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AGGRESSION IN CHILDREN WITH 7Q11.23 DUPLICATION SYNDROME

by

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ABSTRACT

AGGRESSION IN CHILDREN WITH 7Q11.23 DUPLICATION SYNDROME

by

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The University of Wisconsin-Milwaukee, 2017
Under the Supervision of Professor Bonita P. Klein-Tasman, Ph.D.

7q11.23 duplication syndrome (Dup7) is a recently identified genetic disorder that is caused by a duplication of the same set of genes deleted in Williams syndrome (WS). Dup7 is highly variable and associated with several cognitive, behavioral, and medical characteristics, a wide range of cognitive abilities, language delay, childhood apraxia of speech, autism spectrum disorders (ASD), anxiety disorders, developmental coordination disorder, and epilepsy. A recent examination of individuals with Dup7 indicated high levels of social anxiety and elevated aggression and oppositional behavior compared to same-aged peers; however, detailed characterization of behavioral outcomes and factors that may contribute to variability in functioning have not been explored. The aim of this study was to characterize the presence and severity of aggression in children with Dup7 and identify potential contributions to levels of aggression utilizing a multi-method, multi-informant approach. Participants included 63 children with Dup7 between the ages of 4 and 18. Results indicate elevated levels of aggression and oppositional behavior. Children who were young and had language delays were more likely to demonstrate aggression as rated by an examiner. Intellectual functioning, expressive language functioning, and ASD severity were not related to aggression; however, children who were rated by their parents as demonstrating behaviors associated with Social

Anxiety Disorder were more likely to be rated as demonstrating behaviors consistent with Oppositional Defiant Disorder. This finding suggests that the presence of social anxiety may contribute to the presence of aggression in children with Dup7. Overall, this study's findings suggest that the genes in the 7q11.23 region duplicated in Dup7, in transaction with the environment, may contribute to aggressive behavior.

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Introduction

Studies of individuals with disorders of known genetic etiology that present with specific behaviors have the strong potential to contribute to better understanding of the relations between genetics and behavior and to inform future investigations on areas of genetic risk. 7q11.23 duplication syndrome (Dup7) is a recently identified genetic disorder that is caused by a duplication of the same set of genes that is deleted in Williams syndrome. Dup7 is a highly variable syndrome associated with several cognitive, behavioral, and medical characteristics. Distinctive facial features (Van der Ana et al., 2009; Dixit et al., 2013), macrocephaly (Morris et al., 2015), hypotonia (Merritt & Lindor, 2008; Merla et al., 2010; Morris et al., 2015), cardiovascular abnormalities (Zarate et al., 2014; Parrott et al., 2015), neurologic abnormalities (Orellana et al., 2009; Van der Ana et al., 2009; Prontera et al., 2014; Morris et al., 2015), speech and language delay (Somerville et al., 2005; Berg et al., 2007, Velleman & Mervis, 2011), mild to severe cognitive delays (Van der Ana et al., 2009; Velleman & Mervis, 2011; Mervis et al., 2015), autism spectrum disorders (Berg et al., 2007; Depienne et al., 2007), schizophrenia (Mulle et al., 2014), anxiety (Mervis et al., 2015), and seizures (Torniero et al., 2007, 2008; Merla et al., 2010; Morris et al., 2015) have all been described as sequelae of Dup7.

A recent examination of the psychological characteristics of individuals with Dup7 (Mervis et al., 2015) indicated elevated levels of aggression and oppositional behavior compared to same-aged peers. While some studies have included mention of behavioral problems in individuals with Dup7 (Berg et al., 2007; Dixit et al., 2013), detailed characterization of behavioral outcomes and factors that may contribute to variability in functioning have not been explored. In particular, examination of the presence and severity of aggression and the potential

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contributions of cognitive functioning and psychosocial factors to levels of aggression will further enable better understanding of the Dup7.

This introduction will be structured as follows. First, I will provide relevant background information about the 7q11.23 region and describe the deletion and duplication syndromes associated with this region. I will briefly describe medical features and the cognitive profile of individuals with Dup7. I will also discuss what is known about the behavioral features of individuals with Dup7. Second, I will review current knowledge on the relations between behavior difficulties and speech/language functioning, given the strong association between speech and language problems and Dup7. Third, I will discuss observed relations between social anxiety and aggression. Fourth, I will discuss relevant literature on aggression in children with neurodevelopmental disorders, given the possible presence of aggression and oppositional defiant behavior in children with Dup7.

7q11.23 duplication syndrome

A surge in research on copy number variation (CNV) has led to the identification of several new genomic disorders. CNVs are the most prevalent type of structural variation in the human genome, suggesting that CNVs contribution to variations in phenotypes is likely to be substantial (Redon et al., 2006). Numerous studies found that CNVs provide insight into the etiology of phenotypes resulting from complex genetic patterns of inheritance, such as neurodevelopmental diseases, autism spectrum disorders (ASD), and schizophrenia (Beckmann et al., 2007). Recent studies of CNVs in a large sample of children with ASD identified a strong relation between autism and the reciprocal duplication of the same region of genes deleted in Williams syndrome (WS) (7q11.23) (Levy et al., 2011; Sanders et al., 2011). Dup7 was first described in a case report a little over 10 years ago (Somerville et al., 2005).

Prevalence estimates range from 1 in 7,500 to 1 in 20,000 based on WS prevalence (Velleman & Mervis, 2011). Although numerous associations have been made to Dup7, ultimately, such characteristics are too subtle, variable, and complex to suspect the presence of Dup7 based on these characteristics alone, given the current knowledge about the associated behavioral phenotype. Rather, detection of Dup7 is based solely on results of genetic microarray analysis. Whereas WS is one of the most well-known and characterized deletion syndromes, much less is known about the Dup7 phenotype. In order to draw links between the duplication of this region and the cognitive and behavioral functioning of individuals with the syndrome, a clearer delineation of the phenotype is warranted.

WS is one of the most well characterized deletion syndromes, with an incidence of 1 in 7,500 (Strømme et al. 2002). Deletion of this gene region results in a number of medical problems, such as cardiovascular anomalies, short stature, dysmorphic facial features, musculoskeletal problems, and developmental delay (Morris & Mervis, 1999; Pober & Dykens, 1996; Hammond et al., 2005). In terms of cognitive features, individuals with WS tend to display a unique pattern of strengths and weaknesses, with particular relative strength in language and auditory memory abilities, and extreme weakness in visuospatial abilities (Mervis et al., 2000). In terms of personality characteristics, studies of individuals with WS have described high levels of sociability, excessive talkativeness and verbal fluency (Bellugi et al., 2000; Klein-Tasman & Mervis, 2003; Vicari et al., 2002).

In the first case report of a child with Dup7, severe expressive language impairment was described, despite low average range functioning on receptive language tasks (Somerville et al., 2005). Since the first description of Dup7, case reports of individuals with the duplication syndrome have accumulated and have been crucial in the identification of characteristics

associated with Dup7 (Somerville et al., 2005; Kriek et al., 2006; Kirchhoff et al., 2007; Depienne et al., 2007; Torniero et al., 2007, 2008; Merritt and Lindor, 2008; Orellana et al., 2008; Degerliyurt et al., 2012; McGrew et al., 2012; Prontera et al., 2014). Speech and language delay, mild to moderate learning difficulties, schizophrenia, anxiety, and epilepsy have all been described in Dup7 literature as associations to this duplication syndrome (Mervis et al., 2015; Somerville et al., 2005; Mulle et al., 2014; Torniero et al., 2007, 2008; Depienne et al., 2007). The most consistent associations to Dup7 are the presence of developmental delay or intellectual disability, ASD symptomatology, and severe speech delay.

Cognitively, most individuals with Dup7 function in the low average range; however, considerable variability exists, with scores ranging from severe disability to high average (Mervis et al., 2015). Individuals with Dup7 also tend to be variable in their patterns of relative strengths and weaknesses. As a group, toddlers with Dup7 appear to demonstrate relative strengths in nonverbal reasoning and receptive language, and a relative weakness in expressive language. Again as a group, 4-17- year-olds with Dup7 appear to demonstrate no significant differences in their verbal, nonverbal reasoning, and spatial abilities; whereas adults with Dup7 appear to demonstrate significantly stronger nonverbal reasoning and spatial abilities compared to their verbal abilities (Mervis et al., 2015).

The presence of speech delay has been especially noted as a characteristic feature of the overall cognitive profile. For example, as part of the first report of a child with Dup7, severe delay in speech and expressive language was noted as the most striking feature of the Dup7 profile (Somerville et al., 2005). The 8-year old boy detailed in the report was described as having receptive language abilities in the low average range; however, his severe impairment in speech and expressive language left him able to pronounce only a few words correctly. Depienne

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and colleagues (2007) described a child with autism spectrum disorder (ASD) and Dup7, whose characteristic features included expression language delay and outbursts of anger. In the authors' descriptions of the child, it was indicated that he was able to understand simple commands and answer simple questions using images or gestures, yet expression was reduced to single words. Speech was noted to include several phonetic alternations, making speech largely intelligible. At 12 years of age, the child's expressive language ability indicated an age equivalence of less than 18 months of age. A later study examining 7 individuals with Dup7 demonstrated that individuals with Dup7 had relatively spared visuospatial skills coupled with severe speech delay (Berg et al., 2007). Consistent with these previous results, Torniero et al. (2008) also reported speech and expressive language delays in a boy and his mother with Dup7. In the adult mother with Dup7, researchers detailed poor expressive language skills with simple sentences, phonological deficits, and defective articulation as a marked deficit of the Dup7 phenotype. Further evidence for this characteristic speech delay in individuals with Dup7 was demonstrated in a study of 14 patients with Dup7 (Van der Aa et al., 2009). Among the findings, researchers reported speech delay as the most consistent clinical finding.

Case studies of children with Dup7 have also indicated a prevalence of aggression and oppositional behavior in children with Dup7 (Berg et al., 2007; Depienne et al., 2007; Dixit et al., 2013). Berg et al (2007) described aggressive tendencies, including pinching, hitting, and increased frequency of temper tantrums, in an 11-year old boy with Dup7. Berg and colleagues also described a 4-year old girl with Dup7 who had a history of aggressiveness and severe tantrums. Depienne et al (2007) described a 12-year old boy with Dup7 who displayed aggressive behavior, including severe outbursts of anger when frustrated. Dixit et al (2013)

described 2 children, a 6-year old boy and 3-year old girl with Dup7, who displayed aggressive behavior.

In the first large-scale study of the phenotype, Mervis and colleagues (2015) examined the presence of developmental delay or intellectual ability, ASD symptomatology, and severe speech delay, along with anxiety and behavioral problems in 63 children with classic Dup7. In addition to high rates of language and speech delay as well as ASD, they found a high incidence of anxiety disorders, with 50% of children diagnosed with Social Phobia, 29% with Selective Mutism, 12.9% with Separation Anxiety Disorder, and 53.2% with Specific Phobia. Twenty-four percent of children were diagnosed with Oppositional Defiant Disorder or Disruptive Behavior Disorder-Not Otherwise Specified. While it is apparent that there are discernable areas of risk, there is considerable variability in both the cognitive and behavioral Dup7 phenotype.

In summary, while the Dup7 phenotype does not seem to be as clearly distinctive and as is the WS phenotype, rather consistent associations to Dup7, such as the presence of developmental delay, ASD symptomatology, and speech delay, have been described. Cognitively abilities of individuals with Dup7 vary widely; however, the majority of individuals with Dup7 have low average intellectual ability. Behaviorally, Dup7 has been associated with high rates of anxiety disorders, particularly social anxiety, as well as ASD-related behaviors and aggression/oppositional behaviors.

Behavior Problems and Language

It is widely acknowledged that children who are able to utilize their language effectively are better able to regulate their emotions, learn new material, and develop social relationships (Beck et al., 2012; Bloom, 1998; Graziano et al., 2007; Kastner et al., 2001; Longoria et al.,

2009). Language abilities play a critical role in an individual's ability to encode, organize, retrieve, and express thoughts that contribute to the ability to regulate emotions and behaviors (Tallal, Dukette, & Curtis, 1989). Effective use of language requires coordination of cognitive, social, and emotional information, which can be challenging for some children. There is a large body of evidence positing that behavior problems often accompany language impairments (Hartas, 2011; Lindsay & Dockrell, 2000; Rodgers-Adkinson & Griffith, 1999; Tallal, Dukette, & Curtiss, 1989). In studies of children with language impairments and disorders, elevated rates of disruptive behavioral problems are consistently described (Benner, 2005; Horowitz, Westlund, & Ljungberg, 2007; van Daal, Verhoeven, & Balkom, 2007). The co-occurrence rate of language and behavioral difficulties in young children is estimated to be 50-70% (Redmond & Rice, 1998), and expressive language disorders, in particular, seem to be more prevalent than receptive language disorders among children with emotional and behavioral difficulties (Camarata et al., 1988; Benner et al., 2002; Benner, 2005). While epidemiological studies report rates of language delays ranging from 3%-15% in the general population (Silva, 1987), rates of language delays in children presenting with disruptive behavior problems can often reach 24%-65% (Benasich, Curtiss, & Tallal, 1993). Conversely, 59-80% of preschool and school-aged children first identified as exhibiting language delays also exhibit disruptive behaviors (Beitchman et al., 1996; Brinton & Fujiki, 1993; Stevenson, Richman, & Graham, 1985), while rates do not exceed 20% in the general population (Lahey, Miller, Gordon, & Riley, 1999).

The relation between behavioral and language difficulties has been found to persist over time. The pattern of behavioral difficulties in children with language impairment remains significant through early years (Benasich, Curtiss, & Tallal, 1993), primary years (Lindsay, Dockrell & Strand, 2007), through adolescence (Conti-Ramsden & Botting, 2004) and into

adulthood (Beitchman et al., 2001). In a longitudinal study of temperament and its relations with the emotional and behavioral development of children from infancy to adolescence, researchers were able to demonstrate that children displaying disruptive behavior during preschool and later school years have higher incidence of expressive language delay (Sanson, Smart, Prior, & Oberklaid, 1993).

Whereas the link between behavior problems and language delays has strong research support, less is known about the mechanism(s) behind this association. Aggression and language development were examined in a large group of 19-month old twins in order to determine the association between physical aggression and language in late infancy (Dionne et al., 2003). Based on data from 562 sets of twins, language skills and aggression were each influenced by genetic or environmental factors. Physical aggression was substantially more influenced by genetic factors, while language skills were more impacted by environmental factors. Overall, these findings lend further support for the association of behavior problems and language delays. In addition, these findings suggest that young children with early signs of language problems should also be screened for disruptive behaviors in order to determine the presence and severity for informing intervention.

Social Anxiety and Aggression

While individuals with social anxiety are generally behaviorally inhibited and risk-averse (Beidel & Turner, 2007), characteristics that are usually associated with lower rates of aggression, there is a subset of individuals with social anxiety disorder displaying elevated rates of aggression. Emerging evidence has demonstrated that adolescents with lifetime anxiety disorders, particularly social anxiety, have a higher prevalence of aggressive outbursts (68.5%) than adolescents without a lifetime anxiety disorder (48.6%) (Keyes et al., 2015).

In studies of children with social anxiety disorder, children who anxiously expect and perceive rejection are more prone to aggression (Ayduk et al., 2000). Despite limited research, anxiety and disruptive behavior disorders have been found to co-occur at significantly higher rates among children and adolescents than would be expected based on individual prevalence rates (Costello et al., 2003; Ford et al., 2003). Additionally, it has been demonstrated that high levels of disinhibition, hostile, and aggressive behaviors often occur in a subset of socially anxious adults (Kashdan et al., 2009). Although limited, these findings suggest that social anxiety may be a risk factor for aggressive behaviors in children.

Risks for Aggression in Children with Neurodevelopmental Disorders

Numerous factors have been associated with the development and persistence of behavioral problems, such as aggression. Research has focused on such factors as child temperament and parenting styles, family functioning, parental stress, peers, and genetic factors. The influence of the presence of developmental disorders in particular has remained central in recent years, as descriptions of aggressive behaviors have been detailed in children with a variety of conditions (Rice et al., 2015; McClintock, Hall, & Oliver, 2003; Emerson et al., 2001). Aggression is one of the most common forms of challenging behavior displayed by individuals with intellectual disability (Emerson & Einfeld, 2011). Prevalence estimates for aggression in individuals with intellectual disability vary from 7% to 25% (Emerson et al., 2001; Holden & Gitlesen, 2006). Certain syndrome groups associated with intellectual disability, such as Cri du Chat, Smith-Magenis, Prader-Willi, and Fragile X syndromes have shown strong associations with aggression as well (Sullivan et al., 2006; Collins & Cornish, 2002; Hagerman & Hagerman, 2002; Einfeld et al., 1999; Clark & Boer, 1998). These syndrome groups evidence relatively higher prevalence rates of aggression, as well as self-injury and destructive behavior, compared

to groups of individuals with intellectual disability of heterogeneous etiology (Arron et al., 2011). In addition to syndrome associations, certain individual-level characteristics also have shown strong associations with the presence of aggression. McClintock and colleagues (2003) found that aggression appeared to more common among males, individuals with expressive language deficits, individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD), and individuals diagnosed with ASD.

While aggression has been known to occur among individuals with ASD, the majority of literature on aggression in the ASD literature focuses on better understanding the function of aggressive behavior. As such, there have been relatively few studies examining the prevalence and risk factors of aggression among children with ASD, and those that have, have inconsistent findings (for review see Fitzpatrick et al., 2016). In one study of 67 children with ASD, presence of aggression was associated with lower IQ, poorer expressive and receptive language, and restricted and repetitive behaviors (Dominick et al., 2007). In the first study to report prevalence rates for aggression in children and adolescents with ASD, Kanne and Mazurek (2011) reported that over two-thirds of parents reported that their child had engaged in some form of aggressive behavior towards them at some point, and nearly half had demonstrated some type of aggressive behavior toward others.

Presently, there are some limitations in the study of aggression in children. One central problem involved with the research on aggression is the lack of consistent definition. In the literature, approximately 200 different definitions of aggression exist ranging from clear acts of interpersonal violence to less physically harmful, more delinquent behaviors (Underwood et al., 2001). Furthermore, aggressive acts can be physical or non-physical (Loudin et al., 2003; Coyne, Archer & Eslea, 2006) and verbal or nonverbal (Archer & Coyne, 2005; Owens, Shute & Slee,

2000). In order to adequately capture and detail the presence and severity of aggression, there needs to be a systematic method in place to define it. The majority of the literature examining childhood aggression has done so using parent and teacher report (Kempes et al., 2005). However, recent studies have begun utilizing behavioral coding of pretend play (Zyga et al, 2015) and, more specifically aggressive behaviors during play, as a method to study aggression in children (Fehr & Russ, 2013). Pretend play, or the use of symbolism and imagination while playing, is an essential aspect of child development (Russ, 2004; Singer & Singer, 1990). Considering that both pretend play and aggressive behavior in children tend to peak during the preschool years (Vitaro et al, 2006), studies on pretend play have begun examining aggressive behaviors as part of play. Different types of aggression have been identified in pretend play, including physical aggression, verbal aggression, and aggressive themes (Zyga et al., 2015; Fehr & Russ, 2013).

Study Rationale

A recent examination of the psychological characteristics of individuals with Dup7 indicated high levels of expressive language deficits and social anxiety, as well as elevated aggression and oppositional behavior compared to same-aged peers (Mervis et al., 2015). While prior case studies have also mentioned behavioral problems- notably aggression- in some individuals with Dup7 (Berg et al., 2007; Dixit et al., 2013), detailed characterization of behavioral outcomes and factors that may contribute to variability in functioning has not been conducted. This study aims to characterize the presence and severity of aggression in children with Dup7 and to identify the potential contributions of intellectual functioning, expressive language abilities, ASD severity, and social anxiety to levels of aggression. The current study utilizes a multimethod, multi-informant approach, with both parent report and examiner-based

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interview and observation measures, in order to simultaneously take a dimensional and a categorical approach to the assessment of constructs. This research contributes to the scarce Dup7 behavioral phenotype literature. Additionally, given the significant impact of aggression, it is hoped that detailed characterized of behavioral outcomes and factors will inform more targeted intervention.

Methods

Participants

Participants are 63 children (25 females, 38 males) between the ages of 4 and 17 years (mean=8.64 years, standard deviation=3.77) and their parents. All children have genetically confirmed classic Dup7. The inclusion of only those with the classical duplication of 7q11.23 was due to evidence suggesting that shorter (Morris et al., 2003) and longer (Stock et al., 2003) deletions of this region results in differing phenotypes. For this reason, it was expected that shorter or longer duplications of this same region would likely result in differing phenotypes as well. Participant demographic data is provided in Table 1.

Procedure

Participants were seen as part of a larger study at the University of Louisville designed to comprehensively describe the cognitive, behavioral, and medical phenotype of children with Dup7. Assessment sessions took place over the period of 3 days and included visits with psychologists, speech-language pathologists, and a physician.

Measures

Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994*).* Primary caregivers were interviewed about ASD symptomology using the ADI-R. The ADI-R is a semi-structured,

standardized clinical interview containing items focusing on behaviors in three content areas: quality of social interaction; communication and language; and repetitive, restricted and stereotyped interests and behavior. The ADI-R is empirically-derived and has demonstrated good internal consistency, interrater reliability, test-retest reliability. Responses are scored by the clinician according to specific operational definitions based on the caregiver's description of the child's current behavior. A classification of ASD is given when scores in all three content areas of communication, social interaction, and patterns of behavior meet or exceed specified cutoffs. In addition, specific items relating to aggression (Item 81: *Aggression toward Caregivers or Family Members*; Item 82:) will be examined for presence and severity of aggression. The *Aggression toward Caregivers or Family Members* item is coded for episodes of aggression within the family and caregivers of sufficient severity and/or frequency to constitute a significant cause for concern. Similarly, the *Aggression toward NonCaregivers or Nonfamily Members* item is coded for episodes of aggression, but with aggression directed toward individuals who are not caregivers or members of the family, including other peers and adults. For each of these two ADI-R items, codes range from 0-3. A code of 0 is assigned when there is no aggression or only rare episodes. A code of 1 is assigned when only mild aggressiveness is present, including threatening without physical contact, or momentary, provoked lashing out. A code of 2 is assigned when there is definite physical aggression involving hitting or biting without use of implements. A code of 3 is assigned when violence that involves the use of implements is present.

 Anxiety Disorders Interview Schedule for DSM-IV: Parent Interview Schedule (ADIS-IV P; Silverman & Albano, 1996*).* The ADIS-IV P has consistently demonstrated good reliability and validity (Silverman et al., 2001). Primary caregivers completed the ADIS-P, a semi-

structured interview designed to assess current anxiety and related disorders, including externalizing disorders, in children and adolescents. For this study, the following sections were examined for the presence of difficulties: Social Phobia (Social Anxiety Disorder), Oppositional Defiant Disorder.

Differential Ability Scales-Second Edition (DAS-II; Elliott, 2007*).* The DAS-II is a commonly used, comprehensive measure of cognitive abilities for children ages 4-17. The DAS-II is empirically derived and demonstrates excellent internal consistency, test retest reliability and correlates highly with other commonly used measures of cognitive abilities (Elliott, 2007). Children were administered the DAS-II in order to assess the cognitive strengths and weaknesses of each child. The Early Years form was administered to children aged 4-8 years and the School-Age form to children aged 9-17 years of the DAS-II were used to assess the cognitive strengths and weaknesses of participants. The DAS-II yields an overall composite score, or General Conceptual Ability (GCA) score that is equivalent to a full-scale IQ score (mean=100, standard deviation=15). The GCA is comprised of three cluster scores: Verbal Abilities, Nonverbal Abilities, and Spatial Abilities. For the purpose of this study, GCA along with Verbal Abilities and Nonverbal Abilities clusters were examined.

Expressive Vocabulary Test, Second Edition (EVT-2; Williams, 2007*).* The EVT-2 measures expressive vocabulary and word retrieval in children aged 2 years, 6 months to adults aged 90 years. The EVT-2 has demonstrated excellent reliability and validity (Williams, 2007). Children were administered the EVT-2 in order to assess single-word expressive vocabulary.

Conners Early Childhood (CE; Conners, 2009*).* Primary caregivers completed the Conners CE in order to assess a wide spectrum of behaviors, emotions, and social problems in

children aged 4-5 (n=18). The Conners CE has demonstrated excellent reliability and validity (Conners, 2009). For this study, particular focus was on the Defiant/Aggressive Behaviors scale.

Conners Comprehensive Behavior Rating Scales (CBRS; Conners, Pitkanen, & Rzepa, 2011*).* Primary caregivers completed the Conners CBRS in order to assess a wide spectrum of behaviors, emotions, academic, and social problems in children aged 6-18 years (n=45). The Conners CBRS has demonstrated excellent reliability and validity (Conners, Pitkanen, & Rzepa, 2011). For the purpose of this study, particular focus was on the following scales and forms from the CBRS: Defiant/Aggressive Behaviors, Violence Potential Indicator, Oppositional Defiant Disorder (ODD), Social Anxiety Disorder.

Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-2; Lord et al., 2012*).* Children were administered the developmentally appropriate module from the ADOS-2 (Module 1, n= 9; Module 2, n= 21; Module 3, n= 33). The ADOS-2 is a semi-structured, standardized assessment of socio-communication, social interaction, play/imaginative play, and restricted and repetitive behaviors or interests. It is considered the "gold standard" observational assessment for diagnosing ASD and demonstrates good reliability and validity. Based on observations made during the activities and interactions, rating codes are assigned for several ASD related symptoms. An empirically-derived subset of the codes is then summed to determine diagnostic classification (i.e. non-spectrum, autism spectrum, autism) based on empirically-derived cutoff scores. ADOS-2 Comparison Scores were also used: ADOS-2 Comparison Scores indicate the level of ASD-related symptomatology of each child, as observed during the ADOS-2 assessment, and are calibrated relative to children who have ASD and are of the same chronological age and language level. In addition, a specific item relating to aggression was examined to determine the degree to which aggression toward the examiner was present during administration of the

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ADOS-2. This ADOS-2 item is coded for any form of anger or disruption beyond communication of mild frustration or whining, with codes ranging from 0-4. A code of 0 is assigned when no disruptive, destructive, negative, or aggressive behavior is present during the assessment. A code of 1 is assigned when a child "displays an example of mild disruption, anger, or aggression or negative behavior to the examiner, including verbal threats, swearing, or a deliberately loud voice." A code of 2 is assigned when "more than one intentionally disruptive or negative incident" occurred. Loud talking or repeated swearing is also coded 2. A code of 3 is assigned when a child engages in "marked or repeated temper tantrums or significant aggression, such as throwing things, hitting, or biting others." In addition, screaming or yelling is assigned a code of 3.

Observational Coding of Behavior. In order to assess the degree to which aggressive behavior and themes were present during play, videotaped assessments of the ADOS-2 were coded using a method based on the modified version of the Affect in Play Scale (APS; Russ, 2004). The APS is a method used to rate cognitive and affective processes involved in play through observation of a standardized play task. The APS rates the frequency, intensity, and variety of affective expression. The APS was previously modified for use on the ADOS-2 "Make-Believe Play" activity for children ages 6-13 (Zyga et al, 2015). For the purpose of this study, particular focus will be on coding the affective processes of anger/aggression, which includes expression of anger, fighting, destruction, or harm to another character or object; or reference to destructive objects (guns, knives) or actions (breaking, destroying). The total number of children demonstrating varying degrees of aggression and frustration/disappointment (see Appendix A) during the "Make-Believe Play", "Create a Story", and "Birthday Party" activities from the ADOS-2 will be reported. In addition, for the purpose of this study, the

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presence of aggressive and/or morbid narrative themes in play were reported. Identification of morbid narrative themes to play, while not a part of the original APS, was included for the purpose of this study.

The original APS has consistently demonstrated high interrater reliability ranging from 0.70 to 0.90 using Cohen's kappa (Russ 2004, 2014). In terms of validity, studies have demonstrated that affect in play is significantly positively correlated with theoretically relevant criteria (Russ 2004, 2014). Although the original APS was not developed for use on the ADOS, when Zyga and colleagues (2015) modified the scale for the ADOS, no issues with reliability and validity were evident given the same coding system as the original APS was utilized. Research assistants were trained in the original and modified APS coding systems to the interrater reliability standard of 0.70 (Seja and Russ, 1999). Reliability among raters was determined by having 50 ADOS-2 videos (80%) coded by two raters to ensure accuracy of the scores obtained and that both raters scored behaviors based on the same interpretations.

Research Questions and Analytic Strategy

Research Question 1: How common and how severe is the aggression shown by children with Dup7?

Question 1a: Do children show elevated levels of aggression on parent-report measures?

Research examining the behavioral phenotype of Dup7 has included case studies mentioning aggression, and elevated rates of oppositional behavior and aggression have been reported in larger studies of children with Dup7. A more in-depth examination of aggression using a dimensional measure is warranted. It is hypothesized that children with Dup7 will show elevated rates of aggression on parental report measures.

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Question 1a Analytic Strategy: Levels of aggression will be examined using parental report from the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales, where the distribution of scores will be reported. One sample t-tests will be used to determine whether scores from Conners scales differ significantly from the normative mean.

Question 1b: What proportion of children with Dup7 show aggression based on parent interview and examiner observation?

In addition, examination of aggression utilizing categorical measures is warranted in order to determine the proportion of children with Dup7 who show aggression based on both parent interview and examiner observation. It is expected that aggression will be commonly reported by parents in a structured interview.

Question 1b Analytic Strategy: Current and lifetime levels of aggression will be examined using parental report from the ADI-R. The percentage of children with each severity rating (0-3) will be reported. Aggression displayed during evaluation will be examined using examiner observation from the ADOS-2. The percentage of children with each severity rating (0-3) will be reported.

Question 1c: What is the nature of the aggression shown by children with Dup7 within a play context?

The study of aggression is limited by use of parent and teacher report alone, as the type and nature of aggression can often not be determined. Given that different types of aggression have been identified using behavior coding (e.g., physical aggression, verbal aggression, aggressive themes), the use of behavioral coding of aggression in children with Dup7 is warranted to gain a more comprehensive description of the nature of aggression observed. Given

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the exploratory nature of this research question, and the sparse literature about aggression in children with Dup7, this research question is exploratory.

Question 1c Analytic Strategy: The nature of aggression within a play context will be determined using a modified version of the APS (see Appendix A). Intensity ratings (1-5) will be assigned to any "aggressive" and "frustration/disappointment/dislike" content. In addition, aggressive or morbid narrative themes will be identified. The percentage of children who display aggression within a play context will be reported, and the percentage of children with each intensity rating (1-5) will be reported.

Research Question 2: What are the potential contributors to the presence and severity of aggression in children with Dup7?

Question 2a: What are the relations between the severity of aggression and the levels of overall cognitive functioning and expressive language functioning in children with Dup7?

Research on aggression in individuals with intellectual disability has demonstrated increased prevalence of aggression compared to the general population. In addition, research clearly suggests that language and behavioral difficulties in young children frequently co-occur. Expressive language disorders, in particular, have been found to be more prevalent than receptive language disorders among children with emotional and behavioral difficulties. Given the relations between aggression and overall cognitive functioning and expressive language have never been examined in children with Dup7, examination of these relations is warranted. It is hypothesized that the severity of aggression will be significantly related to overall cognitive functioning, and the level of expressive language impairment.

Question 2a Analytic Strategy: Relations between the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales and overall cognitive functioning from the DAS-II will be examined using Pearson correlations. Relations between the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales and level of expressive language impairment will be determined using the EVT-2 will also be examined using Pearson correlations. Since the Conners Defiant/Aggressive Behaviors scale is available from all participants, some analyses will include all participants collapsed across the Conners CE and CBRS forms.

Question 2b: What are the relations between the presence and severity of aggression and the presence of social anxiety in children with Dup7 based on parent report?

Although limited, research indicates that a subset of individuals with social anxiety disorder display high rates of aggression. In addition, social anxiety and aggression have been found to co-occur at high rates. Given the high rates of social anxiety and aggression or oppositional behavior recently described in a group of individuals with Dup7, further examination of these relations is warranted. While this question is exploratory in nature, it is expected that parent-reported aggression and parent-reported social anxiety will be significantly related.

Question 2b Analytic Strategy: Relations between the presence and severity of aggression and the presence of social anxiety on the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales and Social Anxiety Disorder scales will be examined using Pearson correlations. In addition, relations between presence and severity of aggression and Social Anxiety or ODD diagnosis based on the ADIS-P will be examined using chi-square analyses.

Question 2c: What are the relations between the presence and severity of aggression based on parent report, and ASD severity?

While aggression has been known to occur among individuals with ASD, little is known about the severity of aggression in relation to ASD severity. Given the exploratory nature of this research question, and the sparse literature about aggression severity in individuals with ASD, this research question is exploratory.

Question 2c Analytic Strategy: The presence and severity of aggression will be determined using the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales. ASD severity will be determined using the ADOS-2 Comparison Score, which takes into account the ADOS-2 Overall Total Score in regards to an individual's chronological age, and relations will be examined using Spearman correlations.

Question 2d: Using examiner-based measures, do group differences exist between aggressive and nonaggressive children with Dup7 in ASD severity and age, and on measures of general cognitive functioning, expressive language, and social anxiety?

Research has demonstrated that certain individual-level characteristics have shown strong associations with the presence of aggression. Individuals with intellectual disability, expressive language deficits, and individuals diagnosed with ASD are at increased risk for demonstrating aggression. For this exploratory question, it is hypothesized that group differences will exist between aggressive and nonaggressive children with Dup7 in ASD status and age, and on measures of general cognitive functioning, expressive language, and social anxiety.

Question 2d Analytic Strategy: Presence of aggression will be determined by either Current ADI-R or ADOS aggression scores of "2" or "3". "Aggressive" group mean scores on

the DAS-II, EVT-2, ASD status derived from the ADOS, and Conners CBRS Social Anxiety

Disorder scale will be compared to data from the "Non-aggressive" group using independent t-

tests and chi-square analyses to examine group differences.

Results

The data were analyzed using IBM SPSS for Windows, version 23. Findings are

interpreted with respect to both statistical significance and effect size. A p-value of .05 was used,

but given the sample size, p-values between .05 and .1 were considered trends and are also

reported to decrease the chances of dismissing significant findings because of low power.

Interpretations of Cohen's d are as follows: negligible effect = 0 – .14; small effect = .15 – .39;

medium effect = .40 – .74; large effect = .75 and above. Pearson product-moment correlation

coefficients and Spearman's rho was used when correlational analyses were conducted and

interpretations of correlation effect size (Cohen, 1988) are as follows: small = .1 – .3; medium =

.3 – .5; large = .5 – 1.

Presence and Severity of Aggression in Children with Dup7

Question 1a: Do children show elevated levels of aggression on parent-report

measures? A detailed summary of parent-reported aggression on the Conners is detailed in

Table 2. On the Conners Defiant/Aggressive Behaviors and Violence Potential Indicator scales

group mean scores fell in the average range; however, analysis using one sample t-tests indicated

significantly higher scores than the normative mean on the Defiant/Aggressive Behaviors scale,

$t(59) = 3.04$, $p = .001$; and Violence Potential Indicator scale, $t(43) = 4.51$, $p = .001$. On the ODD

scale the group mean score fell in the elevated range and one sample t-tests indicated

significantly higher scores than the normative mean, $t(43) = 4.82$, $p = .001$. Figure 1 details the

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distribution of aggression levels falling in the average range (< 60), high average range (60-64), elevated range (65-69), and very elevated range (≥ 70). Elevated or very elevated scores were observed for 27% of children on the Defiant/Aggressive behaviors scale; 34% of children on the Violence Potential Indicator scale; and 43% of children on the ODD scale. There were no significant relations between parent-reported aggression and age, DAS-II GCA, and EVT-2. No gender differences were evident on any scales.

Question 1b: What proportion of children with Dup7 show aggression based on parent interview and examiner observation? A summary of the ADI-R parent interview items relating to aggression is detailed in Table 3. On the ADI-R, a total of 36 children (57%) were reported as currently showing some degree of aggression toward caregivers. Of these 36 children currently demonstrating aggression toward caregivers, 12% were assigned a code of 1 indicating the presence of mild aggression; 40% were assigned a code of 2 indicating the presence of definite physical aggression; and 5% were assigned a code of 3 indicating the presence of violence that involves use of implements. Four additional children were reportedly not showing aggression currently, but were rated as evidencing some degree of aggression in the past. Of these children, 1 child was assigned a code of 1 indicating past presence of mild aggression; 2 children were assigned a code of 2 indicating past presence of definite physical aggression; and 1 child was assigned a code of 3 indicating past presence of violence that involved use of implements.

A total of 15 children (24%) were reported as currently showing some degree of aggression toward non-caregivers. Of these 15 children, 6% were assigned a code of 1 indicating the presence of mild aggression; 16% assigned a code of 2 indicating the presence of definite physical aggression; and 2% were assigned a code of 3 indicating the presence of violence that

involves use of implements. A total of 21 children (33%) were reported as evidencing some degree of aggression towards caregivers "ever" (which includes current aggression). Of these 21 children, 6% were assigned a code of 1 indicating the presence of mild aggression; 24% were assigned a code of 2 indicating the presence of definite physical aggression; and 3% were assigned a code of 3 indicating the presence of violence that involves use of implements.

Spearman rank-order correlation coefficients were used to examine relations between reported aggression toward caregivers and non-caregivers. There were significant positive correlations for both current *(rho = .398, n = 63, p = .001)* and ever (*rho = .53, n= 63, p = .001*), such that children showing more aggression toward caregivers were also more likely show aggression toward non-caregivers. Significant positive correlations were evident for ADI-R Caregiver "ever" and age (*rho = .302, p = .016*). No significant correlations were evident for ADI-R and DAS-II GCA and EVT-2. No differences in gender were evident.

On the ADOS-2 E2 item (see Table 4), a total of 11 children (18%) were rated by examiner observation as showing some degree of aggression during the ADOS-2 assessment. Seven (11%) children were given a rating of 1 for displaying mild disruption, anger, aggression or negative behavior; 3 (5%) were given a rating of 2 for being intentionally disruptive, and 1 (2%) was given a rating of 3 for displaying marked or repeated temper tantrums or significant aggression. A summary of ADOS-2 E2 scores is further detailed in Table 4. When further examining this ADOS-2 item taking into account the module administered, 5 (56%) children administered Module 1 were rated as showing some degree of aggression (M = .89, SD = .93); 5 (24%) of children administered Module 2 were rated as showing some degree of aggression (M = .33, SD = .71); and 1 (3%) child administered Module 3 was rated as showing some degree of aggression (M = .03, SD = .17).

Spearman rank-order correlation coefficients revealed significant negative correlations for the ADOS-2 E2 item and age (*rho* = -.337, *n* = 63, *p* = .007), such that as a group, younger children with Dup7 were more likely to be demonstrate some degree of aggression during the context of the ADOS-2 assessment. Results also revealed significant negative correlations for the ADOS-2 E2 item and DAS-II GCA (*rho* = -.328, *n*= 63, *p* = .009). No significant correlations were evident for ADOS-2 E2 and EVT-2. No differences in gender were evident.

Question 1c: What is the nature of the aggression shown by children with Dup7 within a play context? To detail the nature of aggression shown by children, video recorded portions of the ADOS-2 were coded using a modified version of the APS. Interrater reliability was calculated for this study on 50 randomly chosen participants (80% of the sample) using Cohen's kappa to determine if there was agreement between two coders on intensity ratings and narrative theme ratings for children with Dup7 during a play context. Based on guidelines from Altman (1999), and adapted from Landis & Koch (1977), there was very good agreement for Aggression Intensity, κ = .882; Frustration Intensity, κ = .895; Aggressive Theme, κ = .904; and Morbid Theme, κ =.918. When examining affect ratings, a total of 29 children (46%) were rated as demonstrating some degree of aggression within a play context. Details regarding the intensity of aggression within a play context are defined in Table 5. A total of 14 children (22%) were rated as demonstrating some degree of frustration or disappointment within a play context. Details regarding intensity of frustration and disappointment are defined in Table 6. When examining themes within a play setting, a total of 8 children (13%) were rated as demonstrating an aggressive narrative theme, such that they referred to anger, destruction, or harm within the context of their narrative play. A total of 7 children (11%) were rated as demonstrating a morbid

narrative theme, such that they referred to death or dying within the context of their narrative play.

An independent samples t-test revealed that children expressing morbid themes were significantly older than those who did not express such themes, ($t(62) = -.2.12$, $p = .038$). Spearman rank-order correlation coefficients revealed no significant correlations between narrative theme content intensity and themes to play and DAS-II GCA and EVT-2. No gender differences were evident.

Potential Contributors to the Presence and Severity of Aggression in Children with Dup7

Question 2a: What are the relations between the severity of aggression and the levels of overall cognitive functioning and expressive language functioning in children with Dup7? In order to determine whether performance on measures of overall cognitive and expressive language functioning could help explain the severity of aggression reported by parents, relations between the Conners Defiant/Aggressive Behaviors scale, DAS-II GCA, and EVT-2 were examined using Pearson product-moment correlation coefficients. Results indicated no significant correlations between Conners Defiant/Aggressive Behaviors scale and DAS-II GCA ($r = -.072$, $n = 60$, $p = .585$), or EVT-2 ($r = .013$, $n = 60$, $p = .924$).

Question 2b: What are the relations between the presence and severity of aggression and the presence of social anxiety in children with Dup7 based on parent report? Relations between parent reported aggression (as measured by the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales) and parent reported social anxiety (as measured by the Conners Social Anxiety Disorder scale) were examined using Pearson product-moment correlation coefficients. Results revealed significant positive correlations between the Social

Anxiety Disorder scale and Defiant/Aggressive Behaviors scale ($r =.375$, $n = 44$, $p = .013$);

Violence Potential Indicator scale ($r =.416$, $n = 44$, $p = .006$); and ODD scale ($r =.408$, $n = 44$, $p = .006$). In addition, a chi-square test was performed to examine relations between ADIS ODD

diagnosis and Social Anxiety Disorder diagnosis. Results indicated no significant relation

between ODD diagnosis (n= 16) and Social Anxiety Disorder diagnosis (n= 34), [x^2 (1, n= 63) =

.045, $p = .832$].

Question 2c: What are the relations between the presence and severity of aggression based on parent report, and ASD severity? Relations between parent reported aggression (as measured by the Conners Defiant/Aggressive Behaviors, Violence Potential Indicator, and ODD scales) and ASD severity (as measured by the ADOS-2 comparison score) were examined using Spearman rank-order correlation coefficients. Results indicated no significant correlations between ASD severity and parent reported aggression on the Defiant/Aggressive Behaviors scale (*rho= - .061,* n= 60, *p=.646*), Violence Potential Indicator scale (*rho= - .027, n= 44, p= .862*), and ODD scale (*rho= - .095, n= 44, p= .540*).

Question 2d: Using examiner-based measures, do group differences exist between aggressive and nonaggressive children with Dup7 in ASD severity and age, and on measures of general cognitive functioning, expressive language, and social anxiety? Group differences between aggressive (n=32) and nonaggressive (n=31) children were examined using independent-samples t-test. Results revealed no significant differences between aggressive and nonaggressive children with Dup7 in regards to age (*t(62)* = -.986, $p = .328$), on the ASD Comparison Score (*t(62)* = 1.14, $p = .258$), DAS-II GCA (*t(62)*= .961, $p = .665$); EVT-2 (*t(62)*= -.349, $p = .465$); or the Conners Social Anxiety Disorder scale (*t(43)*= -1.65, $p = .975$). Furthermore, a chi-square test indicated no significant difference in the proportion of aggressive

children diagnosed with ASD (33%) as compared with the proportion of nonaggressive children diagnosed with ASD (66.7%), [$x2$ (1, n= 63) = 1.80, p = .213].

Discussion

The primary aim of this study was to characterize the presence and severity of aggression in children with Dup7. As hypothesized, children with Dup7 showed elevated rates of aggression on a parent reported, norm-referenced measure of aggression and oppositional behavior. Over one-quarter (27%) of parents reported behavior resulting in elevated or very elevated scores on the Defiant/Aggressive Behaviors scale; 34% on the Violence Potential Indicator scale; and nearly half (43%) on the ODD scale. As expected, aggression was also commonly reported by parents in a structured interview. Over half (57%) of parents indicated that their children had engaged in some form of aggressive behavior towards them currently, while nearly two-thirds (64%) of parents indicated that their children had demonstrated some form of aggressive behavior toward them either currently or in the past. In addition, children who demonstrated aggression toward a caregiver were more likely to demonstrate it toward a non-caregiver as well. Furthermore, examination of content and actions in a semi structured play session indicated frequent aggressive statements, as well as aggressive and morbid narrative themes. Overall, a high prevalence of aggression and oppositionality among children with Dup7 in the current study was evident across normative-based measures, and expressions of aggression were evident based on observational coding.

A secondary aim of this study was to identify the potential contributions of intellectual functioning, expressive language abilities, age, ASD severity, and social anxiety to levels of aggression. In the current study, overall cognitive and expressive language functioning, as measured by the EVT-2, were not related to aggression, despite this being a common association

in the typically developing population. In addition, ASD severity was not related to aggression. As expected, children rated by their parents as demonstrating behaviors consistent with social anxiety were also rated as exhibiting aggression and oppositional behavior in the current study. When examining group differences between aggressive and nonaggressive children, no significant relations were found for ASD severity, overall cognitive functioning, expressive language functioning, and social anxiety. No significant relations between aggression and age were observed and no sex differences were found.

Prevalence of Aggression

Recent research delineating the cognitive and behavioral phenotype of individuals with Dup7 suggested that children with Dup7 may have increased rates of aggression and oppositional behavior (Mervis et al., 2015). In addition, certain syndrome groups, particularly those associated with intellectual disability, have shown high rates of aggression compared to groups of 3individuals with intellectual disability of heterogeneous etiology (Arron et al., 2011). Certain individual characteristics have also been known to be associated with aggression in children, such as ASD, expressive language delays, and low IQ (McClintock et al., 2003; Dominick et al., 2007; Lahey et al., 1999; Moffitt et al., 1994; Tremblay, 2000). Furthermore, research has demonstrated that in some syndrome groups, age, gender, and subtype factors are important to consider when examining aggression (Arron et al., 2011; Bailey & Ostrov, 2008; Loesch et al., 2004). While there is likely no single factor that contributes to aggressive and oppositional behavior, increased knowledge of the variables that are more or less associated with aggression and oppositional behavior are clinically useful in increasing awareness of certain syndrome groups, as well as in the development of interventions to prevent or reduce negative consequences associated with these behaviors.

The present study found high rates of aggression on both dimensional and categorical measures of parent-reported aggression. On a norm-referenced dimensional measure, scores on the Conners Defiant/Aggressive Behaviors and Violence Potential Indicator scales were significantly higher than the normative mean despite group mean scores falling in the average range. Specifically, on the Defiant/Aggressive Behaviors scale 27% of children were rated as demonstrating behaviors at an elevated or very elevated level (≥ 65), and on the Violence Potential Indicator scale 34% of children were rated as demonstrating behaviors at an elevated or very elevated level. Group mean scores on the Conners ODD scale were higher, falling in the elevated range, and were also significantly higher than the normative mean. On the ODD scale, 43% of children were rated as demonstrating behaviors at an elevated or very elevated level. These higher rates of elevation on the ODD scale compared to other aggression-related scales suggest that children with Dup7 tend to demonstrate less violent, physically aggressive behaviors, and more argumentative and defiant behaviors. When aggression was examined using a categorical measure based on parent interview, results also revealed much higher rates of aggression compared to rates on a dimensional measure. On the ADI-R, over half of children were reported as currently showing some degree of aggression toward caregivers, and rates of past aggression were even higher. High rates of aggression were also evident when examining aggression toward non-caregivers. For both caregivers and non-caregivers, the majority of children demonstrating aggression both currently or in the past were described as showing definite physical aggression.

The current study's rates of aggression, particularly using a categorical measure, are considerably higher than rates previously reported using measures based on the presence of aggression for individuals with intellectual disabilities (7-11%) (Emerson et al., 2001; Holden &

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Gitlesen, 2006), and ASD (22%) (Hartley et al., 2008), as well as for individuals with both ASD and intellectual disability (15-18%) (Matson & Rivet, 2008). However, a more recent examination of aggression in children and adolescents with ASD found comparable rates to the current study's aggression rates when assessing aggressive behavior toward caregivers and non-caregivers using the ADI-R (Kanne & Mazurek, 2011).

When examining sex differences in aggression, our results indicate that males and females with Dup7 were equally likely to engage in aggression. This finding is consistent with recent research examining aggression in ASD (Kanne & Mazurek, 2011); however, there is a considerable amount of literature that has clearly demonstrated sex differences among the general population (Lahey et al., 2000; NICHD Early Child Care Research Network, 2004), individuals with intellectual disabilities (McClintock, Hall, & Oliver, 2003) and ASD (Archer, 2004; Card et al. 2008), such that rates of aggression are consistently higher among males than females. Given the extensive research that has clearly documented sex differences in aggression among various populations, it may be possible that these differences in findings are due to certain biological mechanisms that occurred as a result of genetic changes in individuals with Dup7 that equal the likelihood of aggression among males and females.

The present study also found high rates of aggression in our sample of children with Dup7 based on examiner observation, particularly for children who are either pre-verbal or are using single words to communicate and were administered Module 1 of the ADOS-2. Eighteen percent of children were rated by examiners as showing some degree of aggression during assessment, with the majority of those children evidencing mild disruption, anger, aggression or negative behavior during the ADOS-2 assessment. Mean aggression scores for children administered Module 1 in the current study (M = .89, SD = .93) were much higher than expected

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based on means for children administered Module 1 with autism (M = .71, SD = 72), non-autism

ASD (M = .52, SD = .71), and non-spectrum (M =.43, SD = .62) based on normative data

provided in the ADOS-2 manual (Lord et al., 2012). Mean aggression scores for children

administered Modules 2 and 3 revealed scores either commensurate to or lower than that

expected for children not on the autism spectrum based on the ADOS-2 manual. Examiner-

observed aggression and age were significantly related, such that as a group, younger children

with Dup7 were more likely to demonstrate some degree of aggression during the context of the

ADOS-2 assessment. Examiner-observed aggression was also found to be related to overall

cognitive functioning, such that as a group, children with Dup7 with lower overall cognitive

functioning were more likely to demonstrate some degree of aggression during the context of the

ADOS-2 assessment. Expressive language functioning, as measured by the EVT-2, while not

related to the presence of some degree of aggression during the context of the ADOS-2

assessment, was notably more delayed for those children administered Module 1. Over half of

children administered Module 1 of the ADOS-2 demonstrated aggression as observed by the

examiner. These findings are consistent with literature demonstrating increased rates of

aggression among individuals with low IQ (Lahey et al., 1999; Moffitt, 1994; Tremblay, 2000),

delayed language (Camarata et al., 1988; Benasich, Curtiss, & Tallal, 1993; Benner, 2005) as

well as with younger children (Hartley et al., 2008; Kanne & Mazurek, 2011). However, despite

the current study's relatively high rates of aggression based on examiner observation, which was

particularly evident on Module 1, the overall observed rate of aggression across participants is

actually lower than has been observed in verbal and nonverbal, as well as high functioning and

low functioning children with ASD when also using the ADOS-2 (De Giacomo et al., 2016).

This difference in rate may be due to significant differences in participants, as Giacomo and

colleagues' participant group was comprised entirely of children with ASD (of unknown severity), mostly of children less than 8 years of age, and most participants were males.

While significant relations between age and aggression observed during the ADOS-2 were evident in the current study, no effect of age on dimensional parent report measures of aggression was apparent. Upon further examination of observed aggression on the ADOS-2 by module administered, it was evident that the pattern of observed aggression varies based on the ADOS-2 module administered. Children who were currently pre-verbal or using single words to communicate, as a group, demonstrated aggression at elevated rates compared to children who were using phrase speech or who were verbally fluent. This effect of module on aggression suggests the role of language delays in the presence of aggression during interaction with a non-caregiver during a semi-structured task.

The varying rates of aggression reported by parents and observed by examiners in the current study for the sample of children is likely due to multiple factors, including the reduced observation and interaction time that clinicians have compared to parents, the novel context of interaction with a new communicative partner, and the generally different relationship of children with parents and professionals. In addition, these observer differences may be indicative of a need for further delineation of the type of aggression exhibited. Previous literature has described aggression with variable frequency, duration, and intensity, and subtypes of aggression have been described. Proactive aggression is goal oriented and calculated, while reactive aggression involves hostile reactions to provocation, and factor analyses have supported these distinct aggression subtypes (Dodge, 1991; Poulin & Boivin, 2000; Raine et al., 2006; Fite, Colder & Pelham, 2006). Furthermore, these subtypes of aggression have also been associated with unique behavioral, social, and emotional outcomes (Card & Little, 2006).

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Contributions to Aggression

In the current study, measures of intellectual functioning and expressive language functioning were not related to aggression. This result is surprising given past research associating low IQ and expressive language delays to aggressive behavior (Lahey et al., 1999; Moffitt, 1993; Tremblay, 2000; Dionne et al., 2003; Stevenson et al., 1985). The current study also found that ASD severity was not related to aggression in our sample of children with Dup7, consistent with findings from Kanne & Mazurek (2011) when assessing relations between ASD severity and aggressive behaviors in children and adolescents with ASD. Furthermore, when examining group differences between aggressive and nonaggressive children based on the presence of definite physical aggression based on examiner-based measures, no significant differences were found for ASD severity, intellectual functioning, expressive language functioning, and social anxiety. This lack of relations and lack of group differences between aggressive and nonaggressive children suggest that the relatively high prevalence of the type of aggression exhibited by children with Dup7 is not due to severity of ASD, intellectual or expressive language functioning.

When examining aggression and social anxiety on a dimensional measure, our results indicate that aggression and social anxiety are significantly related, such that the more behaviors endorsed on scales of aggression and oppositional behavior, the more behaviors were also endorsed on a scale of social anxiety disorder symptomatology. Research examining the co-occurrence of social anxiety and aggression is relatively scarce; however, our findings on the relations between aggression and social anxiety is similar to findings in the ASD literature. Research has demonstrated that for individuals with ASD, social anxiety has been shown to increase hostility and aggression in adults, and has demonstrated strong relations with physical

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aggression in children and adolescents (Ambler et al., 2015; Pugliese et al., 2013; White et al., 2012). Conversely, in the general population social anxiety has been associated with low levels of violence and aggression (Dewall et al., 2010).

Research examining the co-occurrence of internalizing problems, specifically anxiety and depressive symptoms, is less scarce. It has been demonstrated that anxiety and depressive symptoms are associated with anger and aggressive behavior among children (Erwin et al., 2003; Vitaro et al., 2002) and adolescents (Batanova and Loukas, 2011; Fite et al., 2010, Marsee et al., 2008); however, it remains unclear whether anxiety and depressive symptoms precede aggression, or aggression precedes anxiety and depressive symptoms. Research conducted by Vitaro et al. (2002) found that general anxiety symptoms assessed at age 6 were positively related to aggressive behavior at age 10-12 years. However, more recent research suggests aggression predicts later anxiety and depressive symptoms (Slemming et al., 2010). In this study, Slemming and colleagues found that hostile and aggressive behaviors assessed at 3-4 years of age were positively related to internalizing emotional difficulties at 10-12 years of age. Researchers have also posited that the co-occurrence of aggression and anxiety or depressive symptoms may be explained by common factors. Emerging evidence from theoretical developmental psychopathology literature suggests several common mechanisms associated with the fight-flight response that are common to both anxiety and aggression (Kunimatsu & Marsee, 2012) that could explain the observed co-occurrence of anxiety and aggression. Berkowitz (2002) posited that while the flight response is a conscious experience of fear, the activation of the fight response gives rise to feelings of irritation and anger. When considering this conceptualization, it is assumed that internalizing experiences, such as fear or anxiety, precede aggressive behavior.

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It is notable, however, that categorical diagnoses of ODD and Social Anxiety Disorder were not significantly related. This is surprising given the significant relation between the ODD and social anxiety scales on a dimensional measure. When examining ODD and Social Anxiety Disorder items on both the Conners and ADIS-P, it is apparent that there is very little difference in the content of items, as the Conners items are derived directly from symptoms required for diagnostic criteria. However, given that the ADIS-P is used for diagnostic purposes, it also includes items related to level of interference in daily life; whereas the Conners does not. Given this reason, it is possible that levels of opposition in the current sample of children with Dup7 are not interfering with daily functioning in the way that would be expected given the ODD symptoms endorsed. In addition, given that the ADIS-P is an interviewer-based measure, the interviewer is able to take into account context when completing items, and therefore, may take a different perspective on behavior compared to parents.

Conclusions

Summary

The current study is the first to report on levels of aggression and potential contributions to levels of aggression in children with Dup7. Given the variable nature of the term "aggression", it was the current study's aim to utilize a multimethod, multi-informant approach to allow for a more detailed interpretation of data. Elevated levels of aggression and oppositional behavior were observed in this sample of children with Dup7. While intellectual functioning, expressive language functioning, and ASD severity were not related to aggression in the current study, children who were young or had language delays and were administered Module 1 of the ADOS-2 were more likely to demonstrate aggression as rated by an examiner. In addition, children who were rated by their parents as demonstrating behaviors associated with a diagnosis of Social Anxiety Disorder (e.g., avoids social situations, fears of being embarrassed or humiliated, and

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worries what others think of him/her) were more likely to be rated as demonstrating defiant,

aggressive, and violent behaviors, as well as behaviors consistent with ODD (e.g., losing temper,

irritable and easily annoyed, and angry and resentful). This finding suggests that the presence of

social anxiety may contribute to the presence of aggression in this current sample of children

with Dup7.

Overall, this study's findings suggest that the genes in the 7q11.23 region duplicated in

Dup7, in transaction with the environment, may contribute to aggressive behavior. This study

contributes to the scarce Dup7 behavioral phenotype literature, as well as contributes to the

literature linking social anxiety with aggression in certain individuals. In addition, given the

significant impact of aggression, it is expected that the detailed characterization of these

behavioral outcomes and factors that contribute to outcomes will inform more targeted

interventions.

Limitations and Future Directions

The present study is the first to report on levels of aggression and potential contributions

to levels of aggression in children with Dup7 and provides clinically relevant information about

the Dup7 behavioral phenotype. However, there are limitations in the study design that warrant

improvement in future research. First, despite the sample of 63 children in the current study, the

samples remain relatively small given the large age span included and given age limitations on

norm-referenced measures. For example, both the Conners CE (ages 4-5) and CBRS (ages 6-18)

were administered to parents in the current study due to the large age range; however, only one

scale (Defiant/Aggressive Behaviors) used in the current study was available for all participants.

A larger sample of children and adolescents would ensure adequate representation of all ages

across all measures included in the study. Second, the possibility of an ascertainment bias in

favor of children with more significant difficulties exists given that patients with more significant difficulties are more likely to seek medical attention and are more likely to be referred to a geneticist. This ascertainment bias could also result from the fact that Dup7 is typically discovered due to unexplained medical or developmental difficulties, which lead to a microarray being conducted. Third, the current study's use of observational coding during a play context was largely limited by a lack of contrast group, which would have been useful in determining normative levels of aggression and frustration intensities, as well as the presence of aggressive and morbid narrative themes in play.

Future research on aggression in children with Dup7 should also include examination of family and community variables in the prediction and maintenance of aggression. In the general population, certain variables such as demographic and family variables have been shown to contribute to the persistent of aggression. As such, examinations using measures of socioeconomic status, family conflict, parent education, marital status and parenting style would be beneficial in understanding the role of these factors when assessing aggression.

In addition, future longitudinal work will also be important to provide information about the trajectories of aggressive behavior among children with Dup7. Researchers studying children in the general population have differentiated subgroups of children based on patterns of low and high aggression, as well as declining and increasing rates of aggression with age (Broidy et al., 2003; Campbell et al, 2010). This type of approach would allow for more detailed information about the factors contributing to aggression in children with Dup7. It also will be important for determining the predictive utility of the presence of social anxiety for the presence of aggression.

Figure 1: Proportion and Levels of Parent Reported Aggression
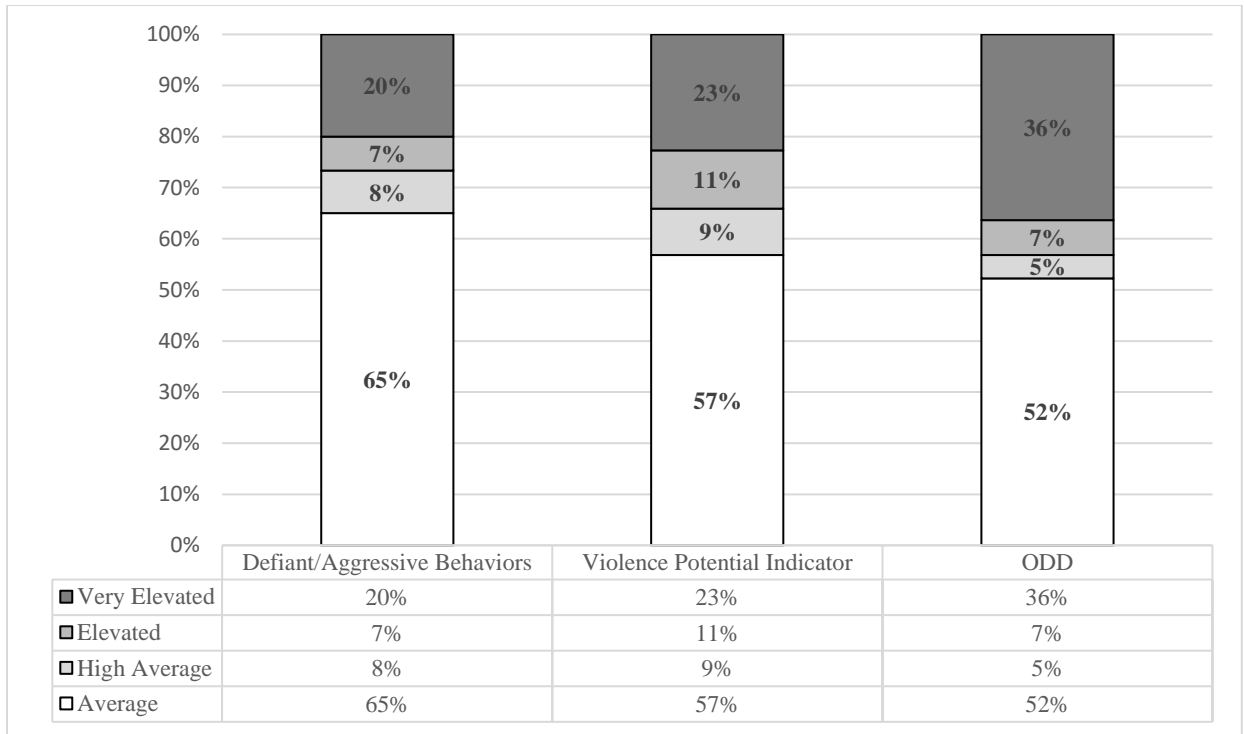

	Defiant/Aggressive Behaviors	Violence Potential Indicator	ODD
■ Very Elevated	20%	23%	36%
■ Elevated	7%	11%	7%
□ High Average	8%	9%	5%
□ Average	65%	57%	52%

Table 1. Participant Demographic Data

Variable	n= 63
Mean Age (*SD*)	8.64 (3.77)
Sex (Frequency/%)	
Females	25 (40)
Males	38 (60)
Mean GCA (*SD*)	79.38 (19.45)
ASD Status (Frequency/%)	
Nonspectrum	51 (81)
ASD	12 (19)

Table 2. Conners Parent Reported Aggression

Conners Scale	M (SD)	Range	d
Defiant/Aggressive Behaviors	57.12 (15.88) ++	36-90	.45
Violence Potential Indicator	59.09 (13.19) ++	42-90	.69
ODD	61.36 (15.61) ++	40-90	.73

Significantly higher than normative mean: + $p < .05$, ++ $p < .01$

Table 3. ADI-R Parent Reported Aggressive Behaviors

Code	Description	Caregiver: Current	Caregiver: Ever	Non-caregiver: Current	Non-caregiver: Ever
0	No Aggression	43%	37%	76%	67%
1	Mild Aggression	12%	14%	6%	6%
2	Definite Physical Aggression	40%	38%	16%	24%
3	Violence with Implements	5%	11%	2%	3%

Table 4. ADOS-2 E2: Tantrum, Aggression, Negative or Disruptive Behavior Descriptives

	N	Age M(SD)	Age Range	DAS-II GCA M(SD)	EVT-2 M(SD)	ADOS-2 E2 M(SD)	Conners Defiant/Aggressive Behaviors Scale M(SD)
Module 1	9	5.20 (1.41)	4.08 – 8.38	53.11 (19.30)	36.11 (22.64)	0.89 (.93)	58.67 (19.45)
Module 2	21	6.31 (2.17)	4.01 – 11.58	78.28 (13.77)	90.28 (11.21)	0.33 (.71)	60.37 (14.56)
Module 3	33	11.05 (3.28)	5.37 – 17.70	87.24 (15.41)	96.36 (9.61)	0.03 (.17)	54.75 (15.24)

Table 5. Aggression Intensity During Play

Code	Description	N	Frequency
0	No aggression present	34	54%
1	Reference to aggressive content	11	17%
2	Personalized reference to aggressive content; mild aggressive play	13	21%
3	Fighting, hitting play; aggressive dialogue with feeling	5	8%
4	Action plus dialogue; strong feeling state	0	0%

Table 6. Frustration Intensity During Play

Code	Description	N	Frequency
0	No frustration/disappointment present	49	77%
1	Non-personalized reference to frustration/disappointment	3	5%
2	Personalized statement of frustration/disappointment	5	8%
3	Current action of frustration/disappointment	5	8%
4	Stating frustration or disappointment with an action	1	2%

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Appendix:

Modified APS for Aggression Behavioral Coding

Total frequency of units of affective expression: A unit is defined as one scorable expression. A unit can be the expression of an affect state, an affect theme, or a combination of the two. An example, of an affect state would be one figure saying "This is fun." An example of an affect theme would be "Here is a bomb that is going to explode." The expression can be verbal ("I hate you") or non-verbal (one figure punching the other). The frequency of affect score is the total number of units of affect expressed in the five-minute period. If non-verbal activity, such as fighting, occurs in a continuous fashion, a new unit is scored every five seconds.

Mean intensity of affective expression (1-5 rating): This rating measure the intensity of the feeling state or content theme. Each unit of affect is rated for intensity on a 1-5 scale.

Affect categories: Aggression, Frustration/Disappointment/Dislike

Narrative themes: Aggressive, Morbid

CRITERIA FOR AFFECT CONTENT AND INTENSITY RATINGS

General Principles

An affect unit is scored when there is an expression of an affect content theme, emotion word, or non-verbal expression of emotion in the play narrative. All of the affect intensity ratings are based on the expression of affect content themes, emotion words, and non-verbal expressions of emotion."I like this hot dog" is comprised of both an affective content theme (hot dog–oral) and an emotional expression word (like). It could also be accompanied by non-verbal expression of positive affect (voice tone, clapping). In general, combinations of emotional expression and emotion word and content themes get higher intensity ratings than the theme alone or emotional expression alone. The general criteria for the 1–5 intensity ratings are:

1. Reference to affect content.

2. Reference to affect content with special emphasis, which implies experiencing

(such as personal referent).

3. Current experiencing, which includes:

      a. Moderate action alone.

      b. Emotion with conversational voice.

      c. Primary process theme plus mild feeling state.

4. Stronger current experiencing, which includes:

      a. Mild action plus mild feeling state.

      b. Strong action alone.

      c. Strong affect alone.

      d. For primary process categories, unusual and strong emotion or

strong theme word.

      e. Primary process theme and moderate affect.

5. Very strong feeling state, which includes:

      a. Action plus strong feeling state.

      b. Extreme primary process theme word.

      c. Extremely strong affect.

      d. Extremely strong action.

In general, affective theme, emotional expression (emotion word, tone, facial expression, etc.) and action are additive components.

SPECIFIC CRITERIA FOR AFFECT CATEGORIES AND INTENSITY RATINGS

Aggression: Expression of anger; fighting, destruction, or harm to another character or object; or reference to destructive objects (guns, knives) or actions (breaking).

Intensity Rating	Specific Criteria	Example
1	Reference to aggressive content	"Here's a toy gun"; "Here's a knife"; "This is broken"
2	Personalized reference to aggressive content; mild bickering; mild aggressive play (poking, scratching)	"I have a knife"; "I'll break it"; "Let's fight"; "No- I don't want to do that"
3	Actual fighting, hitting, tussling; destroying other's property; aggressive dialogue with feeling; angry feeling statement	"I am mad"; "I don't want to do that- that's stupid" (with feeling); "I'll punch you; "I don't like you"; "Let's fight" (with feeling)
4	Action plus dialogue; strong feeling state; strong theme word	Hitting plus "You're stupid; "I hate you"; "Here is a bomb that is going to explode"
5	Strong action and strong dialogue; extreme emotional theme	"I'll kill you"; "I'm going to beat your brains to a pulp"; actions of shooting or stabbing

Frustration/Disappointment/Dislike: Expressions of disappointment and frustration with activities, objects, and limitations.

Intensity Rating	Specific Criteria	Example
1	Reference to frustration/disappointment; non-personalized statement of frustration/disappointment (conversational voice)	"It fell; "Math is boring"; "She seems bored"
2	Personalized statement of frustration/disappointment (conversational tone); current action of frustration/disappointment	"I'm not good at building"; It fell (with affect)
3	Current experience of frustration/disappointment (conversational tone); current action of frustration/disappointment	"This is hard"; "I'm bored"; "I can't do this"; Tapping foot; Making noises like clicking tongue
4	Statement of frustration/disappointment with an action; statement of current experience of frustration/disappointment (exclamation); stronger action	"I can't get this!" (while knocking down blocks); "Boy, is this hard"; "This is a rotten day"; "Ugh, I can't get this"
5	Stronger statement of frustration/disappointment with an action; very strong experiencing statement; very strong action	Slamming down the blocks while saying "I can't do this"; swearing; "I hate this"

CRITERIA FOR NARRATIVE THEMES

Theme	Specific Criteria	Example
Aggressive	Reference to anger, destruction, harm	Fighting; war; shooting or stabbing; threats
Morbid	Reference to death or dying	Airplane crashing; boats sinking, burning buildings, children in graves; "He's dead"