningful social relationships. Exclusionary criteria for controls included any mood or anxiety disorders, as well as other disorders that could account for social deficits, including schizophrenia, traumatic brain injury (TBI), other neurological disorders, and autism spectrum disorders.

Table 2

Inclusion/Exclusion Criteria

22q11.2+MD	22q11.2-MD	Control
Meet criteria for MDD, BPD, Dysthymia, Depressive Disorder NOS; no diagnosis of psychosis, Social Phobia (as determined by K-SADS-PL) or ASD (as determined by ADI-R)	No comorbid diagnosis of mood disorder, Social Phobia, psychosis (as determined by K-SADS-PL) or ASD (as determined by ADI-R)	No diagnosis of mood disorder, anxiety disorder, TBI, psychosis, neurological disorder, ASD

Note. 22q11.2 = 22q11.2 Deletion Syndrome; MD = Mood Disorder; MDD = Major Depressive Disorder; BPD = Bipolar Disorder; NOS = Not Otherwise Specified; K-SADS-PL = Kiddie Schedule for Affective Disorder and Schizophrenia, Present-Lifetime Version; ASD = Autism Spectrum Disorder; ADI-R = Autism Diagnostic Interview, Revised; TBI = Traumatic Brain Injury.

Procedures

As the participants completed assessments at three time points, with each time point separated by approximately three years, evaluators were blinded to findings from the previous time points. Informed consent and child assent was obtained from parents and children under protocols approved by the medical center's institutional review board. As described in previous studies (Aneja et al., 2007; Antshel et al., 2010; Antshel et al., 2007; Antshel et al., 2006), each participant and parent/caregiver completed measures of cognitive and/or social, emotional, and behavioral functioning. All diagnostic interviews were completed by a licensed psychiatrist or psychologist, and all neuropsychological measures were administered by an experienced doctoral-level examiner. Due to the facial features characteristic of 22q11.2DS, evaluator blindness to group assignment was not possible. The neuropsychological test battery took approximately three hours to complete, and each participant received a 15-minute break halfway through the battery. A licensed psychologist or trained student assistant familiar with the measures double scored all protocols to ensure scoring accuracy. Caregivers completed behavior rating scales and background information while the children and adolescents were completing neuropsychological measures.

Measures

Vineland Adaptive Behavior Scales, Second Edition (VABS-II). The VABS-II is a measure of adaptive functioning administered via interview or a Parent/Caregiver Rating Form (Sparrow, Cicchetti, & Balla, 2005). The Parent/Caregiver Rating Form, which was used for the purposes of this study, allows a parent or guardian to rate an individual's adaptive and problem behaviors in various settings. The VABS-II provides age-based standard scores (M = 100, SD = 15) in the domains of Communication, Daily Living Skills,

Socialization, Motor Skills, in addition to an Adaptive Behavior Composite. Each domain consists of two to three subdomains (i.e., receptive, expressive, and written communication). Norms for the VABS-II were based on a large national sample of individuals from birth to age 90, representative of the U.S. population with regard to race/ethnicity, geographic region, and socioeconomic status (Sparrow, Cicchetti, & Balla, 2005). Reliability data for the VABS-II are very good overall, with approximately 75% of the internal consistency subdomain reliabilities having a value of .75 or higher, and domain/Adaptive Behavior Composite scores ranging from the upper .80s to low .90s (Sparrow, Cicchetti, & Balla, 2005). Similarly, validity data for the VABS-II indicate that correlations between subdomain and domain scores reflect valid functional relationships, with the Socialization subdomains showing especially high correlations (e.g., in the low .70s). In addition, confirmatory factor analysis supported the theoretical structure of the VABS-II (Sparrow, Cicchetti, & Balla, 2005). For the purposes of this study, three domain scores (Communication, Daily Living Skills, and Adaptive Behavior Composite) were used to measure adaptive functioning, while the Socialization domain score was used as a measure of social functioning.

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL). The K-SADS-PL is a DSM-IV-compatible semi-structured interview suitable for use with children and adolescents from age six to 18 (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996). It covers a wide variety of affective disorders, physical disorders, psychoses, anxiety disorders, behavioral disorders, as well as others. The interviewer first completes a screening, and then based on the results, of the screening, administers various modules in order to help determine whether the participant meets DSM-IV criteria for specific diagnoses.

Various studies have examined interrater reliability and test-retest reliability for the K-SADS. Kappa coefficients (κ) demonstrate greater precision among raters in later versions of the K-SADS, with data indicating 100% agreement for MDD, minor depression/dysthymic disorder, generalized anxiety disorder, separation anxiety disorder, and oppositional defiant disorder (Ambrosini, 2000; Kaufman et al., 1997). Predictive and construct validity have been examined with the K-SADS. Predictive validity has been examined via the relationship between diagnosis with the K-SADS and other events occurring before, during, and after administration. Construct validity of K-SADS diagnosis has been demonstrated using methods developed by the original developers, and has helped identify distinct psychosocial impairment in depressed children as compared to nondepressed controls (Ambrosini, 2000).

The K-SADS-PL screener was completed with all study participants, and modules were administered appropriately to identify psychiatric disorders present in the population, including Major Depressive Disorder, Anxiety Disorders, Bipolar Disorder, Attention Deficit/Hyperactivity Disorder, and Psychosis. The κ coefficient for this data set (based on 12 interviews) was 0.91, indicating adequate interrater reliability (Antshel et al., 2010; Antshel et al., 2007; Antshel et al., 2006).

Social Responsiveness Scale (SRS). The SRS is a 65-item questionnaire used to assess the different dimensions of interpersonal behavior, communication, and repetitive/stereotypic behaviors that are characteristic of autism spectrum disorders (Constantino & Gruber, 2005). The SRS Total T-score was used to help assess for social difficulties in all individuals. Psychometric properties of the SRS are good, with total score alpha coefficients above 0.90 for both males and females in both clinical and normative

sample. In addition, alpha coefficients for the Treatment subscales range from 0.76 to 0.91 (Constantino & Gruber, 2005).

Silent Animations/Triangles Test. The Silent Animations (Triangles) Test (Abell, Happe, & Frith, 2000) was developed to measure ToM skills. It is a computer-based task in which participants view 12 animations of two triangles (one large, one small) that move on screen in three different conditions: 1) random movement, in which the triangles float freely; 2) goal-directed activity, such as fighting or chasing; or 3) theory of mind activity, such as the large "parent" triangle trying to coax the smaller "child" triangle out of an enclosure (Abell, Happe, & Frith, 2000). The various conditions are presented in a semi-random order. After each animation, the participant is asked to describe what happened in each cartoon. Responses are then scored for accuracy with a 0 (incorrect), 1 (partially correct), or 2 (correct). Responses are also scored on the degree to which the participant describes mentalization (Table 3). Studies have shown that individuals with autism spectrum disorder use fewer and less accurate mentalization descriptions than normal controls (Abell, Happe, & Frith, 2000; Castelli, Frith, Happé, & Frith, 2002).

The Triangles Test was completed with all study participants. Individual accuracy scores for the videos in the random and ToM categories were summed, providing a maximum total accuracy score of 8. For the mentalization scores, participant descriptions were scored categorically (action, interaction, or mentalization). In order to receive a code of mentalization, the participant's response had to include the attribution of a mental state (e.g., "happy" or "pretending"). The sum of the number of ToM condition videos in which the participant used mentalization was calculated, providing a total mentalization score between 0 and 4.

Table 3

Examples of Scoring Criteria for the Triangles Test

Accuracy/Condition	Description	Point Value
Overall Accuracy	Accurate description of story or actions represented.	2
	Partial description of sequence; description related to sequence, but may be imprecise or incomplete.	1
	Bizarre or clearly incorrect descriptions; responses that focus on unimportant aspect of sequence.	0
Random Movement Sequences	Anything that implies random or purposeless movement (bouncing, moving).	2
	Purposeful movement without interaction (turning around, getting dizzy).	1
	Purposeful movement implying interaction between triangles (copying each other, avoiding each other).	0
Goal-directed sequence - Chasing	Description conveys idea of a chase.	2
	Description that is related to but not specifically defined as a chase.	1
	Action that does not relate to chasing.	0
Theory of Mind sequence - Coaxing	Description that conveys child's reluctance to leave and mother's attempts to help child leave.	2
	Partially correct description focused on one aspect or character (mother pushing child).	1
	Actions not related to events or only related to a minor aspect of sequence (dancing together).	0

Note. Adapted from Abell, Happé, & Frith, 2000.

Wechsler Intelligence Scale for Children, Third Edition (WISC-III) and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III). The WISC-III (Wechsler, 1991) and WAIS-III (Wechsler, 1997) are tests of cognitive ability that provide intelligence quotient (IQ) scores, including a Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ

(PIQ). The WISC-III was developed for children age 6-16 years, and the WAIS-III is used with individuals 16 years of age and older. Both the WISC-III and WAIS-III consist of several subtests (mean = 10, SD = 3), which measure various domains, including visual perceptual skills. Subtest scaled scores for the Block Design subtest will be used to measure visuospatial functioning. Block Design is a visuospatial task in which individuals are asked to replicate stimuli of two color designs using blocks.

Both the WISC-III and WAIS-III have outstanding reliability, with internal consistency reliability coefficients for the WISC-III FSIQ, VIQ and PIQ at 0.89 or above for all ages in the standardization group, and at or above 0.93 for the WAIS-III FSIQ, VIQ, and PIQ (Sattler, 2001). Similarly, internal consistency coefficients for individual subtests are also very high. For example, the reliability coefficient for WAIS-III Block Design subtest is 0.86, and 0.87 for the WISC-III (Sattler, 2001).

Wisconsin Card Sorting Test (WCST). The WCST (Heaton, 1981) is an executive functioning task designed to examine nonverbal problem solving, mental flexibility, and ability to maintain set. Participants are asked to sort a deck of response cards to four key cards that vary with respect to shape, color, and number. Minimal feedback is given to the participant during the task; he or she is only told whether or not the card matched is correct or incorrect. The sorting principle changes after the participant provides a certain number of correct responses. T-Scores are obtained for the number of total errors, perseverative responses, perseverative errors, and nonperseverative errors. Performance on the WCST has been found to be negatively correlated with scores on the Thought Problems subscale of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) among children with

22q11.2DS, suggesting the possibility for future psychiatric problems among this population (Lajiness-O'Neill et al., 2006).

Behavioral Assessment Scale for Children, Second Edition (BASC-2). The BASC-2 Parent Rating Scales (PRS) allow a parent or guardian to rate the child's adaptive and problem behaviors in the home and community settings. The PRS consists of three forms for three age levels: preschool (age 2-5 years), child (age 6-11 years), and adolescent (age 12-21 years). Norms for the BASC-2 were based on large representative samples, and are differentiated according to the child's age, sex, and clinical status. Reliability and validity data for the BASC-2 PRS are very good overall (Reynolds & Kamphaus, 2004).

Research Design

The design of this study was a quasi-experimental between groups cross-sectional design which compared psychometric data on tasks of social, visuospatial, theory of mind, and executive functioning obtained from children from four groups: 22q11.2D+MD, 22q11.2DS-MD, sibling control and community control. The design was between groups in an effort to determine group differences, as individuals were assigned to groups based on diagnosis.

Chapter 3: Analysis

Initial analyses included an examination of the distributional properties to explore the scores on psychometric tests. The data collected was assumed to be from normally distributed populations, and homogeneity of variance is assumed, meaning that the variances would be the same throughout the data. Homogeneity of variance was examined using Levene's test to determine whether or not the variances among groups were equal. If Levene's test is not significant ($p > .05$), the difference between the variances is zero, indicating that the variances are nearly equal, thus meeting this assumption (Field, 2005). An additional assumption of parametric tests requires that the psychometric test data are being measured at the interval level, meaning that the distance between points on a scale are equal at all parts of the scale. Finally, the data was assumed to be independent, meaning that data from different participants were independent of one another (Field, 2005). This assumption was not met for the sibling control group, as they were related to the individuals with 22q11.2DS.

Statistical Analyses

A between-groups analysis of variance (ANOVA) was conducted in order to determine if there were any significant age or intellectual differences between individuals with 22q11.2DS+MD, 22q11.2DS-MD, siblings, and community controls. Chi-square statistics were computed to examine gender differences, as well as medication prevalence, between the groups. Any significant differences that were found between groups were entered as covariates.

Formal Tests of Specific Aim 1

The goal of Specific Aim 1 was to demonstrate social, visuospatial, and executive functioning problems among individuals with 22q11.2DS+MD, 22q11.2DS-MD, as compared to sibling and community controls.

Hypothesis 1. In order to examine differences in social functioning, an ANOVA was computed to test for differences between diagnostic group (22q11.2DS+MD, 22q11.2DS-MD, and TD) on scores from the Socialization scale of the VABS-II and Total scores of the SRS. Post-hoc analysis using Tukey's test was used due to the fact that it is a more powerful post-hoc procedure when testing large numbers of means (Field, 2005).

Hypothesis 2. An ANOVA was computed to test for differences between groups (22q11.2DS+MD, 22q11.2DS-MD, TD) on visuospatial measures (WISC-III or WAIS-III Block Design scaled score).

Hypothesis 3. ANOVAs were computed to test for differences between groups (22q11.2DS+MD, 22q11.2DS-MD, TD) on executive functioning measures (WCST Total Correct raw score, number of categories completed raw score, and Perseverative Error standard scores).

Formal Test of Specific Aim 2

The goal of Specific Aim 2 was to compare performance between groups (22q11.2DS+MD, 22q11.2DS-MD and TD) on the Triangles Test, a measure of theory of mind.

Hypothesis 1. In order to examine differences between scores on the Triangles Test, an ANOVA was computed to test the difference between diagnostic group (22q11.2DS+MD, 22q11.2DS-MD, sibling, and community controls) and scores from the Triangles Test. Post-

hoc analysis using Tukey's test was used due to the fact that it is a more powerful post-hoc procedure when testing large numbers of means (Field, 2005).

Formal Test of Specific Aim 3

The goal of Specific Aim 3 was to examine adaptive functioning in individuals with 22q11.2DS+MD, individuals with 22q11.2DS-MD and typically developing controls in order to demonstrate group differences in functional outcomes.

Hypothesis 1. Differences in functional outcomes between individuals with 22q11.2DS+MD, individuals with 22q11.2DS-MD, sibling and community controls were examined using an ANOVA to compare scores on the Daily Living Skills, Socialization, Communication, and Adaptive Behavior Composite scales of the VABS-II.

Formal Tests of Specific Aim 4

The goal of Specific Aim 4 was to assess the relationship between social, perceptual, and executive functioning and functional outcome in individuals with 22q11.2DS and neurotypicals.

Hypothesis 1. In order to examine the relationship between social functioning and functional outcome, Pearson product-moment (r) correlations were computed to assess the relationship between scores on a parent report measure of social functioning (SRS Total Score) and specific scales related to functional outcome on the VABS-II (Daily Living Skills, Socialization, Communication, Adaptive Behavior Composite).

Hypothesis 2. Pearson *r* correlations were also computed to assess the relationship between the WISC-III/WAIS-III Block Design scaled score and the Daily Living Skills, Socialization, Communication, Adaptive Behavior Composite scores on the VABS-II.

Hypothesis 3. Pearson *r* correlations were computed to assess the relationship between the WCST Total Correct raw score, total number of categories completed, and Perseverative Error standard score and the Daily Living Skills, Socialization, Communication, and Adaptive Behavior Composite scores on the VABS-II.

Formal Test of Specific Aim 5

The goal of Specific Aim 5 was to assess the relationship between theory of mind (Triangles Test) and adaptive functioning in all groups.

Hypothesis 1. Pearson *r* correlations were computed to assess possible relationships between scores on a measure of theory of mind (Triangles Test) and adaptive functioning scores on the VABS-II (Daily Living Skills, Socialization, Communication, Adaptive Behavior Composite).

Formal Test of Specific Aim 6

The goal of Specific Aim 6 was to examine the contributions of visuospatial processing, theory of mind, social functioning, and executive functioning as predictors of mood disorder in individuals with 22q11.2DS.

Hypothesis 1. A multiple mediation model was used in order to examine the degree to which visuospatial processing, theory of mind, social, and executive functioning contributed to a diagnosis of mood disorder in individuals with 22q11.2DS. Since this study examined the theory that all four variables play a role in the development of mood disorder in 22q11.2DS, all of the variables (WISC-III/WAIS-III Block Design scaled score, VABS-II Socialization score, WCST Perseverative Error Standard Score, Triangles Test ToM Mentalization score) were placed into the model simultaneously, so that parameter estimates could be calculated. The multiple mediation model was preferable to testing several separate

mediation models because it allowed for calculation of the total indirect effect, as well as the relative magnitudes related to indirect effects that were associated with all mediators (Preacher & Hayes, 2008). Bootstrap resampling, which involves the computation of thousands of random iterations of the data, was used to create confidence intervals around the estimated indirect effects; thus, a minimum sample size was not required (Preacher & Hayes, 2008).

Chapter 4: Results

Descriptive Statistics

As previously discussed, at the time point examined in this study (Time 3), data was available for a total of 77 individuals with 22q11.2DS (mean age = 18.08 years, SD = 2.17), 26 siblings of individuals with 22q11.2DS (mean age = 18.51 years, SD = 1.73) and 30 community controls (mean age = 17.64 years, SD = 1.38) who participated in the study. No age, F (2, 120) = 0.44, p = .673, η^2 = .01, or gender differences, χ^2 (2) = 0.91, p = .686, existed between the groups.

After inclusion/exclusion criteria were applied, groups were divided into 22q11.2+MD, 22q11.2-MD, Sibling control, and Community control. The group of individuals with 22q11.2+MD was small (N = 11), and further analyses indicated that data for the Triangles Test, which measured the major construct of the study, was only available for five of these individuals. Due to concerns regarding statistical power, a re-evaluation of the data collected led to re-examination of the inclusion criteria for diagnosis. It was decided that to be included in the 22q11.2+MD group, a score of 70 or greater (Clinically Significant) on the BASC-2 Parent Rating Scale Depression subscale would be utilized. This increased the size of the 22q11.2+MD group to 15 (Figure 3). In addition, data on the Triangles Test was available for 12 individuals in the 22q11.2+MD group according to this reclassification. Although this number was still smaller than the minimum suggested 19 per group for a large effect size, it helped improve statistical power. The exclusion criteria remained the same (i.e., no diagnosis of Autism Spectrum Disorder, Schizophrenia, etc.). In the sibling control group, four individuals were excluded due to a diagnosis of Social Phobia (N = 3) or had a BASC-2 Depression score greater than 70 (N = 1). In the community control group, four

individuals were excluded due to a diagnosis of Social Phobia (*N* = 1) or a BASC-2 Depression score greater than 70 (*N* = 3). Thus, all statistical analyses reported herein are based on these reclassifications. Descriptive Statistics are shown in Table 4.

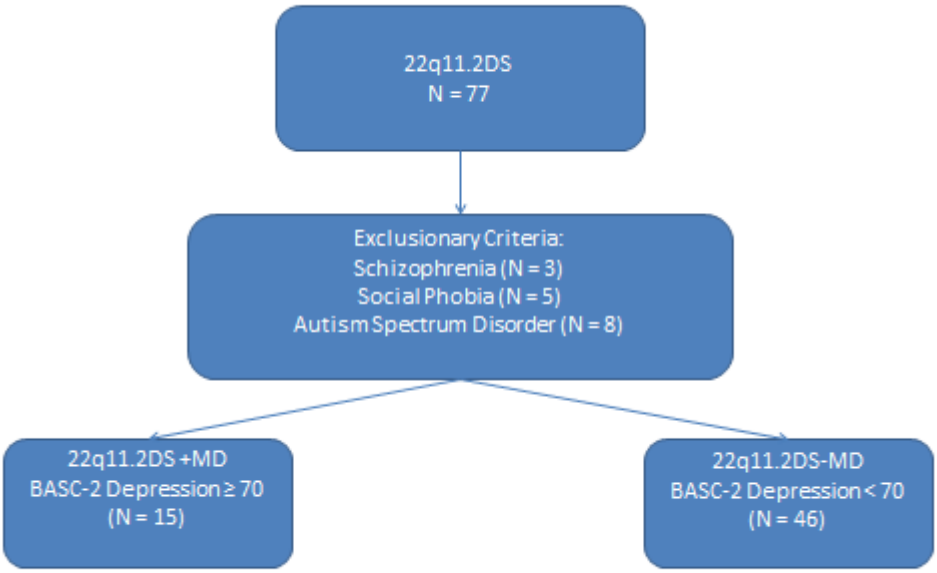

Figure 3. Breakdown of 22q11.2DS groups. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; BASC-2 = Behavioral Assessment System for Children, Second Edition.

Table 4

Descriptive Statistics for Age and Full Scale IQ

Dependent Variable	*N*	*M*	*SD*	Range
Age				
22q11.2DS+MD	15	18.52	2.47	15.00 – 24.00
22q11.2DS-MD	46	18.01	2.21	15.00 – 23.00
Sibling Control	22	18.51	1.82	15.00 – 22.00
Community Control	26	17.60	1.35	16.00 – 21.00
Total	109	18.08	2.00	15.00 – 24.00
FSIQ				
22q11.2DS+MD	14	74.07	13.09	50.00 – 93.00
22q11.2DS-MD	45	73.76	13.46	40.00 – 98.00
Sibling Control	21	110.90	17.25	71.00 – 141.00
Community Control	26	106.58	18.73	68.00 – 153.00
Total	106	89.21	23.22	40.00 – 153.00

Note. 22q11.2DS = 22q11.2 Deletion Syndrome. MD = Mood Disorder. FSIQ = Full Scale IQ.

Levene's test of homogeneity was significant for age, $W(3, 105) = 3.24$, $p = .025$, indicating that variance differed between the groups. Therefore, the assumption of the homogeneity of variance was violated, which was most likely due to unequal group size. As a result, the Welch statistic was examined along with the results of the ANOVA. The Welch *F* ratio is similar to the test statistic provided by an ANOVA, but makes adjustments to residual degrees of freedom in an effort to adjust for problems that may result from violating the assumption of homogeneity of variance (Field, 2005). In addition, it controls the Type I error rate well, so that when there is no effect in the population, the statistic is non-significant

(Field, 2005). Levene's test was not significant for FSIQ, $W(3, 102) = 0.697$, $p = .556$, indicating no difference in variance between groups.

The Welch statistic for age did not indicate a significant effect of group, *Welch's* $F(3, 43.31) = 1.50$, $p = .228$; nor did the results of the ANOVA, $F(3, 105) = 1.10$, $p = .353$. However, the ANOVA for FSIQ did demonstrate a significant effect of group, $F(3, 102) = 43.23$, $p < .001$; both 22q11.2DS groups had significantly lower FSIQ scores than the sibling and community control groups. It was deemed inappropriate to covary for FSIQ, due to nonrandom assignment to group and the fact that lower FSIQ is a core deficit in, and therefore characteristic of, individuals with 22q11.2DS (Dennis, Landry, Barnes, & Fletcher, 2006; Miller & Chapman, 2001). There were no significant gender, $\chi^2(3) = 3.22$, $p = 0.372$, or medication, $\chi^2(3) = 7.71$, $p = .052$, effects. Therefore, age, FSIQ, gender, and medication were not entered as covariates for the remainder of the statistical analyses. Post hoc Tukey HSD multiple comparisons for FSIQ are presented in Table 5.

Table 5

Results of Tukey HSD Post-hoc Tests for Full-Scale IQ

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*
T3 FSIQ	22q11.2DS+MD	22q11.2DS-MD	0.316	4.783	1.00
		Sibling Control	-36.833	5.393	< .001
		Community Control	-32.505	5.181	< .001
	22q11.2DS-MD	22q11.2DS+MD	-0.316	4.783	1.00
		Sibling Control	-37.149	4.131	< .001
		Community Control	-32.821	3.850	< .001
	Sibling Control	22q11.2DS+MD	36.833	5.393	< .001
		22q11.2DS-MD	37.149	4.131	< .001
		Community Control	4.328	4.586	.781
	Community Control	22q11.2+MD	32.505	5.181	< .001
		22q11.2-MD	32.821	3.850	< .001
		Sibling Control	-4.328	4.586	.781

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; FSIQ = Full Scale IQ.

Specific Aim 1

The goal of Specific Aim 1 was to replicate past research by demonstrating greater problems in the social, perceptual, and executive functioning domains in youth and emerging adults with 22q11.2DS as compared to unaffected typically developing (TD) controls.

Hypothesis 1. Hypothesis 1 stated that individuals with 22q11.2DS+MD would show greater impairment in social functioning than individuals with 22q11.2DS-MD, who would show a moderate level of impairment (as demonstrated by effect size) in social functioning as compared to TD controls, as evidenced by higher scores measured by the Total T-score on the SRS and lower scores as measured by the Socialization scale of the VABS-II.

Levene's test for homogeneity of variance for both variables was not significant, SRS Total T-score $W(3, 104) = 1.80$, $p = .152$ and VABS-II Socialization $W(3, 101) = 0.97$, $p = .411$, indicating equal variance between groups. The ANOVA for SRS Total T-score demonstrated a significant effect of group, $F(3, 104) = 57.70$, $p < .001$, as well as the ANOVA for VABS-II Socialization score, $F(3, 101) = 34.32$, $p < .001$. Means and standard deviations for the SRS Total T-score and VABS-II Socialization scale are presented by group in Table 6.

Table 6

Descriptive Statistics for Social Functioning Variables

Dependent Variable	*N*	*M*	*SD*	Range
SRS Total T-score				
22q11.2DS+MD	15	83.73	7.40	65.00 – 90.00
22q11.2DS-MD	46	65.24	12.38	42.00 – 90.00
Sibling Control	21	45.47	9.87	36.00 – 72.00
Community Control	26	45.12	9.57	34.00 – 72.00
Total	108	59.14	17.22	34.00 – 90.00
VABS-II Socialization				
22q11.2DS+MD	14	66.79	11.89	46.00 – 87.00
22q11.2DS-MD	44	76.86	11.14	56.00 – 110.00
Sibling Control	21	95.62	12.23	76.00 – 113.00
Community Control	26	99.15	13.68	73.00 – 119.00
Total	107	84.81	16.87	46.00 – 119.00

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; SRS = Social Responsiveness Scale; VABS-II = Vineland Adaptive Behavior Scales, Second Edition.

Post-hoc comparisons are shown in Table 7 and indicated that the group of individuals with 22q11.2DS+MD rated significantly higher than the group of individuals with 22q11.2DS-MD on the SRS Total scale (Figure 4). In turn, the group of individuals with 22q11.2DS-MD rated significantly higher than both the sibling and community control groups (Figure 3). Post-hoc comparisons also indicated similar group differences on the VABS-II Socialization scale, with the group of individuals with 22q11.2DS+MD scoring significantly lower than the group of individuals with 22q11.2DS-MD, who scored significantly lower than both the sibling and community control groups (Table 7 and Figure 5). Analysis of effect sizes indicated a large effect for group for both the SRS, partial η^2 = .63, and VABS-II Socialization, partial η^2 = .51. Examination of pairwise comparisons again demonstrated large effects of group for the SRS and VABS-II Socialization (Table 7), using Cohen's (1988) guidelines for effect size magnitude (small: d = 0.20, medium: d = 0.50, large: d = 0.80). These results provided support for Hypothesis 1.

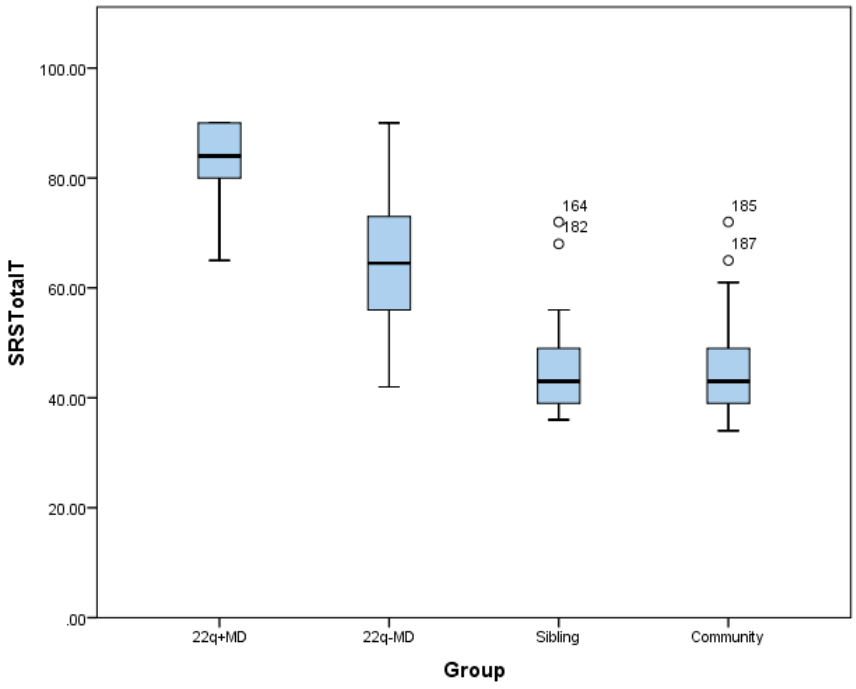

Figure 4. Boxplot of SRS Total T-scores. SRS = Social Responsiveness Scale; 22q = 22q11.2 Deletion Syndrome; MD = Mood Disorder.

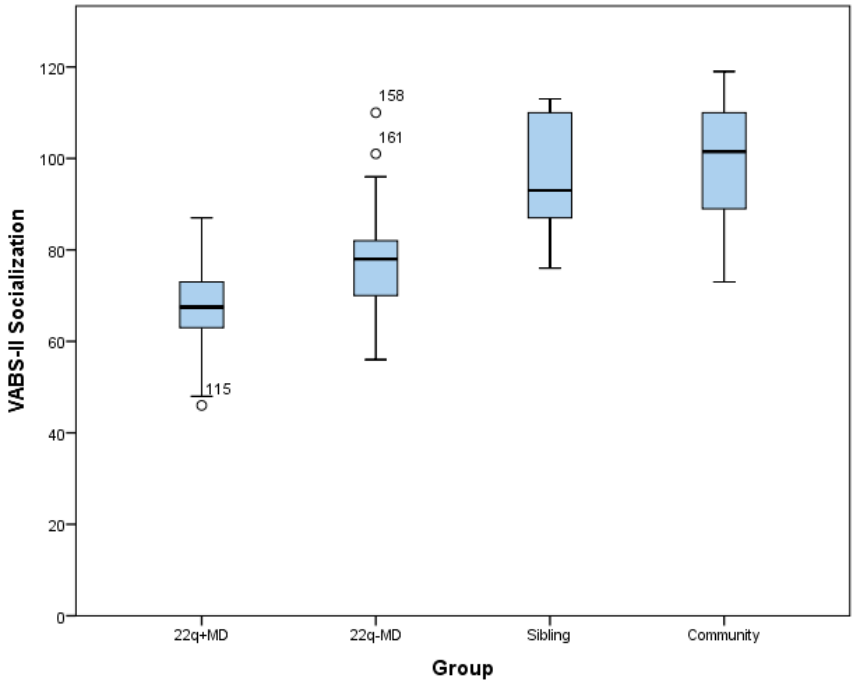

Figure 5. Boxplot of VABS-II Socialization scores. VABS-II = Vineland Adaptive Behavior Scales, Second Edition; 22q = 22q11.2 Deletion Syndrome; MD = Mood Disorder.

Table 7

Results of Tukey HSD Post-hoc Tests for Social Functioning

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*	*d*
SRS Total T-Score	22q11.2DS+MD	22q11.2DS-MD	18.494*	3.181	< .001	1.81
		Sibling Control	38.257*	3.617	< .001	4.39
		Community Control	38.618*	3.469	< .001	4.51
	22q11.2DS-MD	22q11.2DS+MD	-18.494*	3.181	< .001	-1.81
		Sibling Control	19.763*	2.818	< .001	1.76
		Community Control	20.124*	2.625	< .001	1.82
	Sibling Control	22q11.2DS+MD	-38.257*	3.617	< .001	-4.39
		22q11.2DS-MD	-19.763*	2.818	< .001	-1.76
		Community Control	0.361	3.139	.999	
	Community Control	22q11.2DS+MD	-38.618*	3.469	< .001	-4.51
		22q11.2DS-MD	-20.124*	2.625	< .001	-1.82
		Sibling Control	-0.361	3.139	.999	
VABS-II Socialization	22q11.2DS+MD	22q11.2DS-MD	-10.078*	3.720	.039	-0.87
		Sibling Control	-28.833*	4.183	< .001	-2.39
		Community Control	-32.368*	4.019	< .001	-2.53
	22q11.2DS-MD	22q11.2DS+MD	10.078*	3.720	.039	0.87
		Sibling Control	-18.755*	3.215	< .001	-1.60
		Community Control	-22.290*	2.999	< .001	-1.79
	Sibling Control	22q11.2DS+MD	28.833*	4.183	< .001	2.39
		22q11.2DS-MD	18.755*	3.215	< .001	1.60
		Community Control	-3.535	3.557	.753	
	Community Control	22q11.2+MD	32.368*	4.019	< .001	2.53
		22q11.2-MD	22.290*	2.999	< .001	1.79
		Sibling Control	3.535	3.557	.753	

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; SRS = Social Responsiveness Scale; VABS-II = Vineland Adaptive Behavior Scales, Second Edition.

Hypothesis 2. Hypothesis 2 stated that individuals with 22q11.2DS+MD would show greater impairment (lower scores) in visuospatial skills as measured by the WISC-III or WAIS-III Block Design subtest scaled scores as compared to individuals with 22q11.2DS-MD. In turn, individuals with 22q11.2DS-MD would show a moderate level (as demonstrated by effect size) of impairment in visuospatial skills as compared to TD controls. Levene's test of homogeneity was not significant, $W(3, 102) = 0.79$, $p = .502$, indicating equal variance between groups. The ANOVA for WISC-III/WAIS-III Block Design scaled score demonstrated a significant effect of group, $F(3, 102) = 32.53$, $p < .001$. Descriptive statistics are presented in Table 8. Post-hoc comparisons using Tukey's HSD are presented in Table 9 and demonstrated no significant differences between the two groups of individuals with 22q11.2DS. However, the 22q11.2DS+MD and 22q11.2DS-MD groups had significantly lower average scores than the two control groups.

In order to examine whether or not additional subtests scores (i.e., Matrix Reasoning and Picture Completion on the WAIS-III; Picture Completion, Picture Arrangement, and Object Assembly on the WISC-III) would have an effect, an ANOVA was computed for scores on the WAIS-III/WISC-III Perceptual Organization Index (POI). Again, Levene's test of homogeneity was not significant, $W(3, 102) = 0.85$, $p = .472$, indicating equal variance between groups. The ANOVA for POI demonstrated a significant effect of group, $F(3, 102) = 51.07$, $p < .001$, and provided results similar to those found with Block Design (Table 8), demonstrating that a comorbid mood disorder does not appear to present additional burden to visuospatial functioning in individuals with 22q11.2DS. Post-hoc comparisons are presented in Table 9. Results provided partial support for Hypothesis 2.

Table 8

Descriptive Statistics for Visuospatial Functioning Variables

Dependent Variable	*N*	*M*	*SD*	Range
WAIS-III/WISC-III Block Design Scaled Score				
22q11.2DS+MD	14	5.64	3.29	1 - 12
22q11.2DS-MD	45	5.33	3.17	1 - 12
Sibling Control	21	12.86	3.04	5 - 18
Community Control	26	11.12	4.10	1 - 19
Total	106	8.28	4.71	1 - 19
WAIS-III/WISC-III POI				
22q11.2DS+MD	14	75.86	12.99	50.00 – 97.00
22q11.2DS-MD	45	75.18	12.94	50.00 – 99.00
Sibling Control	21	113.19	14.94	76.00 – 138.00
Community Control	26	107.73	17.13	70.00 – 138.00
Total	106	90.81	22.56	50.00 – 138.00

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; WAIS-III = Wechsler Adult Intelligence Scale, 3rd edition; WISC-III = Wechsler Intelligence Scale for Children, 3rd edition; POI = Perceptual Organization Index.

Table 9

Results of Tukey HSD Post-hoc Tests for Visuospatial Functioning

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*	*d*
Block Design Scaled Score	22q11.2DS+MD	22q11.2DS-MD	0.310	1.045	.991	
		Sibling Control	-7.214*	1.178	< .001	-2.28
		Community Control	-5.473*	1.132	< .001	-1.47
	22q11.2DS-MD	22q11.2DS+MD	-0.310	1.045	.991	
		Sibling Control	-7.524*	0.902	< .001	-2.43
		Community Control	-5.782*	0.841	< .001	-1.58
	Sibling Control	22q11.2DS+MD	7.214*	1.178	< .001	2.28
		22q11.2DS-MD	7.524*	0.902	< .001	2.43
		Community Control	1.742	1.001	.309	
	Community Control	22q11.2DS+MD	5.473*	1.132	< .001	1.47
		22q11.2DS-MD	5.782*	0.841	< .001	1.58
		Sibling Control	-1.742	1.001	.309	
POI	22q11.2DS+MD	22q11.2DS-MD	0.679	4.429	.999	
		Sibling Control	-37.333*	4.994	< .001	-2.67
		Community Control	-31.874*	4.798	< .001	-2.10
	22q11.2DS-MD	22q11.2DS+MD	-0.679	4.429	.999	
		Sibling Control	-38.013*	3.825	< .001	-2.50
		Community Control	-32.553*	3.565	< .001	-2.14
	Sibling Control	22q11.2DS+MD	37.333*	4.994	< .001	2.67
		22q11.2DS-MD	38.013*	3.825	< .001	2.50
		Community Control	5.460	4.246	.574	
	Community Control	22q11.2+MD	31.874*	4.798	< .001	2.10
		22q11.2-MD	32.553*	3.565	< .001	2.14
		Sibling Control	-5.460	4.246	.574	

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; POI = Perceptual Organization Index.

Hypothesis 3. Hypothesis 3 stated that individuals with 22q11.2DS+MD would show greater impairment (lower scores) in executive functioning skills as measured by the Wisconsin Card Sorting Test (WCST) Total Correct raw score, number of categories completed, and Perseverative Error standard scores. Individuals with 22q11.2-MD would show a moderate level (as demonstrated by effect size) of impairment in executive functioning skills as compared to TD controls.

Levene's test of homogeneity for WCST Total Correct and Categories Completed was significant, $W(3, 102) = 5.27$, $p = .002$ and $W(3, 102) = 31.62$, $p < .001$, respectively, indicating unequal variance between groups. Therefore, the assumption of the homogeneity of variance was violated. As a result, the Welch statistic was examined along with the results of the ANOVA. In addition, the Games-Howell procedure was used as a post-hoc evaluation for these variables, since it does not include the assumption of equal variances and offers the most powerful results when group size is unequal (Field, 2005). Levene's test was not significant for WCST Perseverative Errors, $W(3, 102) = 0.11$, $p = .956$; therefore, the ANOVA and Tukey's post-hoc procedure were used for this variable.

The Welch statistic for WCST Total Correct did not show a significant effect for group, *Welch's* $F(3, 42.00) = 1.90$, $p = .144$, similar to results of the ANOVA, $F(3, 102) = 1.63$, $p = .188$. The Welch statistic could not be computed for WCST Categories Completed, as the Sibling control group had no variance; all scores were the same. However, the ANOVA did show a significant effect for group, $F(3, 102) = 6.87$, $p < .001$. The ANOVA for Perseverative Errors Standard Score did show a significant effect of group, $F(3, 102) = 12.61$, $p < .001$. Descriptive statistics for executive functioning variables are presented in Table 10.

Table 10

Descriptive Statistics for Executive Functioning Variables

Dependent Variable	*N*	*M*	*SD*	Range
WCST Total Correct Raw				
22q11.2DS+MD	14	70.14	13.47	44 - 88
22q11.2DS-MD	45	70.40	12.49	33 - 88
Sibling Control	21	75.00	5.04	66 - 85
Community Control	26	74.50	5.81	58 - 85
Total	106	72.28	10.28	33 - 88
WCST Categories Completed				
22q11.2DS+MD	14	4.00	1.52	1 - 5
22q11.2DS-MD	45	4.02	1.36	1 - 5
Sibling Control	21	5.00	0	5
Community Control	26	4.92	0.39	3 - 5
Total	106	4.43	1.14	1 - 5
WCST Perseverative Errors SS				
22q11.2DS+MD	14	85.79	14.42	55 - 104
22q11.2DS-MD	45	92.29	17.39	55 - 137
Sibling Control	21	112.62	16.58	80 - 145
Community Control	26	108.77	17.51	67 - 145
Total	106	99.50	19.52	55 - 145

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; WCST = Wisconsin Card Sorting Test; SS = Standard Score.

Post-hoc comparisons are shown in Table 11 and indicated no significant differences between the 22q11.2DS groups; however, the group of individuals with 22q11.2DS-MD scored significantly lower than both control groups on WCST Categories Completed. In addition, both groups of individuals with 22q11.2DS scored lower than both control groups on WCST Perseverative Errors. These results provided partial support for Hypothesis 3.

Table 11

Results of Post-hoc Tests for Executive Functioning

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*	*d*
WCST Categories Completed (Games-Howell)	22q11.2DS+MD	22q11.2DS-MD	-0.022	0.454	1.00	
		Sibling Control	-1.000	0.406	.114	
		Community Control	-0.923	0.413	.162	
	22q11.2DS-MD	22q11.2DS+MD	0.022	0.454	1.00	
		Sibling Control	-0.978*	0.202	< .001	-1.02
		Community Control	-0.901*	0.216	.001	-0.90
	Sibling Control	22q11.2DS+MD	1.00	0.406	.114	
		22q11.2DS-MD	0.978*	0.202	< .001	1.02
		Community Control	0.077	0.077	.751	
	Community Control	22q11.2DS+MD	0.923	0.413	.162	
		22q11.2DS-MD	0.901*	0.216	< .001	0.90
		Sibling Control	-0.077	0.077	.751	
WCST Perseverative Error Standard Score (Tukey HSD)	22q11.2DS+MD	22q11.2DS-MD	-6.503	5.176	.593	
		Sibling Control	-26.833*	5.836	< .001	-1.73
		Community Control	-22.984*	5.607	< .001	-1.43
	22q11.2DS-MD	22q11.2DS+MD	6.503	5.176	.593	
		Sibling Control	-20.330*	4.470	< .001	-1.20
		Community Control	-16.480*	4.166	.001	-0.94
	Sibling Control	22q11.2DS+MD	26.833*	5.836	< .001	1.73
		22q11.2DS-MD	20.330*	4.470	< .001	1.20
		Community Control	3.850	4.962	.865	
	Community Control	22q11.2DS+MD	22.984*	5.607	< .001	1.43
		22q11.2DS-MD	16.480*	4.166	.001	0.94
		Sibling Control	-3.850	4.962	.865	

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; WCST = Wisconsin Card Sorting Test.

Specific Aim 2

The goal of Specific Aim 2 was to compare performance on a task of ToM, the Triangles Test, in individuals with 22q11.2DS+MD and 22q11.2DS-MD to typically developing controls.

Hypothesis 1. Hypothesis 1 stated that individuals with 22q11.2DS+MD would score lower on a measure of ToM as measured by the Triangles Test compared to individuals with 22q11.2DS-MD. In addition, hypothesis 1 stated that individuals with 22q11.2DS-MD would show moderately reduced scores (based on effect size) on the Triangles Test compared to the TD group.

Levene's test for homogeneity of variance was significant for both scores on the Triangles Test; ToM Accuracy: $W(3, 80) = 5.25$, $p = .002$; ToM Mentalization: $W(3, 80) = 5.81$, $p = .001$, indicating differences in variance between the groups (Figures 6 and 7). Therefore, the assumption of the homogeneity of variance was violated. As a result, the Welch statistic was examined along with the results of the ANOVA. In addition, the Games-Howell procedure was used as a post-hoc evaluation for these variables, since it does not include the assumption of equal variances and offers the most powerful results when group size is unequal (Field, 2005).

The Welch statistic for the ToM variables showed a significant effect for group: Triangles ToM Accuracy *Welch's* $F(3, 34.92) = 9.63$, $p < .001$; and Triangles ToM Mentalization *Welch's* $F(3, 35.64) = 7.50$, $p = .001$. Similarly, the ANOVAs for both the ToM Accuracy and ToM Mentalization scores demonstrated significant effects of group, $F(3, 80) = 8.79$, $p < .001$ and $F(3, 80) = 5.88$, $p = .001$, respectively. Descriptive statistics for the Triangles Test variables are presented in Table 12.

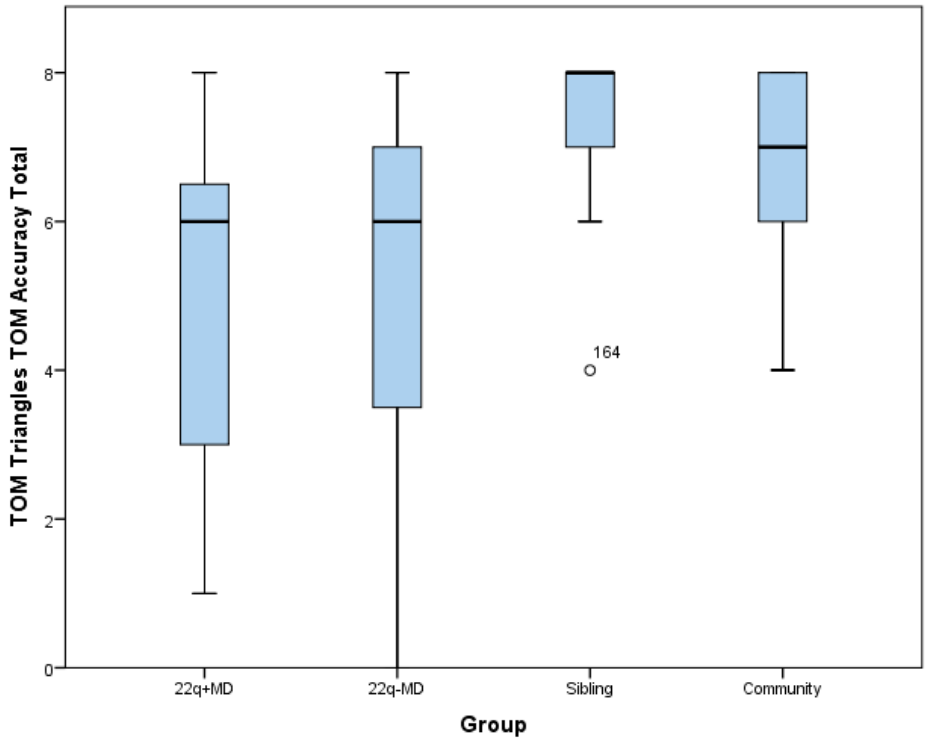

Figure 6. Boxplot of theory of mind accuracy scores. TOM = Theory of Mind; 22q = 22q11.2 Deletion Syndrome; MD = Mood Disorder.

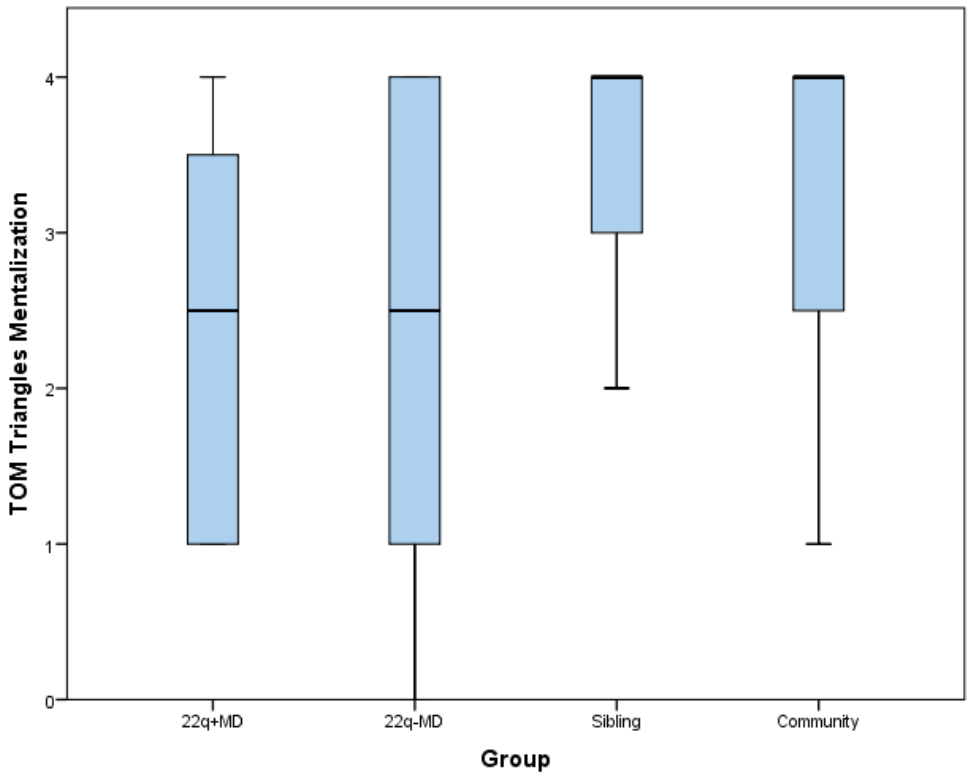

Figure 7. Boxplot of theory of mind mentalization scores. TOM = Theory of Mind; 22q = 22q11.2 Deletion Syndrome; MD = Mood Disorder.

Table 12

Descriptive Statistics for Theory of Mind Variables

Dependent Variable	*N*	*M*	*SD*	Range
Triangles ToM Accuracy				
22q11.2DS+MD	12	5.00	2.22	1.0 – 8.0
22q11.2DS-MD	32	5.25	2.03	0 – 8.0
Sibling Control	17	7.35	1.06	4.0 – 8.0
Community Control	23	6.87	1.29	4.0 – 8.0
Total	84	6.08	1.95	0 – 8.0
Triangles ToM Mentalization				
22q11.2DS+MD	12	2.42	1.24	1.0 – 4.0
22q11.2DS-MD	32	2.41	1.32	0 – 4.0
Sibling Control	17	3.59	0.62	2.0 – 4.0
Community Control	23	3.30	1.06	1.0 – 4.0
Total	84	2.89	1.22	0 – 4.0

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; ToM = Theory of Mind.

Post-hoc comparisons are shown in Table 13 and again indicated no significant differences between the two groups of individuals with 22q11.2DS on ToM scores. However, the group of individuals with 22q11.2DS+MD did have a significantly lower average score than sibling controls on ToM Accuracy, and the group of individuals with 22q11.2DS-MD had a significantly lower average score than both control groups. For ToM Mentalization scores, both groups of individuals with 22q11.2DS had a significantly lower average score than the sibling control group. In addition, the group of individuals with

22q11.2DS-MD had a significantly lower average score than the community control group. These results provided partial support for Hypothesis 1.

Table 13

Results of Games-Howell Post-hoc Procedure for Triangles Test- Theory of Mind

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*	*d*
ToM Accuracy	22q11.2DS+MD	22q11.2DS-MD	-0.250	0.734	.986	
		Sibling Control	-2.353*	0.689	.019	-1.35
		Community Control	-1.870	0.694	.071	
	22q11.2DS-MD	22q11.2DS+MD	0.250	0.734	.986	
		Sibling Control	-2.103*	0.441	< .001	-1.30
		Community Control	-1.620*	0.449	.004	-0.95
	Sibling Control	22q11.2DS+MD	2.353*	0.689	.019	1.35
		22q11.2DS-MD	2.103*	0.441	< .001	1.30
		Community Control	0.483	0.372	.568	
	Community Control	22q11.2DS+MD	1.870	0.694	.071	
		22q11.2DS-MD	1.620*	0.449	.004	0.95
		Sibling Control	-0.483	0.372	.568	
ToM Mentalization	22q11.2DS+MD	22q11.2DS-MD	0.010	0.427	1.00	
		Sibling Control	-1.172*	0.388	.039	-1.19
		Community Control	-0.888	0.421	.185	
	22q11.2DS-MD	22q11.2DS+MD	-0.010	0.427	1.00	
		Sibling Control	-1.182*	0.277	.001	-1.15
		Community Control	-0.898*	0.321	.035	-0.74
	Sibling Control	22q11.2DS+MD	1.172*	0.388	.039	1.19
		22q11.2DS-MD	1.182*	0.277	.001	1.15
		Community Control	0.284	0.268	.715	
	Community Control	22q11.2+MD	0.888	0.421	.185	
		22q11.2-MD	0.898*	0.321	.035	0.74
		Sibling Control	-0.284	0.268	.715	

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; ToM = Theory of Mind.

Specific Aim 3

The goal of Specific Aim 3 was to compare performance in adaptive functioning as measured by scores on the VABS-II in youth and emerging adults with 22q11.2DS+MD and youth and emerging adults with 22q11.2DS-MD to typically developing controls.

Hypothesis 1. Hypothesis 1 stated that individuals with 22q11.2DS+MD would show poorer functional outcomes (lower scores on the Daily Living Skills, Communication, Socialization, and Adaptive Composite scales of the VABS-II) compared to individuals with 22q11.2DS-MD. Individuals with 22q11.2-MD would show a moderate degree of functional outcome impairment (as determined by effect size) compared to the TD group.

Levene's test for homogeneity of variance was significant for the Communication and Adaptive Composite scales on the VABS-II, $W(3, 101) = 9.59$, $p < .001$ and $W(3, 101) = 5.71$, $p = .001$, respectively, indicating differences in variance between groups on these scales. Therefore, the assumption of the homogeneity of variance was violated. As a result, the Welch statistic was examined along with the results of the ANOVA. In addition, the Games-Howell procedure was used as a post-hoc evaluation for these variables, since it does not include the assumption of equal variances and offers the most powerful results when group size is unequal (Field, 2005). Levene's test was not significant for the Daily Living Skills, $W(3, 101) = 1.07$, $p = .364$, or Socialization, $W(3, 101) = 0.97$, $p = .411$, scales on the VABS-II, indicating equal variance between groups.

The Welch statistic for VABS-II Communication and VABS-II Adaptive Composite scales variables showed a significant effect for group, *Welch's* $F(3, 43.84) = 46.67$, $p < .001$ and *Welch's* $F(3, 41.92) = 32.76$, $p < .001$, respectively. Similarly, the ANOVA results for all four variables indicated a significant effect for group: VABS-II Communication $F(3, 101)$

= 46.24, $p < .001$; VABS-II Socialization $F(3, 101) = 34.32$, $p < .001$; VABS-II Daily Living Skills $F(3, 101) = 14.71$, $p < .001$; and VABS-II Adaptive Composite $F(3, 101) = 33.49$, $p < .001$. Descriptive statistics for the VABS-II variables are presented in Table 14.

Table 14

Descriptive Statistics for Adaptive Functioning Variables

Dependent Variable	*N*	*M*	*SD*	Range
VABS-II Communication				
22q11.2DS+MD	14	69.07	5.07	63.00 – 78.00
22q11.2DS-MD	44	74.93	7.86	57.00 – 93.00
Sibling Control	21	98.67	14.39	71.00 – 117.00
Community Control	26	98.77	14.34	61.00 – 117.00
Total	105	84.80	16.63	57.00 – 117.00
VABS-II Socialization				
22q11.2DS+MD	14	66.79	11.89	46.00 – 87.00
22q11.2DS-MD	44	76.86	11.14	56.00 – 110.00
Sibling Control	21	95.62	12.23	76.00 – 113.00
Community Control	26	99.15	13.68	73.00 – 119.00
Total	105	84.79	16.98	46.00 – 119.00
VABS-II Daily Living Skills				
22q11.2DS+MD	14	73.50	11.10	56.00 – 96.00
22q11.2DS-MD	44	78.80	13.10	51.00 – 114.00
Sibling Control	21	95.24	16.55	66.00 – 130.00
Community Control	26	94.58	12.84	71.00 – 116.00
Total	105	85.29	16.03	51.00 – 130.00
VABS-II Adaptive Composite				
22q11.2DS+MD	14	67.79	7.11	59.00 – 84.00
22q11.2DS-MD	44	74.32	9.04	55.00 – 103.00
Sibling Control	21	95.52	15.98	71.00 – 133.00
Community Control	26	96.58	14.75	66.00 – 121.00
Total	105	83.20	16.80	55.00 – 133.00

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; VABS-II = Vineland Adaptive Behavior Scales, Second Edition.

Post-hoc comparisons are shown in Table 15 and indicated that the group of individuals with 22q11.2DS+MD had a significantly lower average score than the group of individuals with 22q11.2DS-MD on the VABS-II Communication and Adaptive Composite scales (VABS-II Socialization was previously reported in Table 7, p. 56). In addition, both 22q11.2DS groups had significantly lower average scores on these scales than both control groups. Analysis of effect sizes indicated a large effect for group for the Communication (partial η^2 = .579), Socialization (partial η^2 = .505), and Adaptive Composite (partial η^2 = .499) scores. Examination of pairwise comparisons again demonstrated large effects of group for the VABS-II Communication, and Adaptive Composite scores (Table 15; VABS-II Socialization previously reported in Table 7, p. 56), using Cohen's (1988) guidelines for effect size magnitude (small: d = 0.20, medium: d = 0.50, large: d = 0.80). There were no significant differences between the two groups of individuals with 22q11.2DS for the VABS-II Daily Living Skills scale, but post-hoc comparisons did demonstrate that both groups of individuals with 22q11.2DS had significantly lower average scores on this scale than both control groups. These results provided partial support for Hypothesis 1.

Table 15

Results of Post-hoc Procedures for Adaptive Functioning

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	*p*	*d*
VABS-II Communication (Games-Howell)	22q11.2DS+MD	22q11.2DS-MD	-5.860*	1.801	.013	-0.89
		Sibling Control	-29.595*	3.421	< .001	-2.74
		Community Control	-29.698*	3.122	< .001	-2.76
	22q11.2DS-MD	22q11.2DS+MD	5.860*	1.801	.013	0.89
		Sibling Control	-23.735*	3.357	< .001	-2.04
		Community Control	-23.837*	3.052	< .001	-2.06
	Sibling Control	22q11.2DS+MD	29.595*	3.421	< .001	2.74
		22q11.2DS-MD	23.735*	3.357	< .001	2.04
		Community Control	-0.103	4.216	1.00	
	Community Control	22q11.2DS+MD	29.698*	3.122	< .001	2.76
		22q11.2DS-MD	23.837*	3.052	< .001	2.06
		Sibling Control	0.103	4.216	1.00	
VABS-II Daily Living Skills (Tukey HSD)	22q11.2DS+MD	22q11.2DS-MD	-5.295	4.162	.583	
		Sibling Control	-21.738*	4.680	< .001	-1.54
		Community Control	-21.077*	4.497	< .001	-1.76
	22q11.2DS-MD	22q11.2DS+MD	5.295	4.162	.583	
		Sibling Control	-16.443*	3.598	< .001	-1.10
		Community Control	-15.781*	3.355	< .001	-1.22
	Sibling Control	22q11.2DS+MD	21.738*	4.680	< .001	1.54
		22q11.2DS-MD	16.443*	3.598	< .001	1.10
		Community Control	0.661	3.980	.998	
	Community Control	22q11.2+MD	21.077*	4.497	< .001	1.76
		22q11.2-MD	15.781*	3.355	< .001	1.22
		Sibling Control	-0.661	3.980	.998	
VABS-II Adaptive Composite (Games-Howell)	22q11.2DS+MD	22q11.2DS-MD	-6.532*	2.337	.044	-0.80
		Sibling Control	-27.738*	3.971	< .001	-2.24
		Community Control	-28.791*	3.460	< .001	-2.49
	22q11.2DS-MD	22q11.2DS+MD	6.532*	2.337	.044	0.80
		Sibling Control	-21.206*	3.744	< .001	-1.63
		Community Control	-22.259*	3.197	< .001	-1.82
	Sibling Control	22q11.2DS+MD	27.738*	3.971	< .001	2.24
		22q11.2DS-MD	21.206*	3.744	< .001	1.63
		Community Control	-1.053	4.531	.996	
	Community Control	22q11.2+MD	28.791*	3.460	< .001	2.49
		22q11.2-MD	22.259*	3.197	< .001	1.82
		Sibling Control	1.053	4.531	.996	

Note. 22q11.2DS = 22q11.2 Deletion Syndrome; MD = Mood Disorder; VABS-II = Vineland Adaptive Behavior Scales, Second Edition.

Specific Aim 4

The goal of specific aim 4 was to demonstrate that social, perceptual, and executive functioning were related to functional outcome in individuals with 22q11.2DS and neurotypicals.

Hypothesis 1. Hypothesis 1 stated that scores on the Total scale on the SRS would be negatively correlated with functional outcomes as measured by the Socialization, Daily Living Skills, Communication, and Adaptive Composite scales of the VABS-II.

Results of Pearson correlational analyses demonstrated significant moderate negative linear relationships between VABS-II Socialization and Adaptive Composite scores and the SRS Total T-score among individuals with 22q11.2DS+MD and Sibling Control group. In addition, a significant moderate negative correlation was found between VABS-II Communication and SRS Total T-score in the Sibling Control group. Among individuals with 22q11.2DS-MD, similar significant moderate negative linear relationships were found between all VABS-II scores and the SRS Total T-score. Stronger significant negative relationships were found between all VABS-II scores and the SRS Total T-score in the Community Control group. Hypothesis 1 was partially supported. Pearson correlation results are presented by group in Table 16.

Table 16

Pearson Correlation Coefficients for Social and Adaptive Functioning

Group	VABS-II Comm.	VABS-II DLS	VABS-II Social.	VABS-II Composite
22q11.2DS+MD				
SRS Total T-score	-.157	-.197	-.631**	-.507*
22q11.2DS-MD				
SRS Total T-score	-.603**	-.465**	-.540**	-.539**
Sibling Control				
SRS Total T-score	-.590**	-.059	-.662**	-.474*
Community Control				
SRS Total T-score	-.725**	-.647**	-.824**	-.755**

Note. VABS-II = Vineland Adaptive Behavior Scales, Second Edition; Comm. = Communication; DLS = Daily Living Skills; Social. = Socialization, SRS = Social Responsiveness Scale.

* $p < .05$, one-tailed. ** $p < .01$, one-tailed.

Hypothesis 2. Hypothesis 2 stated that scaled scores on the WISC-III/WAIS-III Block Design would be positively correlated with functional outcomes as measured by the Daily Living Skills, Communication, and Adaptive Composite scales of the VABS-II.

Results of Pearson correlational analyses demonstrated significant small positive linear relationships between VABS-II Communication, Daily Living Skills, and Adaptive Composite and the Block Design scaled scores, as well as VABS-II Communication and the Wechsler POI in the 22q11.2DS-MD group. Somewhat stronger significant positive linear relationships were found between VABS-II Communication and Block Design scaled scores in the Sibling and Community Control groups, as well as between VABS-II Communication and POI in the Community Control group. There were no significant relationships between visuospatial functioning variables and the VABS-II Socialization scale for any groups.

Results provided partial support for Hypothesis 2. Pearson correlation results are presented by group in Table 17.

Table 17

Pearson Correlation Coefficients for Visuospatial and Adaptive Functioning

Group		VABS-II Comm.	VABS-II DLS	VABS-II Social.	VABS-II Composite
22q11.2DS+MD					
	Block Design	.126	-.121	.230	.108
	POI	.244	-.047	.267	.208
22q11.2DS-MD					
	Block Design	.253*	.306*	.156	.267*
	POI	.270*	.228	.124	.204
Sibling Control					
	Block Design	.469*	.222	.258	.308
	POI	.362	.232	.272	.272
Community Control					
	Block Design	.421*	.289	.309	.327
	POI	.370*	.291	.263	.294

Note. VABS-II = Vineland Adaptive Behavior Scales, Second Edition; Comm. = Communication; DLS = Daily Living Skills; Social. = Socialization; POI = Perceptual Organization Index.

* $p < .05$, one-tailed.

Hypothesis 3. Hypothesis 3 stated that scores on the WCST (Total Correct raw score, categories completed, Perseverative Error standard score) would be positively correlated with functional outcome as measured by the Daily Living Skills, Communication, and Adaptive Composite scales of the VABS-II.

Results of Pearson correlational analyses demonstrated the strongest significant moderate positive linear relationships between the VABS-II Communication scale and the WCST Total Correct and Categories Completed scores for the 22q11.2DS+MD group. The results also showed significant moderate positive linear relationships between all variables in the 22q11.2DS-MD group. There was a significant moderate positive correlation between VABS-II Communication and WCST Perseverative Error Standard Score in the Sibling Control group; however, correlations were not computed for the WCST Categories Completed score due to the fact that all individuals achieved the same score on that particular scale. There were also significant moderate positive correlations between VABS-II Communication and all three WCST variables, as well as significant weak to moderate positive correlations for all VABS-II variables and WCST Categories Completed for the Community Control group. Finally, a smaller significant positive linear relationship was noted between the VABS-II Composite and WCST Perseverative Error Standard Score for the Community Control group. The pattern of observed positive relationships provided partial support for Hypothesis 3. Pearson correlation results are presented by group in Table 18.

Table 18

Pearson Correlation Coefficients for Executive and Adaptive Functioning

Group	VABS-II Comm.	VABS-II DLS	VABS-II Social.	VABS-II Composite
22q11.2DS+MD				
WCST Total Correct	.621**	.320	.191	.425
WCST Categories Completed	.579*	.470*	.115	.449
WCST Perseverative Error SS	.336	.317	-.016	.254
22q11.2DS-MD				
WCST Total Correct	.387**	.463**	.318*	.428**
WCST Categories Completed	.569**	.486**	.405**	.512**
WCST Perseverative Error SS	.473**	.407**	.442**	.463**
Sibling Control				
WCST Total Correct	.078	.226	.019	.158
WCST Categories Completed	-	-	-	-
WCST Perseverative Error SS	.495*	-.018	.313	.246
Community Control				
WCST Total Correct	.565**	-.006	.317	.311
WCST Categories Completed	.537**	.374*	.390*	.423*
WCST Perseverative Error SS	.541**	.261	.246	.341*

Note. VABS-II = Vineland Adaptive Behavior Scales, Second Edition; Comm. = Communication; DLS = Daily Living Skills; Social. = Socialization; WCST = Wisconsin Card Sorting Test; SS = Standard Score.

*$p < .05$, one-tailed. **$p < .01$, one-tailed.

Specific Aim 5

The goal of Specific Aim 5 was to examine the relationship between ToM (as measured by the Triangles Test) and functional outcomes in individuals with 22q11.2DS+MD, individuals with 22q11.2DS-MD, and neurotypical youth and emerging adults, as measured by the VABS-II.

Hypothesis 1. Hypothesis 1 stated that scores on the Triangles Test would be positively correlated with functional outcomes as measured by the Communication, Daily Living Skills, Socialization, and Adaptive Composite scales of the VABS-II in all groups.

Results of Pearson correlational analyses demonstrated no strong significant linear relationships between the VABS-II variables and ToM variables, with the exception of a significant weak positive linear relationship between VABS-II Communication and ToM Mentalization in the group of individuals with 22q11.2DS-MD. Based on these results, this hypothesis was not supported. Pearson correlation results are presented by group in Table 19.

Table 19

Pearson Correlation Coefficients for Theory of Mind and Adaptive Functioning

Group	VABS-II Comm.	VABS-II DLS	VABS-II Social.	VABS-II Composite
22q11.2DS+MD				
Triangles ToM Accuracy	.234	-.004	-.004	.087
Triangles ToM Mentalization	.292	-.110	-.157	-.035
22q11.2DS-MD				
Triangles ToM Accuracy	.256	.104	.119	.129
Triangles ToM Mentalization	.330*	.228	.275	.284
Sibling Control				
Triangles ToM Accuracy	.342	.072	.072	.260
Triangles ToM Mentalization	.102	-.212	-.212	.016
Community Control				
Triangles ToM Accuracy	.101	-.069	.129	-.036
Triangles ToM Mentalization	.074	-.155	.111	-.082

Note. VABS-II = Vineland Adaptive Behavior Scales, Second Edition; Comm. = Communication; DLS = Daily Living Skills; Social. = Socialization; ToM = Theory of Mind.

*$p < .05$, one-tailed.

Specific Aim 6

The goal of Specific Aim 6 was to examine the contributions of visuospatial processing, theory of mind, social functioning, and executive functioning as mediators of mood disorder diagnosis in individuals with 22q11.2DS.

Hypothesis 1. Hypothesis 1 stated that lower visuospatial functioning performance (as measured by the WISC-III or WAIS-III Block Design scaled score), lower ToM performance (as measured by the Triangles Test Mentalization score), lower social functioning performance (as measured by the VABS-II Socialization Scale), and lower executive functioning performance (as measured by the WCST Perseverative Error Standard Score) would lead to greater likelihood of a mood disorder diagnosis (as determined by the BASC-2) in individuals with 22q11.2DS.

A mediation model was tested for which the association between 22q11.2DS and mood disorder was explained by visuospatial, social, executive and ToM functioning. Due to the fact that the VABS-II Socialization score gives a broader measure of overall social functioning (i.e., interpersonal relationships, play and leisure time, and coping skills), as opposed to the SRS, which was specifically designed to measure social functioning features related to Autism Spectrum Disorder (i.e., social cognition, social awareness, autistic mannerisms), the VABS-II was used for this particular analysis. The model constructed simultaneously tested multiple mediated paths and employed bootstrap resampling to create confidence intervals around the estimated indirect effects (Preacher & Hayes, 2008). See Figure 8 for a visual depiction of the tested model.

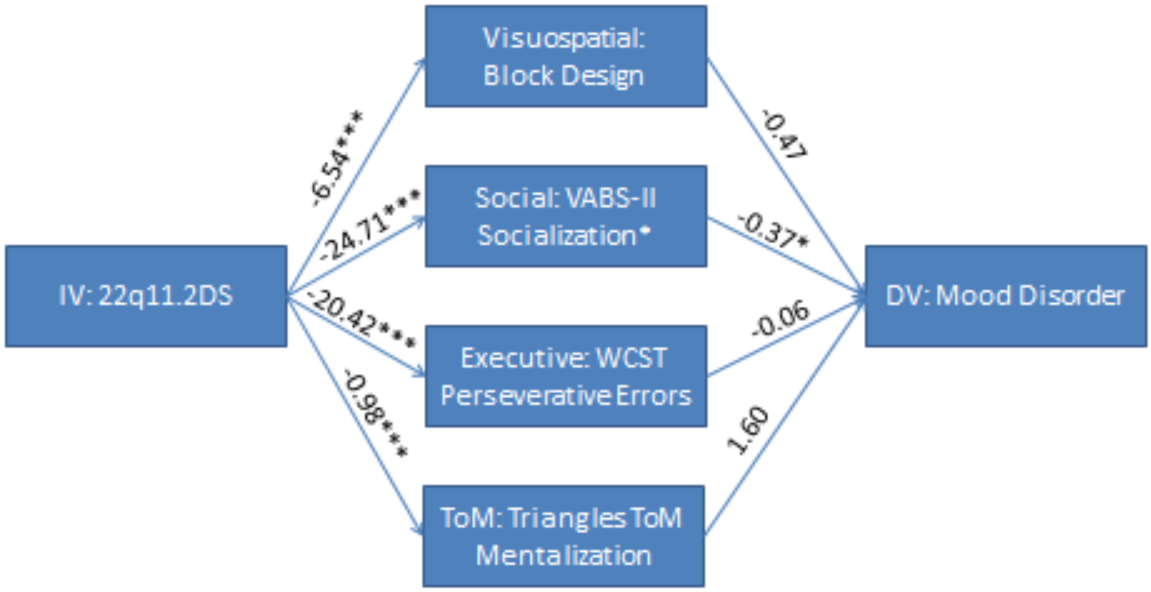

Figure 8. Results of multiple mediator model. Weights presented are unstandardized regression weights that were obtained from a model appropriate for multiple mediators that employed 5000 bootstrap resamples. The asterisk connected to the mediator label indicates that the bias corrected 95% confidence interval estimating the indirect effect is significantly different from zero for that indirect pathway. 22q11.DS = 22q11.2 Deletion Syndrome; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; WCST = Wisconsin Card Sorting Test; ToM = Theory of Mind.

* $p < .05$. *** $p < .0001$.

Upon the addition of the four mediators, the previously significant association between 22q11.2DS and mood disorder (β = 15.69, $t(79) = 5.35$, $p < .001$) dropped to nonsignificance (β = 3.78, $t(79) = 0.84$, $p = .4055$). Examining the indirect effect, results from bias corrected 95% confidence intervals (CIs) suggest that the overall indirect effect was significantly different from zero [3.85, 24.62]. More specifically, the indirect effect between 22q11.2DS and mood disorder through VABS-II Socialization was significantly different from zero [2.69, 18.16], whereas the indirect effects through Block Design [-4.53, 13.78], WCST Perseverative Errors [-4.13, 5.90], and ToM Mentalization [-5.97, 1.15] were not (Table 20). Therefore, the VABS-II Socialization variable accounts for the mediating effect.

Table 20

Mediation of the Effect of 22q11.2DS on a Diagnosis of Mood Disorder through Visuospatial, Executive, ToM, and Social Functioning

				Bootstrapping	
	Point	Product of Coefficients		BC 95% CI	
	Estimate	*SE*	*Z*	Lower	Upper
Block Design	3.0913	3.1784	0.9726	-4.5264	13.7825
ToM Ment.	-1.5684	1.3158	-1.1920	-5.9725	1.1483
WCST Pers. Err.	1.2131	2.1541	0.5632	-4.1315	5.8956
VABS-II Soc.	9.1758	2.9669	3.0927	2.6852	18.1640
TOTAL	11.9118	3.6511	3.2626	3.8499	24.6222

Note. BC = Bias Corrected; ToM = Theory of Mind; Ment. = Mentalization; WCST = Wisconsin Card Sorting Test; Pers. Err. = Perseverative Errors; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; Soc. = Socialization.

Chapter 5: Discussion

This study examined the social, visuospatial, ToM, and executive functioning abilities of youth and emerging adults with 22q11.2DS and comorbid mood disorder. Results were compared to youth and emerging adults with 22q11.2DS and no mood disorder, sibling, and community controls. The study also explored relationships between adaptive functioning and social, visuospatial, executive, and ToM functioning. In addition, the study examined a multiple mediator model that explored visuospatial, social, ToM, and executive functioning as potential mediators that could contribute to mood disorder among individuals with 22q11.2DS.

Specific Aim 1

Social functioning differences. A large effect for group was found for SRS Total T-score, with individuals with 22q11.2DS and comorbid mood disorder showing more social difficulties, as evidenced by higher scores, than the group of individuals with 22q11.2DS and no mood disorder. Group membership had a large effect, accounting for 62.5 percent of the variance. Similarly, VABS-II Socialization scores also showed a large effect for group. Once again, individuals with 22q11.2DS and comorbid mood disorder showed more social difficulties, as evidenced by lower scores, than the group of individuals with 22q11.2DS and no mood disorder. Group membership again had a large effect, accounting for 50.5% of the variance.

These findings may be explained by the withdrawal and anhedonia that often accompanies a diagnosis of mood disorder, particularly MDD. These findings also indicate that the SRS, which was designed to measure social problems characteristic of Autism Spectrum Disorder (i.e., social cognition, social awareness, social communication, autistic

mannerisms), also appears to detect social difficulties in individuals with mood disorder. Unfortunately, examination of the specific treatment scales was not possible for the purposes of this study, as many of the participants completed an adult version of the test, which only included the Total T-score. Further exploration of treatment subscales among individuals with mood disorder may help identify whether social cognition in particular plays a role in these social difficulties.

Another consideration involves the fact that the VABS-II measures overall social functioning (i.e., interpersonal relationships, play and leisure time, and coping skills). The findings from the present study indicate that individuals with 22q11.2DS and comorbid mood disorder experience more difficulties in these areas than individuals with 22q11.2DS and no mood disorder. This finding could be an indication of target areas for intervention among individuals with 22q11.2DS and comorbid mood disorders; teaching relationship management and coping skills, in particular, could prove beneficial in improving social functioning in individuals with 22q11.2DS.

Visuospatial functioning differences. Individuals with 22q11.2DS demonstrated greater difficulty with visuospatial functioning as measured by both the block design subtest and the POI on the WAIS-III/WISC-III than both unaffected control groups, regardless of mood disorder diagnosis. This is an intriguing finding considering the subtests involved. Block Design (WAIS-III and WISC-III), Picture Completion (WAIS-III and WISC-III), Picture Arrangement (WISC-III) and Object Assembly (WISC-III) are all timed subtests, which factors into the scaled scores. Individuals with mood disorder, particularly MDD, often experience psychomotor retardation (APA, 2013), and would therefore be expected to demonstrate more impaired performance on these tasks, which was not the case in the present

study. The genetic condition therefore appears to better explain the differences in visuospatial functioning, a result consistent with past research that poorer performance on visuospatial tasks is a well-established phenotypic characteristic of the 22q11.2DS population (De Smedt et al., 2007; Golding-Kushner et al., 1985; Lajiness-O'Neill et al., 2006; Moss et al., 1999; Niklasson et al., 2002; Shprintzen, 2000; Swillen et al., 1997).

Executive functioning differences. Examination of the WCST variables, an objective measure of set shifting, again indicated that a comorbid mood disorder does not appear to present an additional burden to executive functioning skills among individuals with 22q11.2DS. Instead, much like the visuospatial functioning results, the executive functioning variables examined in this study demonstrated differences between both groups of individuals with 22q11.2DS and controls.

Studies of executive functioning, particularly set shifting, have shown contradictory results among individuals with mood disorder. For example, Stordal and colleagues (2004) found significant impairment in executive functioning among adults with moderate to severe recurrent MDD compared to controls, as evidenced by lower scores on WCST Perseverative Errors, but not WCST Categories Completed. Similarly, Channon (1996) found that dysphoric first and second year university students made more perseverative errors on the WCST than nonaffected controls, attributing this performance to difficulties related to making adequate use of feedback in order to determine the correct sorting principle. Finally, Martin, Oren, and Boone (1991) found that a diagnosis of MDD (based on clinical diagnostic interview and self-report measures) predicted poorer scores on WCST Perseverative Errors and Conceptual Level responses, and more severe depressive symptomatology predicted

poorer performance on WCST Total Errors, Failure to Maintain Set, and Perseverative Responses.

A possible explanation of the current findings may relate to the fact that mood disorder was based on parent report, and therefore a formal diagnosis by a professional was not utilized. In addition, it is possible that lower general cognitive ability (FSIQ) among the 22q11.2DS groups is responsible for the lack of difference. Follow up correlational analyses did confirm significant positive moderate relationships between both WCST Categories Completed and FSIQ ($r = 0.534$, $p < .001$, 2-tailed) and WCST Perseverative Errors and FSIQ ($r = 0.766$, $p < .001$, 2-tailed). Therefore, higher executive functioning scores were associated with higher FSIQ scores. Although this is not a causal explanation, these results provide support for the idea that cognitive difficulties associated with 22q11.2DS appear to play a role in the executive functioning findings. In addition, the results of the present study highlight the importance of considering both objective and parent report measures of executive functioning, as the present results were contradictory to those of Antshel and colleagues (2006), who found more impaired executive functioning via parent report among individuals with 22q11.2DS and comorbid MDD.

Specific Aim 2

Theory of mind differences. The results for ToM were similar to the results for visuospatial and executive functioning; contrary to the hypothesis, a comorbid mood disorder was not associated with ToM functioning in individuals with 22q11.2DS. However, individuals with 22q11.2DS did demonstrate poorer performance than the sibling and community control groups. Of note, the findings of the present study are consistent with findings of ToM abilities in individuals with 22q11.2DS with and without comorbid ASD

diagnosis (Ho et al., 2013). Given that ToM difficulties are a hallmark feature of ASD, this finding is particularly intriguing. Several factors could account for these findings. The Triangles Test is a first-order ToM task, one that involves more basic ToM skills. It is possible that, much like studies completed in adults with mood disorder, performance would be impaired on tasks that measure second order ToM abilities (Inoue, Tonooka, Yamada, & Kanba, 2004). In addition, the group of individuals with 22q11.2DS and comorbid mood disorder was much smaller than the group of individuals with 22q11.2DS and no mood disorder. Although the study used post-hoc statistical procedures that accounted for differences in group size, the study likely suffered from low statistical power. It is therefore possible that differences would emerge in a study that includes a larger sample size.

Finally, much like the executive functioning findings, it is also possible that lower general cognitive ability (FSIQ) among the 22q11.2DS groups played a role in the lack of difference. Follow up correlational analyses did demonstrate a significant moderate positive relationship between ToM Accuracy and FSIQ ($r = 0.655$, $p < .001$, 2-tailed), as well as between ToM Mentalization and FSIQ ($r = 0.537$, $p < .001$, 2-tailed). Therefore, higher ToM scores were associated with higher FSIQ scores. As stated previously, FSIQ is known to be quite variable in the 22q11.2DS population. It is therefore possible that the ToM deficits seen in the 22q11.2DS group are due to lower IQ, instead of a diagnosis of 22q11.2DS. Although it was initially suggested that IQ be included as a covariate in these analyses, this idea has been discussed in previous studies and it was determined inappropriate to do so due to the fact that FSIQ is a group-defining variable (Campbell et al., 2011; Miller & Chapman, 2001).

Specific Aim 3

Adaptive functioning differences. Findings from the VABS-II indicated that comorbid mood disorder was associated with additional burden to adaptive functioning among individuals with 22q11.2DS in the areas of communication and overall functioning (Adaptive Composite). In addition, both groups of individuals with 22q11.2DS scored lower than typically developing controls on these scales. The difference between 22q11.2DS groups was not found on the Daily Living Skills scale.

Communication. The VABS-II Communication scale evaluates receptive (e.g., how well the individual listens and understands), expressive (e.g., how well he or she uses words and sentences) and written (e.g., how well he or she expresses him/herself via writing) communication. The findings from the present study indicated that individuals with 22q11.2DS and comorbid mood disorder experienced more difficulty with these types of tasks than individuals with 22q11.2DS and no mood disorder. A possible explanation for this result may be that individuals with mood disorder, particularly MDD, often experience fatigue and a diminished ability to think or concentrate (APA, 2013). Therefore, the ability to express oneself and understand what is said may be affected and reflected in the lower Communication scores among the 22q11.2DS+MD group. This finding may also be related to the diminished interest or pleasure in activities (anhedonia) that accompanies MDD, in that the affected individual no longer enjoys interacting with others as much as he/she may have previously.

Socialization. As previously reported, the VABS-II Socialization scores showed a large effect for group. Individuals with 22q11.2DS and comorbid mood disorder showed more social difficulties, as evidenced by lower scores, than the group of individuals with

22q11.2DS and no mood disorder. Group membership had a large effect, accounting for 50.5% of the variance. As previously discussed in Specific Aim 1, this may be explained by the withdrawal and anhedonia that often accompanies a diagnosis of mood disorder, particularly MDD. This finding also provides further support for early social skills intervention in the 22q11.2DS population.

Daily living skills. The VABS-II Daily Living Skills scale evaluates personal (e.g., how the individual dresses, practices personal hygiene), domestic (e.g., what types of household tasks he/she performs), and community (e.g., how he/she uses time and money) skills. The findings from the present study indicated that a comorbid mood disorder was not associated with significant burden in Daily Living Skills among individuals with 22q11.2DS. Instead, both groups of individuals with 22q11.2DS had significantly lower scores than typically developing controls. Although the individuals with 22q11.2DS scored lower than typically developing controls, these findings did not indicate a significant level of impairment. That is, scores for the 22q11.2DS+MD group (M = 73.50, SD = 11.10) and 22q11.2DS-MD group (M = 78.80, SD =13.10) were in the borderline range, consistent with what would be expected for their general cognitive ability (FSIQ). Therefore, it appears that individuals with 22q11.2DS in this study were able to complete typical daily activities as expected, although they may need occasional assistance.

Adaptive composite. The VABS-II Adaptive Composite scale is a composite of all VABS-II subscales (Communication, Daily Living Skills, Socialization, and Motor Skills). The findings from the present study again indicated that individuals with 22q11.2DS and comorbid mood disorder had significantly lower average scores than individuals with 22q11.2DS and no mood disorder on this scale. Given the previously described similar

significant group differences in Socialization and Communication, this finding was not surprising. In addition, a diagnosis of MDD requires that the symptoms cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning" (APA, 2013, p. 161). The VABS-II includes analyses of these domains and may therefore be a useful tool in helping to determine the degree to which MDD contributes to individual impairment.

Specific Aim 4

Relationships between social and adaptive functioning. Findings from the present study indicated significant moderate negative relationships between the SRS Total T-Score and VABS-II Socialization, Adaptive composite scores among the group of individuals with 22q11.2DS and comorbid mood disorder. In other words, lower (poorer) scores on the VABS-II were associated with higher (poorer) scores on the SRS. However, no significant relationships were found between the SRS Total T-Score and VABS-II Communication or Daily Living Skills in this group. Whereas the previously discussed findings related to adaptive functioning indicated more communication difficulties among individuals with 22q11.2DS and comorbid mood disorder, such communication difficulties do not appear to be related to the SRS. As mentioned previously, the SRS is more specific to social difficulties associated with Autism Spectrum Disorder (i.e., social cognition, autistic mannerisms), which may help explain this finding.

In contrast, significant moderate negative relationships were found between all VABS-II variables and the SRS Total T-score in the group of individuals with 22q11.2DS and no mood disorder. In other words, higher SRS scores were associated with lower VABS-II scores for all adaptive functioning domains, consistent with the hypothesis.

Significant moderate to strong negative relationships were found between all adaptive functioning variables (with the exception of Daily Living Skills in the sibling group, which was not significant) and the SRS Total T-score for both control groups. This pattern was the reverse of what was found for individuals with 22q11.2DS, in that higher (better) VABS-II scores were associated with lower (better) SRS Total T-scores. These findings were expected for these typically developing groups.

Relationships between visuospatial and adaptive functioning. The results from the correlational analyses between visuospatial and adaptive functioning indicated no significant positive associations between visuospatial functioning and adaptive functioning variables in the group of individuals with 22q11.2DS and comorbid mood disorder. Similarly, few significant positive associations between visuospatial functioning and adaptive functioning were found in both control groups. However, many more small significant positive associations were found between WAIS-III/WISC-III Block Design scaled scores and all adaptive functioning variables, in addition to Wechsler POI and VABS-II Communication for individuals with 22q11.2DS and no mood disorder. It is unclear from these data as to why this particular group showed more significant correlations. One possibility may be that a third variable, such as motor skills (which is included on the VABS-II but was not examined for the purposes of this study) influenced the results. Nevertheless, the results of these correlational analyses were relatively weak, and not significant in the other groups. Replication of these results is needed in order to determine whether these constructs are related and therefore warrant further investigation.

Relationships between executive and adaptive functioning. Results from the correlational analyses between executive and adaptive functioning showed the strongest

significant moderate positive relationships between the VABS-II Communication scale and WCST Total Correct and Categories Completed scores in the group of individuals with 22q11.2DS+MD. A slightly smaller significant moderate positive relationship between VABS-II Daily Living Skills and WCST Categories Completed was also found in this group. By contrast, results indicated more significant moderate positive relationships in the group of individuals with 22q11.2DS-MD; correlations between all adaptive functioning variables and all executive functioning variables were significant for this group. Results for the sibling control group indicated only one significant moderate relationship between VABS-II Communication and WCST Perseverative Errors, while the community control group demonstrated significant moderate positive relationships between VABS-II Communication and all three WCST variables. These findings related to executive functioning variables and communication were notable, and highlight a possible relationship between the need to employ receptive communication skills to effectively incorporate feedback (i.e., correct vs. incorrect) in order to perform better on the WCST. These data highlighted an interesting relationship that warrants further study, particularly in individuals with MDD.

Specific Aim 5

Relationships between ToM and adaptive functioning. The present study also sought to examine the relationship between performance on a ToM task and adaptive functioning. Contrary to the hypothesis, results indicated only one weak significant linear relationship between the ToM Mentalization score and VABS-II Communication among the group of individuals with 22q11.2DS and no mood disorder. All other correlations were not significant. It therefore appears that ToM, as measured by the Triangles Test, was not related to functional outcomes. This finding was rather surprising, particularly given that ToM skills

were expected to be associated with VABS-II Socialization. Although ToM is a social cognitive construct, the results of this study indicated that ToM does not appear to be related to social functioning as measured by the VABS-II. Again, this is in contrast with the hypotheses proposed in the study. A possible explanation may relate to the Triangles Test as a first-order ToM task, as opposed to one that involves a second order false-belief task (e.g., what does he think that she thinks he thinks). In other words, it is possible that a second-order ToM task, which involves more cognitive manipulation, would show a stronger relationship to adaptive and social functioning. It is also possible that scores on the Triangles Test were impacted by poorer verbal skills among individuals with 22q11.2DS, due to the fact that the Triangles Test requires specific verbalization of the perceived relationships between the triangles. In addition, as previously mentioned, group sizes were unequal, and it is possible that significant relationships were not detected due to low statistical power. This may be especially true given that ToM scores were available for only 12 individuals in the 22q11.2DS+MD group. Finally, a third variable (e.g., FSIQ) may have also affected the relationship between ToM and adaptive functioning. As previously discussed, ToM scores were significantly positively correlated with FSIQ, which may be a potential confound.

Specific Aim 6

Multiple mediator model. The results of the multiple mediator model, which examined the effects of visuospatial, social, executive, and ToM functioning as mediators to a diagnosis of mood disorder in individuals with 22q11.2DS, demonstrated that social functioning was the only significant mediator after all four variables were entered into the model. Thus, although lower scores on all four variables were associated with 22q11.2DS, social functioning was the only variable to demonstrate a mediating effect on mood disorder

in this population. This finding is to be expected, given that results of visuospatial, social, executive, and ToM functioning discussed previously indicated no significant differences between individuals with 22q11.2DS+MD and individuals with 22q11.2DS-MD on these measures. A suggestion for future research would be to follow up with this sample at a future time point in order to determine whether scores on these Time 3 variables are predictive of mood disorder diagnosis at Time 4.

Limitations

Although the present study demonstrated some intriguing findings, some limitations should be noted. This study was cross-sectional in nature, and it is therefore difficult to generalize conclusions based on the findings at one time point. The data examined were part of a larger longitudinal study; however, the main construct of interest (ToM) was only measured at the third time point. Future studies should examine longitudinal ToM data in order to better understand ToM skills and determine at what age ToM difficulties first begin in the 22q11.2DS population, as well as explore possible relationships between ToM difficulties and psychosis. In addition, inclusion of a second-order ToM task would help to further elucidate relationships between cognitive and social cognitive abilities in individuals with 22q11.2DS.

Another limitation of the present study relates to the relatively small sample size. Although the sample of individuals with 22q11.2DS was rather large, the groups were unequal, with significantly fewer participants in the group of individuals with 22q11.2DS+MD. Although statistical methods (e.g., Welch's F ratio) were utilized in order to correct for these differences, the study most likely suffered from reduced statistical power.

Therefore, differences that may have shown up with a larger sample size may not have been detected. Future studies would benefit from equally sized, larger groups.

Finally, diagnosis of mood disorder/MDD was based on parent report. Although the BASC-2 is a reliable and valid instrument, it is not intended to diagnose mood disorder. The study originally aimed to be the first to use a structured clinical interview as a method of diagnosis; however, this method limited the size of the group of individuals with 22q11.2DS and comorbid mood disorder. Future studies may benefit from clinically derived diagnosis, or inclusion of a measure specifically designed to measure depressive symptomatology (e.g., Beck Depression Inventory, Second Edition).

Conclusions

Overall, findings from this study indicated that the visuospatial, ToM, or executive function tasks examined do not appear to be related to greater likelihood of a mood disorder diagnosis among youth and emerging adults with 22q11.2DS. However, impaired social functioning in youth and emerging adults with 22q11.2DS, as evidenced by parent/caregiver report on the VABS-II and SRS, does appear to be related to mood disorder in youth and emerging adults with 22q11.2DS. Visuospatial and executive functioning have been previously identified as areas of known difficulty for individuals with 22q11.2DS, and ToM has recently emerged as an area of interest. This study supports further exploration of ToM skills, particularly second order ToM tasks, in individuals with 22q11.2DS. In addition, early attention (i.e., during childhood) to social skills development may be of help in preventing the development of mood disorder in adolescents and emerging adults with 22q11.2DS.

References

Aalto-Setala, T., Marttunen, M., Tuulio-Henriksson, A., Poikolainen, K., & Lonnqvist, J. (2002). Depressive symptoms in adolescence as predictors of early adulthood depressive disorders and maladjustment. *American Journal of Psychiatry, 159,* 1235-1237.

Abell, F., Happé, F., & Frith, U. (2000). Do triangles play tricks? Attribution of mental states to animated shapes in normal and abnormal development. *Cognitive Development, 15,* 1-16.

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA school-age forms and profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology, 11,* 231-239.

Ambrosini, P. J. (2000). Historical development and present status of the schedule for affective disorders and schizophrenia for school-age children (K-SADS). *Journal of the American Academy of Child Adolescent Psychiatry, 39*(1), 49-58.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, D.C.: Author.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, D.C.: Author.

Andersson, F., Glaser, B., Spiridon, M., Debanne, M., Vuilleumier, P., & Eliez, S. (2008). Impaired activation of face processing networks revealed by functional magnetic resonance imaging in 22q11.2 deletion syndrome. *Biological Psychiatry, 63,* 49-57.

Aneja, A., Fremont, W. P., Antshel, K. M., Faraone, S. V., AbdulSabur, N., Higgins, A. M.,...Kates, W. R. (2007). Manic symptoms and behavioral dysregulation in youth with velocardiofacial syndrome (22q11.2 deletion syndrome). *Journal of Child and Adolescent Psychopharmacology, 17*, 105-114.

Antshel, K. M., Fremont, W., Roizen, N. J., Shprintzen, R.; Higgins, A. M., Dhamoon, A., & Kates, W. R. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(5), 596-603.

Antshel, K. M., Shprintzen, R., Fremont, W., Higgins, A. M., Faraone, S. V., & Kates, W. R. (2010). Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: A 3-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(4), 333-344.

Antshel, K. M., Stallone, K., AbdulSabur, N., Shprintzen, R., Roizen, N., Higgins, A. M., & Kates, W. R. (2007). Temperament in velocardiofacial syndrome. *Journal of Intellectual Disability Research, 51*, 218-227.

Arnold, P. D., Siegel-Bartelt, J., Cytrynbaum, C., Teshima, I., & Schachar, R. (2001). Velo-cardio-facial syndrome: Implications of microdeletion 22q11 for schizophrenia and mood disorders. *American Journal of Medical Genetics, 105*, 354-362.

Baker, K. D., & Skuse, D. H. (2005). Adolescents and young adults with 22q11 deletion syndrome: Psychopathology in an at-risk group. *British Journal of Psychiatry, 186*, 115-120.

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind?" *Cognition, 21*, 37-46.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry, 42,* 241-251.

Bearden, C. E., Jawad, A. F., Lynch, D. R., Monterosso, J. R., Sokol, S., McDonald-McGinn, D. M.,…Simon, T. J. (2005). Effects of COMT genotype on behavioral symptomatology in the 22q11.2 deletion syndrome. *Child Neuropsychology, 11,* 109-117.

Bornstein, M. H., & Arterberry, M. E. (2003). Recognition, discrimination and categorization of smiling by 5-month-old infants. *Developmental Science, 6,* 585-599.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A.,…Campbell, R. M. (2003). A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics, 112,* 101-107.

Bremner, J. D., Innis, R. B., Salomon, R. M., Staib, L. H., Ng, C. K., Miller, H. L., …Charney, D. S. (1997). Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Archives of General Psychiatry, 54,* 364-374.

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in major depression. *The American Journal of Psychiatry, 157*(1), 115-118.

Bremner, J. D., Vythilingam, M., Ng, C. K., Vermetten, E., Nazeer, A., Oren, D. A.,…Charney, D. S. (2003). Regional brain metabolic correlates of α-methylparatyrosine-induced depressive symptoms. *Journal of the American Medical Association, 289*(23), 3125-3134.

Brotman, M. A., Guyer, A. E., Lawson, E. S., Horsey, S. E., Rich, B. A., Dickstein, D. P.,…Leibenluft, E. (2008). Facial emotion labeling deficits in children and adolescents at risk for bipolar disorder. *The American Journal of Psychiatry, 165*(3), 385-389.

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: Does cortisol play a role? *Biological Psychiatry, 55*, 1-9.

Bruce, V., Campbell, R. N., Doherty-Sneddon, G., Import, A., Langton, S., McAuley, S., & Wright, R. (2000). Testing face processing skills in children. *British Journal of Developmental Psychology, 18*, 319-333.

Brumariu, L., & Kerns, K. (2010). Parent-child attachment and internalizing symptoms in childhood and adolescence: A review of empirical findings and future directions. *Development and Psychopathology, 22*(1), 177-203.

Brüne, M., & Brüne-Cohrs, U. (2006). Theory of mind--evolution, ontogeny, brain mechanisms and psychopathology. *Neuroscience and Biobehavioral Reviews, 30*(4), 437-455. doi:10.1016/jneubiorev.2005.08.001

Campbell, L., McCabe, K., Leadbeater, K., Schall, U., Loughland, C., & Rich, D. (2010). Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes? *Psychiatry Research, 177*, 211-215.

Campbell, L. E., Stevens, A. F., McCabe, K., Cruickshank, L., Morris, R. G., Murphy, D. G., & Murphy, K. C. (2011). Is theory of mind related to social dysfunction and emotional problems in 22q11.2 deletion syndrome (velo-cardio-facial syndrome)? *Journal of Neurodevelopmental Disorders, 3,* 152-161. doi: 10.1007/s11689-011-9082-7

Castelli, F., Frith, C., Happé, F., & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain, 125,* 1839-1849.

Channon, S. (1996). Executive function in depression: The Wisconsin Card Sorting Test. *Journal of Affective Disorders, 39,* 107-114.

Choudhury, S., Blakemore, S. -J., & Charman, T. (2006). Social cognitive development during adolescence. *Social Cognitive and Affective Neuroscience (SCAN), 1,* 165-174. doi: 10.1093/scan/ns1024

Chrisman, A., Egger, H., Compton, S. N., Curry, J., & Goldston, D. B. (2006). Assessment of childhood depression. *Child and Adolescent Mental Health, 11*(2), 111-116.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Colle, L., Baron-Cohen, S., & Hill, J. (2007). Do children with autism have a theory of mind? A non-verbal test of autism vs. specific language impairment. *Journal of Autism and Developmental Disorders, 37,* 716-723.

Combs, D. R., Penn, D. L., Wicher, M., & Waldheter, E. (2007). The Ambiguous Intention Hostility Questionnaire (AIHQ): A new measure for evaluating hostile social-cognitive biases in paranoia. *Cognitive Neuropsychiatry, 12,* 128-143.

Constantino, J. N., & Gruber, C. P. (2005). *Social responsiveness scale (SRS) manual.* Los Angeles, CA: Western Psychological Services.

Costanzo, M., & Archer, D. (1989). Interpreting the expressive behavior of others: The Interpersonal Perception Task. *Journal of Nonverbal Behavior, 13,* 225-245.

Cusi, A. M., Nazarov, A., Holshausen, K., MacQueen, G. M., & McKinnon, M. C. (2012). Systematic review of the neural basis of social cognition in patients with mood disorders. *Journal of Psychiatry and Neuroscience, 37,* 159-169.

Davies, D. (2004). Attachment as a context of development. *Child development: A practitioner's guide* (2nd ed., pp. 7-38). New York: The Guilford Press.

Dennis, M., Landry, S. H., Barnes, M., & Fletcher, J. M. (2006). A model of neurocognitive function in spina bifida over the life span. *Journal of the International Neuropsychological Society, 12,* 285-296.

Driscoll, D. A., Budarf, M. L., & Emanuel, B. S. (1992). A genetic etiology for DiGeorge syndrome: Consistent deletions and microdeletions of 22q11. *American Journal of Human Genetics, 50,* 924-933.

Erdfelder, E., Faul, F., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers, 28,* 1-11.

Fabbro, A., Rizzi, E., Schneider, M., Debanne, M., & Eliez, S. (2012). Depression and anxiety disorders in children and adolescents with velo-cardio-facial syndrome (22Q11.2DS). *European Journal of Child and Adolescent Psychiatry, 21,* 379-385.

Field, A. (2005). *Discovering statistics using SPSS* (2nd ed.). Thousand Oaks, CA: Sage Publications Inc.

Frith, U., & Frith, C. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions - Royal Society, Biological Sciences, 358*(1431), 459-473.

Gautier, L., Cope, L., Bolstad, B. M., & Irizarry, R. A. (2004). Affy- analysis of Affymetrix GeneChip data at the probe level. *Bioinformatics, 20,* 307-315.

Geller, B., Bolhofner, K., Craney, J. L., Williams, M., DelBello, M. P., & Gundersen, K. (2000). Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *Journal of the American Academy of Child Adolescent Psychiatry, 39*(12), 1543-1548.

George, M. S., Ketter, T. A., & Post, R. M. (1994). Prefrontal cortex dysfunction in clinical depression. *Depression, 2,* 59-72.

Glaser, B., Debanne, M., Ottet, M. -C., Vuilleumier, P., Zesiger, P., Antonarakis, S. E., & Eliez, S. (2010). Eye gaze during face processing in children and adolescents with 22q11.2 deletion syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 49,* 665-674.

Golding-Kushner, K. J., Weller, G., & Shprintzen, R. J. (1985). Velo-cardio-facial syndrome: Language and psychological profiles. Journal of Craniofacial Genetics and Developmental Biology, 5, 259-266.

Gothelf, D. (2007). Velocardiofacial syndrome. Child and Adolescent Psychiatric Clinics of North America, 16(3), 677-693. doi:10.1016/j.chc.2007.03.005

Green, T., Gothelf, D., Glaser, B., Debanne, M., Frisch, A., Kotler, M.,…Eliez, S. (2009). Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(11), 1060-1068.

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. E.,…Heinssen, R. (2008). Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. *Schizophrenia Bulletin, 34*, 1211-1220.

Guyer, A. E., McClure, E. B., Adler, A. D., Brotman, M. A., Rich, B. A., Kimes, A.,…Leibenluft, E. (2007). Specificity of facial expression labeling deficits in childhood psychopathology. *Journal of Child Psychology and Psychiatry, 48*(9), 863-871. doi:10.1111/j.1469-7610.2007.01758.x

Happé, F. (1994). An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *Journal of Autism and Developmental Disorders, 24*(2), 129-154.

Heaton, R. K. (1981). *Wisconsin Card Sorting Test manual.* Odessa, FL: Psychological Assessment Resources, Inc.

Herbert, G. L., McCormack, V., & Callahan, J. L. (2010). An investigation of the object relations theory of depression. *Psychoanalytic Psychology, 27*(2), 219-234.

Hesse, E., & Main, M. (2000). Disorganized infant, child, and adult attachment: Collapse in behavioral and attentional strategies. *Journal of the American Psychoanalytic Association, 48,* 1097-1127.

Ho, J. S., Radoeva, P. D., Jalbrzikowski, M., Chow, C., Hopkins, J., Tran, W. -C.,…Bearden, C. E. (2012). Deficits in mental state attributions in individuals with 22q11.2 deletion syndrome (Velo-cardio-facial syndrome). *Autism Research, 5*(6), 407-418.

Inoue, Y., Yamada, K., & Kanba, S. (2006). Deficit in theory of mind is a risk for relapse of major depression. *Journal of Affective Disorders, 95*(1-3), 125-127.

Inoue, Y., Tonooka, Y., Yamada, K., & Kanba, S. (2004). Deficiency of theory of mind in patients with remitted mood disorder. *Journal of Affective Disorders, 82*(3), 403-409.

Jalbrzikowski, M., Carter, C., Senturk, D., Chow, C., Hopkins, J. M., Green, M. F.,…Bearden, C. E. (2012). Social cognition in 22q11.2 microdeletion syndrome: Relevance to psychosis? *Schizophrenia Research, 142,* 99-107.

Jolin, E. M., Weller, R. A., Jessani, N. R., Zackai, E. H., McDonald-McGinn, D. M., & Weller, E. B. (2009). Affective disorders and other psychiatric diagnoses in children and adolescents with 22q11.2 deletion syndrome. *Journal of Affective Disorders, 119,* 177-180.

Jolin, E. M., Weller, R. A., & Weller, E. B. (2012). Occurrence of affective disorders compared to other psychiatric disorders in children and adolescents with 22q11.2 deletion syndrome. *Journal of Affective Disorders, 136,* 222-228.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P.,…Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 980-988.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., & Ryan, N. (1996). *Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version (K-SADS-PL).* Accessed from http://www.psychiatry.pitt.edu/node/8233

Kaur, S., Sassi, R. B., Axelson, D., Nicoletti, M., Brambilla, P., Monkul, E. S.,…Soares, J. C. (2005). Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. *The American Journal of Psychiatry, 162*(9), 1637-1643.

Kerr, N., Dunbar, R. I. M., & Bentall, R. (2003). Theory of mind deficits in bipolar affective disorder. *Journal of Affective Disorders, 73*(3), 253-259.

Kettle, J. W. L., O'Brien-Simpson, L., & Allen, N. (2008). Impaired theory of mind in first-episode schizophrenia: Comparison with community, university and depressed controls. *Schizophrenia Research, 99*(1-3), 96-102. doi:10.1016/j.schres.2001.11.011

Kiley-Brabeck, K., & Sobin, C. (2006). Social skills and executive function deficits in children with the 22q11 deletion syndrome. *Applied Neuropsychology, 13*(4), 258-268.

Kinderman, P. & Bentall, R. P. (1996). The internal, personal, and situational attributions questionnaire. *Personality and Individual Differences, 20,* 261-264.

Klein, D., Dougherty, L., & Olino, T. (2005). Toward guidelines for evidence-based assessment of depression in children and adolescents. *Journal of Clinical Child and Adolescent Psychology, 34*(3), 412-432.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J.,…Gur, R. C. (2003). Facial emotion recognition in schizophrenia: Intensity effects and error pattern. *American Journal of Psychiatry, 160,* 1768-1774.

Kovacs, M. (2001). Gender and the course of major depressive disorder through adolescence in clinically referred youngsters. *Journal of the American Academy of Child Adolescent Psychiatry, 40*(9), 1079-1085.

Kovacs, M., & Goldston, D. (1991). Cognitive and social cognitive development of depressed children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 388-392.

Lack, C. W., & Green, A. L. (2009). Mood disorders in children and adolescents. *Journal of Pediatric Nursing, 24*(1), 13-25.

Lajiness-O'Neill, R., Beaulieu, I., Asamoah, A., Titus, J. B., Bawle, E., Ahmad, S….. Pollack, R. (2006). The neuropsychological phenotype of velocardiofacial syndrome (22Q11.2DS): Relationship to psychopathology. *Archives of Clinical Neuropsychology, 21*, 175-184.

Lee, A., Ogle, W., & Sapolsky, R. (2002). Stress and depression: Possible links to neuron death in the hippocampus. *Bipolar Disorders, 4*(2), 117-128.

Lee, L., Harkness, K., Sabbagh, M., & Jacobson, J. (2005). Mental state decoding abilities in clinical depression. *Journal of Affective Disorders, 86*(2-3), 247-258.

Levendosky, A. A., Okun, A., & Parker, J. G. (1995). Depression and maltreatment as predictors of social competence and social problem-solving skills in school-age children. *Child Abuse & Neglect, 19*(10), 1183-1195.

Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (1998a). Major depressive disorder in older adolescents: Prevalence, risk factors, and clinical implications. *Clinical Psychology Review, 18*(7), 765-794.

Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (1998b). Treatment of adolescent depression: Frequency of services and impact on functioning in young adulthood. *Depression and Anxiety, 7*(1), 47-52.

Lewinsohn, P. M., Rohde, P., Seeley, J. R., Klein, D. N., & Gotlib, I. H. (2000). Natural course of adolescent major depressive disorder in a community sample: Predictors of recurrence in young adults. *The American Journal of Psychiatry, 157*(10), 1584-1591.

Liu, Z., Xu, C., Xu, Y., Wang, Y., Zhao, B., Lv, Y.,…Du, C. (2010). Decreased regional homogeneity in insula and cerebellum: A resting-state fMRI study in patients with major depression and subjects at high risk for major depression. *Psychiatry Research,182,* 211-215.

Martin, D. J., Oren, Z., & Boone, K. (1991). Major depressives' and dysthymics' performance on the Wisconsin Card Sorting Test. *Journal of Clinical Psychology, 47,* 684-690.

Masi, G. & Brovedani, P. (2011). The hippocampus, neurotrophic factors and depression: Possible implications for the pharmacotherapy of depression. *CNS Drugs, 25,* 913-931.

Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology, 110,* 40-48.

Monk, C. S., Weng, S. J., Wiggins, J. L., Kurapati, N., Louro, H. M., Carrasco, M.,…Lord, C. (2010). Neural circuitry of emotional face processing in autism spectrum disorders. *Journal of Psychiatry Neuroscience : JPN, 35*(2), 105-114.

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry, 56*(10), 940-945.

Nelson, C. A. (2001). The development and neural bases of face recognition. *Infant and Child Development, 10,* 3-18. doi: 10.1002/icd.239

Nemeroff, C. B. (1996). The corticotrophin-releasing factor (CRF) hypothesis of depression: New findings and new directions. *Molecular Psychiatry, 1,* 336-342.

Nemeroff, C. B., & Vale, W. W. (2005). The neurobiology of depression: Inroads to treatment and new drug discovery. *Journal of Clinical Psychiatry, 66* (supplement 7), 5-13.

Niarchou, M., Zammit, S., van Goozen, S. H. M., Thapar, A., Tierling, H. M., Owen, M. J., & van den Bree, M. B. M. (2014). Psychopathology and cognition in children with 22q11.2 deletion syndrome. *British Journal of Psychiatry, 204*, 46-54.

Niklasson, L. & Gillberg, C. (2010). The neuropsychology of 22q11 deletion syndrome: A neuropsychiatric study of 100 individuals. *Research in Developmental Disabilities, 31*, 185-194.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., & Gillberg, C. (2001). Neuropsychiatric disorders in the 22q11 deletion syndrome. *Genetics in Medicine, 3*, 79-84.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., & Gillberg, C. (2002). Chromosome 22q11 deletion syndrome (CATCH 22): Neuropsychiatric and neuropsychological aspects. *Developmental Medicine and Child Neurology, 44*, 44-50.

Nolen-Hoeksema, S., Girgus, J. S., & Seligman, M. E. (1986). Learned helplessness in children: A longitudinal study of depression, achievement, and explanatory style. *Journal of Personality and Social Psychology, 51*(2), 435-442.

Nowicki, S. & Duke, M. P. (1994). Individual differences in the nonverbal communication of affect: The Diagnostic Analysis of Nonverbal Accuracy Scale. *Journal of Nonverbal Behavior, 18*, 9-35.

Papolos, D. F., Faedda, G. L., Veit, S., Goldberg, R., Morrow, B., Kucherlapati, R., & Shprintzen, R. J. (1996). Does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *American Journal of Psychiatry, 153*, 1541-1547.

Papolos, D. F., & Papolos, J. (1999). *The bipolar child*. New York: Broadway Books.

Pelkonen, M., Marttunen, M., Kaprio, J., Huurre, T., & Aro, H. (2008). Adolescent risk factors for episodic and persistent depression in adulthood. A 16-year prospective follow-up study of adolescents. *Journal of Affective Disorders, 106*, 123-131.

Peterson, C., & Seligman, M. E. (1984). Causal explanations as a risk factor for depression: Theory and evidence. *Psychological Review, 91*(3), 347-374.

Pinkham, A. E., Penn, D. L., Green, M. F., Buck, B., Healey, K., & Harvey, P. D. (2013). The social cognition psychometric evaluation study: Results of the expert survey and RAND panel. *Schizophrenia Bulletin,* doi: 10.1093/schbul/sbt081

Preacher, K. J. & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods, 40,* 879-891. doi: 10.3758/BRM.40.3.879

Puig-Antich, J., Lukens, E., Davies, M., Goetz, D., Brennan-Quattrock, J., & Todak, G. (1985). Psychosocial functioning in prepubertal major depressive disorders I: Interpersonal relationships during the depressive episode. *Archives of General Psychiatry, 42*(5), 500-507.

Rich, B. A., Fromm, S. J., Berghorst, L. H., Dickstein, D. P., Brotman, M. A., Pine, D. S., & Leibenluft, E. (2008). Neural connectivity in children with bipolar disorder: Impairment in the face emotion processing circuit. *Journal of Child Psychology and Psychiatry, 49,* 88-96. doi:10.1111/j.1469-7610.2007.01819.x

Rich, B. A., Grimley, M. E., Schmajuk, M., Blair, K. S., Blair, R. J. R., & Leibenluft, E. (2008). Face emotion labeling deficits in children with bipolar disorder and severe mood dysregulation. *Development and Psychopathology, 20*(2), 529-546. doi:10.1017/S0954579408000266

Rich, B. A., Vinton, D. T., Roberson-Nay, R., Hommer, R. E., Berghorst, L. H., McClure, E. B.,…Leibenluft, E. (2006). Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proceedings of the National Academy of Sciences of the United States of America, 103*(23), 8900-8905.

Rockhill, C. M., Fan, M., Katon, W. J., McCauley, E., Crick, N. R., & Pleck, J. H. (2007). Friendship interactions in children with and without depressive symptoms: Observation of emotion during game-playing interactions and post-game evaluations. *Journal of Abnormal Child Psychology, 35*, 429-441.

Rudolph, K. D., Hammen, C., & Burge, D. (1994). Interpersonal functioning and depressive symptoms in childhood: Addressing the issues of specificity and comorbidity. *Journal of Abnormal Child Psychology, 2*(3), 355-371.

Rulcovius, G. & Reinhard, H. G. (1990). Cognitive theories of depression: Implications for the investigation of emotional disturbances in childhood and adolescence. *Acta Paedopsychiatrica, 53*, 62-70.

Ryan, A. K., Goodship, J. A., Wilson, D. I., Philip, N., Levy, A., Seidel, H.,…Scambler, P. J. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A European collaborative study. *Journal of Medical Genetics, 34*, 798-804.

Sapolsky, R. M. (2001). Depression, antidepressants, and the shrinking hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 98*(22), 12320-12322.

Schenkel, L. S., Marlow-O'Connor, M., Moss, M., Sweeney, J. A., & Pavuluri, M. N. (2008). Theory of mind and social inference in children and adolescents with bipolar disorder. *Psychological Medicine, 38*(6), 791-800.

Schenkel, L., Pavuluri, M., Herbener, E., Harral, E., & Sweeney, J. (2007). Facial emotion processing in acutely ill and euthymic patients with pediatric bipolar disorder. *Journal of the American Academy of Child Adolescent Psychiatry, 46*(8), 1070-1079.

Schildkraut, J. J., & Kety, S. S. (1967). Biogenic amines and emotion. *Science, 156*(771), 21-37.

Schneider, M., Debanne, M., Bassett, A. S., Chow, E. W. C., Fung, W. L. A., van den Bree, M. B. M.,…Eliez, S. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. *American Journal of Psychiatry in Advance,* 1-13.

Seligman, M. E., Peterson, C., Kaslow, N. J., Tanenbaum, R. L., Alloy, L. B., & Abramson, L. Y. (1984). Attributional style and depressive symptoms among children. *Journal of Abnormal Psychology, 93*(2), 235-238.

Shashi, V., Veerapandiyan, A., Schoch, K., Kwapil, T., Keshavan, M., Ip, E., & Hooper, S. (2012). Social skills and associated psychopathology in children with chromosome 22q11.2 deletion syndrome: Implications for interventions. *Journal of Intellectual Disability Research, 56*(9), 865-878.

Shprintzen, R. J. (2000). Velo-cardio-facial syndrome: A distinctive behavioral phenotype. *Mental Retardation and Developmental Disabilities Research Reviews, 6*, 142-147.

Shyn, S. I., & Hamilton, S. P. (2010). The genetics of major depression: Moving beyond the monoamine hypothesis. *Psychiatric Clinics of North America, 33*, 125-140. doi: 10.1016/j.psc.2009.10.004

Simon, T. J., Bearden, C. E., Moss, E. M., McDonald-McGinn, D., Zackai, E., & Wang, P. (2002). Cognitive development in 22Q11.2DS. *Progress in Pediatric Cardiology, 15,* 109-117.

Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2005). *Vineland Adaptive Behavior Scales, Second Edition, Survey Forms Manual.* Minneapolis, MN: NCS Pearson, Inc.

Spreen, O., & Strauss, E. (1998). Executive functions. *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed., pp. 171-231). New York: Oxford University Press.

Sprong, M., Schothorst, P., Vos, E., Hox, J., & van Engeland, H. (2007). Theory of mind in schizophrenia: Meta-analysis. *The British Journal of Psychiatry, 191,* 5-13. doi: 10.1192/bjp.bp.107.035899

Stordal, K. I., Lundervold, A. I., Egeland, J., Mykletun, A., Asbjornsen, A., Landro, N. I.,...Lund, A. (2004). Impairment across executive functions in recurrent major depression. *Nordic Journal of Psychiatry, 51,* 41-47.

Swillen, A., Devriendt, K., Legius, E., Eyskens, B., Dumoulin, M., Gewillig, M., & Fryns, J. P. (1997). Intelligence and psychosocial adjustment in velocardiofacial syndrome: A study of 37 children and adolescents with 22Q11.2DS. *Journal of Medical Genetics, 34,* 453-458.

Tang, S. X., Yi, J. J., Calkins, M. E., Whinna, D. A., Kohler, C. G., Souders, M. C.,…Gur, R. E. (2014). Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. *Psychological Medicine, 44,* 1267-1277. doi: 10.1017/S0033291713001669

Thirion-Marissiaux, A., & Nader-Grosbois, N. (2008a). Theory of mind "beliefs," developmental characteristics and social understanding in children and adolescents with intellectual disabilities. *Research in Developmental Disabilities, 29*(6), 547-566.

Thirion-Marissiaux, A., & Nader-Grosbois, N. (2008b). Theory of mind "emotion," developmental characteristics and social understanding in children and adolescents with intellectual disabilities. *Research in Developmental Disabilities, 29*(5), 414-430.

Tillman, R., Geller, B., Bolhofner, K., Craney, J., Williams, M., & Zimerman, B. (2003). Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *Journal of the American Academy of Child Adolescent Psychiatry*, *42*(12), 1486-1493.

Uekermann, J., Channon, S., Lehmkämper, C., Abdel-Hamid, M., Vollmoeller, W., & Daum, I. (2008). Executive function, mentalizing and humor in major depression. *Journal of the International Neuropsychological Society: JINS, 14*, 55-62. doi:10.1017/S1355617708080016

van Amelsvoort, T., Schmitz, N., Daly, E., Deeley, Q., Critchley, H., Henry, J.,…Murphy, D. G. (2006). Processing facial emotions in adults with velo-cardio-facial syndrome: Functional magnetic resonance imaging. *British Journal of Psychiatry*, *189*, 560-561.

Vivona, J. M. (2000). Parental attachment styles of late adolescents: Qualities of attachment relationships and consequences for adjustment. *Journal of Counseling Psychology, 47*(3), 316-329.

Wang, Y., Wang, Y., Chen, S., Zhu, C., & Wang, K. (2008). Theory of mind disability in major depression with or without psychotic symptoms: A componential view. *Psychiatry Research, 161*(2), 153-161.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children, Third Edition.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale, Third Edition.* San Antonio, TX: The Psychological Corporation.

White, S., Hill, E., Happé, F., & Frith, U. (2009). Revisiting the strange stories: Revealing mentalizing impairments in autism. *Child Development, 80*(4), 1097-1117.

Wicks-Nelson, R., & Israel, A. C. (2003). Mood disorders. *Behavior disorders of childhood* (5th ed., pp. 155-188). Upper Saddle River, NJ: Prentice Hall.

Woodin, M., Wang, P. P., Aleman, D., McDonald-McGinn, D., Zackai, E., & Moss, E. (2001). Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genetics in Medicine, 3,* 34-39.

Young, J. E., Rygh, J. L., Weinberger, A. D., & Beck, A. T. (2008). Cognitive therapy for depression. In D.H. Barlow (Ed.), *Clinical handbook of psychological disorders: A step-by-step treatment manual* (4th ed., pp. 250-305). New York: The Guilford Press.

Zobel, I., Werden, D., Linster, H., Dykierek, P., Drieling, T., Berger, M., & Schramm, E. (2010). Theory of mind deficits in chronically depressed patients. *Depression and Anxiety, 9,* 821-828. doi:10.1002/da.20713

Appendix: Human Subjects Approval Letter

EASTERN MICHIGAN UNIVERSITY *Education First*

July 25, 2014 **UHSRC INITIAL APPROVAL: EXEMPT**

To: **Amy Olszewski**
Eastern Michigan University

Re: **UHSRC: # 140709S**
Category: Exempt # 4
Approval Date: July 25, 2014
Expiration Date: Exempt

Title: **Theory of Mind in Youth and Emerging Adults with 22q11.2 Deletion Syndrome and Comorbid Mood Disorder**

The Eastern Michigan University Human Subjects Review Committee (UHSRC) has completed their review of your project. I am pleased to advise you that **your research has been deemed as exempt** in accordance with federal regulations.

The UHSRC has found that your research project meets the criteria for exempt status and the criteria for the protection of human subjects in exempt research. **Under our exempt policy the Principal Investigator assumes the responsibility for the protection of human subjects** in this project as outlined in the assurance letter and exempt educational material.

Renewals: Exempt protocols do not need to be renewed. If the project is completed, please submit the **Human Subjects Study Completion Form** (found on the UHSRC website).

Revisions: Exempt protocols do not require revisions. However, if changes are made to a protocol that may no longer meet the exempt criteria, a **Human Subjects Minor Modification Form** or new **Human Subjects Approval Request Form** (if major changes) will be required (see UHSRC website for forms).

Problems: If issues should arise during the conduct of the research, such as unanticipated problems, adverse events, or any problem that may increase the risk to human subjects and change the category of review, notify the UHSRC office within 24 hours. Any complaints from participants regarding the risk and benefits of the project must be reported to the UHSRC.

Follow-up: If your exempt project is not completed and closed after **three years**, the UHSRC office will contact you regarding the status of the project and to verify that no changes have occurred that may affect exempt status.

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 734-487-0042 or via e-mail at gs_human_subjects@emich.edu. Thank you for your cooperation.

Sincerely,

Jennifer K. Fritz

Dr. Jennifer Kellman Fritz
Faculty Co-Chair
University Human Subjects Review Committee

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The EMU UHSRC complies with the Title 45 Code of Federal Regulations part 46 (45 CFR 46) under FWA00000050.