EFFECTS OF ONLINE RESPONSE INHIBITION TRAINING IN CHILDREN WITH WILLIAMS SYNDROME: A PILOT STUDY

by

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ABSTRACT
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Williams syndrome (WS) is a genetic neurodevelopmental disorder which is often accompanied by challenges such as attention difficulties, anxiety, and overfriendliness. While research is mixed, a substantial body of literature suggests that deficits in response inhibition may underlie these difficulties in WS, making response inhibition a possible focus of intervention. However, research to date has not explored interventions that may affect response inhibition in individuals with WS. A recently developed computerized response inhibition training program has shown promise at improving response inhibition in other populations, but research on computerized training for people with WS has not been conducted. The aim of this pilot study was to use a randomized controlled trial with waitlist crossover design to investigate the utility of an online training program at improving response inhibition (as measured by a Go/No-Go task) and parent report of everyday attention difficulties in children and adolescents with Williams syndrome. Results indicated that an immediate treatment effect was not present for the sample and that the treatment group did not show more error reduction than the waitlist group. Overall, improvement in clinical outcomes was not reported by parents after treatment. Error reduction on the lab-based task appeared to be related to symptom reduction at post-treatment but not at follow-up. Scores on the lab-based task three months after completion of training suggest that there may be delayed treatment effects for some participants; the degree of improvement was predicted by the degree

of baseline ADHD symptomatology. Implications and future directions for the use of computerized training for individuals with WS are discussed.

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Effects of Online Response Inhibition Training in Children with Williams Syndrome: A Pilot Study

Williams syndrome (WS) is a genetic neurodevelopmental disorder resulting from a microdeletion on chromosome 7q11.23 (Hillier et al., 2003). Estimates of prevalence suggest that the syndrome occurs in 1 in about every 7,500 births (Stromme, Bjornstad, & Ramstad, 2002). Individuals with WS generally show mild to moderate intellectual difficulties, learning problems, personal strengths in verbal memory and language, and overfriendliness. They typically face significant challenges in the areas of attention, inhibition, and anxiety (Mervis & Klein-Tasman, 2000; Morris & Mervis, 2000). Specifically, those with WS usually exhibit attention difficulties, including hyperactivity and impulsivity, with high rates of comorbid Attention Deficit/Hyperactivity Disorder (ADHD), as well as social disinhibition or 'hypersociability,' anticipatory question asking, excessive talking, specific phobias (e.g., to loud noises), and non-social anxiety (Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Mervis & Klein-Tasman, 2000; Rhodes, Riby, Matthews, & Coghill, 2011).

Neuroimaging and behavioral studies indicate that many of the difficulties characteristic of WS are thought to be related in some way to inhibitory deficits (Frigerio et al., 2006; Gothelf et al., 2008; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Porter, Coltheart, & Langdon, 2007; Milad et al., 2007; Mobbs et al., 2007). Recently, computerized intervention programs targeting inhibition in other populations have been developed and have shown favorable results, but no such interventions have been tested in the WS population. Poor inhibition interferes with day-to-day life in social, home, and academic settings; computerized training shows promise as an intervention to help improve inhibitory deficits, which could result in better psychosocial functioning in this population.

‘Response inhibition’ (RI) is the term used for the neural process that provides us with the ability to stop an intended or ongoing movement or inhibit a pre-potent stimulus-response association. An impairment in RI - this ability to inhibit unwanted or inappropriate behavior - preserves the unwanted behavior. RI difficulties in Williams syndrome are manifest in the behavioral phenotype of this population (Mobbs et al., 2007; Porter et al., 2007); poor inhibition can sometimes be expressed through attention problems, a low threshold for frustration, and overfriendliness to strangers (Tomc, Williamson, & Pauli, 1990). Links between inhibitory control and attention problems, impulsivity, hypersociability, and anxiety are suggested in WS, indicating that the effects of inhibitory deficits are far-reaching and likely impair daily functioning for people with WS and increase vulnerability in both the present and the future (Davies, Howlin, & Udwin, 1997; Davies et al., 1998; Howlin & Udwin, 2006).

This introduction will be organized as follows: First, neuroanatomical differences in WS will be reviewed, and three main features of the Williams syndrome behavioral phenotype (attention problems, hypersociability, and anxiety) will be explored in relation to inhibition and neural structure and function. Second, the utility of cognitive training, in particular for inhibitory difficulties, will be examined and computerized training will be highlighted. Finally, aims and hypotheses of the current pilot study will be presented as a means of expanding the field of computerized cognitive training to target inhibitory difficulties in the WS child population.

Inhibitory Control and the Williams Syndrome Brain and Behavioral Phenotype

Neuroanatomical findings. In general, there is agreement that neuroanatomical abnormalities exist in WS, and some research suggests inhibitory deficits in this population that may be related to brain structure and function. Key structural neuroimaging studies in WS have reported reduced brain volume overall (Fahim et al., 2012; Reiss et al., 2004, Cherniske et al.

2004; Kippenhan et al., 2005; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001a), enlarged areas (e.g., amygdala; ventral anterior prefrontal cortex [PFC]; fusiform face area; cerebellum) (Gothelf et al., 2008; Martens, Wilsonc, Dudgeonc, & Reutens, 2009; Schmitt, Eliez, Bellugi, & Reiss, 2001b), atypical folding, high variability between layers, larger and less densely packed brain cells, and a short central sulcus (Avery, Thornton-Wells, Anderson, & Blackford, 2012; Galaburda & Bellugi, 2000). Most neuroimaging in WS to date has taken place in adults; in children, increased gyrification (especially in the parietal lobe) and less cortical complexity in frontal and parietal areas (Fahim et al., 2012) are reported. Structural abnormalities and related functional atypicalities likely contribute to the observed difficulty in the three key areas of behavior explained below.

ADHD and inhibition. A common comorbidity in WS is attention problems, with prevalence estimates of ADHD in WS at about 64% (Leyfer et al., 2006). Research on the behavioral, neuropsychological, and neuroimaging profiles of individuals with WS indicate that executive function characteristics in WS are similar to those of people with ADHD (Mobbs et al., 2007; Rhodes, Riby, Park, Fraser, & Campbell, 2010; Rhodes et al., 2011). Difficulties associated with ADHD, including impulsivity, inhibiting responses, attending, concentrating, and recovering from errors to appropriately focus attention have been noted in WS (Greer, Riby, Hamiliton, & Riby, 2013; Menghini, Addona, Costanzo, & Vicari, 2010; Porter et al., 2007; Rhodes et al., 2011). Greer and colleagues (2013) investigated attention and inhibition in adults with WS, finding inhibitory deficits and problems engaging in tasks, specifically focusing attention after mistakes (Greer et al., 2013). Of note, this study used a lab measure that relates to difficulty with inhibitory and attentional functioning in the real world (Smilek, Carriere, & Cheyne, 2011), so it is possible that difficulties with inhibition observed in a lab setting may

indicate everyday inhibition difficulties. In a direct comparison of individuals with ADHD to individuals with WS, Rhodes and colleagues (2011) found that the groups showed similar levels of severity on an ADHD rating scale and similarities when assessed using neuropsychological measures (Rhodes et al., 2011); this provides further support for parallels between the two disorders in both brain function and observed everyday behavior.

Mobbs and colleagues (2007) used fMRI to investigate neural bases for poor RI and poor attention in WS. They found that people with WS show significantly less activation in fronto-striatal circuitry compared to age-matched typically-developing controls during a RI (Go/No-Go) task, suggesting failure to appropriately activate brain regions essential for behavioral inhibition. Cognitive ability and response time were not significantly related to differences in brain activity, implying that the syndrome itself is likely an important factor in the poor levels of activation observed (Mobbs et al., 2007).

Horn and colleagues (2003) found that brain areas involved in RI (specifically, the right orbitofrontal cortex was indicated) must be strongly engaged to inhibit behavior in people who show higher degrees of impulsivity (Horn et al., 2003). Furthermore, difficulties with inhibition are present in ADHD (Lipszyc & Schachar, 2010), and while additional investigation is needed, research supports that ADHD involves deficits in the executive system's role of inhibiting pre-potent responses (Nigg, 2001). Neuroimaging research with healthy individuals reveals that biomarkers for ADHD are found during examination of inhibitory brain pathways, helping to classify ADHD with 77% accuracy (Hart et al., 2014). The links between inhibitory deficits and ADHD, as well as the combination of abnormal frontal lobe functioning and a high incidence of comorbid ADHD or ADHD symptoms in WS, suggest that RI is impaired in a large proportion

of the WS population. Therefore, the problem of RI difficulties in WS from an attention standpoint deserves consideration and intervention.

Hypersociability and inhibition. An impressive amount of research has been dedicated to the social profile of individuals with WS, and this is where most of the literature on inhibition in WS originates. While this research focuses on explaining the disinhibited social behavior that is characteristic in WS, it has provided a wealth of information about brain structure and function, which provides clues about inhibition in general in WS.

Encounters with individuals with WS are usually memorable due to abnormal social behavior, especially hypersociability, characterized by an over-friendly interaction style and disinhibited social approach which extends even to strangers (Jones et al., 2000). Individuals with WS also show increased use of social engagement techniques and social language during interactions (Reilly, Losh, Bellugi, & Wulfeck, 2004), even when inappropriate, which suggests that the ability to inhibit social advances is impaired (Gothelf et al., 2008). Structural and functional abnormalities, particularly in the prefrontal cortex, fusiform face area, and amygdala, have given rise to two main hypotheses for the characteristic hypersociability: the frontal lobe hypothesis and the amygdala hypothesis.

Frontal lobe impairments are hypothesized to be responsible for hypersociability in WS because of a failure to properly inhibit other parts of the brain. Individuals with frontal lobe damage show disinhibited social behavior as well as perseveration on a prior target (Rolls, Hornak, Wade, & McGrath, 1994), representing varying manifestations of poor inhibition related to frontal functioning. Furthermore, poor inhibition of action is related to impulsive behavior (Donfrancesco, Mugnaini, & Dell'Uomo, 2005), and the failure of RI is hypothesized to be responsible for the disinhibited social profile in WS (Mobbs et al., 2007). Finally, unique neural

patterns of attraction to faces suggest that a person with WS's strong drive to interact overrides frontal inhibitory processes (Dodd & Porter, 2010; Golarai et al., 2010; Gothelf et al., 2008; Mobbs et al., 2004).

Amygdala volume and dysfunction are also suggested to be related to hypersociability; this is known as the amygdala hypothesis. Research suggests that abnormally increased amygdala volume and unique or impaired amygdala function contributes to the unique social approach behavior in WS (Bellugi, Adolphs, Cassady, & Chiles, 1999; Martens et al., 2009; Reiss et al, 2004). Findings are mixed about approachability and amygdala characteristics with regard to how people with WS rate expressions compared to controls (i.e., Bellugi et al., 1999; Martens et al., 2009; Frigerio et al., 2006). A wealth of research suggests that atypical processing of social stimuli (faces) is associated with approachability ratings and disengagement problems and may be a product of right amygdala volume (Martens et al., 2009; Paul et al., 2009), amygdala-prefrontal connections (Meyer-Lindenberg et al., 2005; Muñoz et al., 2010), or spikes or reductions in amygdala activity for positive or negative social stimuli, respectively (Haas et al., 2009; Mimura et al., 2010; Thornton-Wells, Avery, & Blackford, 2011). Frigerio and colleagues (2006) found that people with WS do not always rate unfamiliar faces to be approachable, suggesting that individuals with WS can discriminate approachability but cannot *inhibit* their approach. They further suggest that beyond difficulties with inhibition or amygdala function, a strong attraction to social stimuli drives hypersociability.

Porter and colleagues (2007) attempted to directly compare the frontal and amygdala hypotheses for hypersociability, ultimately supporting the frontal hypothesis and attributing behavior to impaired RI. Because individuals with WS showed poor RI on a neuropsychological task but performed similarly to controls on a social approach task, they are thought to have a

dissociation between knowing the appropriate response and actually *engaging* in that response (i.e., in everyday life they approach despite knowing they should not), a suggestion supporting findings by Frigerio and colleagues (2006). In similar research, Little and colleagues (2013) found that RI, controlled by frontal regions, is the most important variable involved in predicting social approach behavior, which tends to be quite variable in individuals with WS. In this investigation, subtypes of social approach behavior were best differentiated by RI. This supports the hypothesis that indiscriminate social approach in WS is due to impaired frontal lobe functioning, specifically RI, rather than abnormal activity in other regions (Little et al., 2013).

An investigation by Capitao and colleagues (2011) compared the frontal and amygdala hypotheses for hypersociability using emotion recognition, approach, and RI tasks. Compared to unaffected controls matched for both chronological and mental age, those with WS showed impaired ability in labeling negative facial emotional expressions, a skill which relies on contributions from the amygdala, though the ability to rate approachability was spared. In line with the implications of research by Frigerio et al. (2006) and Porter et al. (2007), Capitao and colleagues propose that individuals with WS can distinguish components of social threat (e.g., angry faces) and rate emotional expressions and approachability, but despite this, they still find it difficult to *inhibit* approach behavior. The authors conclude that contributions from both the frontal lobe and the amygdala influence RI in WS.

Anxiety and inhibition. Anxiety is highly comorbid with WS, with prevalence estimates of anxiety disorders as high as 65% in adults (Cherniske et al., 2004). Across the lifespan, specific phobia and generalized anxiety are most common (35% and 16%, respectively; Dykens, 2003; Stinton, Elison, & Howlin, 2010). The most common anxiety diagnoses in children and adolescents with WS are specific phobia and generalized anxiety disorder (53.8% and 12%,

respectively; Leyfer et al., 2006), with prevalence of an anxiety disorder ranging from 51-83% over a 5-year period (Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010).

Attentional control theory may serve as a framework for considering anxiety as a contributor to RI difficulties in the WS brain. This theory proposes that anxiety reduces the amount of attentional control for goal-directed activity and sways the focus of attention to threatening stimuli, impairing proper functioning of the inhibition and shifting systems (Eysenck, Derakshan, Santos, & Calvo, 2007).Children with WS already show high rates of ADHD. That symptomatology, coupled with anxiety that may interact with attentional processes, likely compounds RI difficulties. Attentional control theory would suggest that the anxious affect and behavior so characteristic in WS, including attention to threatening stimuli, impair executive functions (notably inhibition) in this population, supporting the suggestion that executive functions and anxiety are related in WS (Woodruff-Borden et al., 2010). For example, combined anxiety and poor inhibition may result in the repeated question-asking about upcoming events often noted in those with WS. This perseverative question-asking might be indicative of the executive system's inability to inhibit anxiety about upcoming events and direct attention elsewhere.

Mixed nature of the research. While pervasive RI deficits have been found in individuals with WS and may play a role in the behavioral phenotype (Carney, Brown, & Henry, 2013; Mobbs et al., 2007), other research has indicated spared inhibitory function in that individuals with WS do not show performance problems on RI tasks. In the study by Capitao and colleagues (2011), individuals with WS did not show inhibitory deficits (had no more commission errors on a Go/No-Go task) compared to a mental-age matched control group or, after controlling for cognitive ability, a chronological-age matched group (Capitao et al., 2011).

The authors acknowledge that prefrontal involvement remains a possibility in disinhibited behavior but recommend against a completely modular approach to viewing the involvement of brain structures in observed behavior.

In support of these findings, Costanzo and colleagues (2013) measured RI amid a battery of executive tasks in individuals with WS, Down syndrome, and unaffected controls. Results indicated that those with WS performed similarly to controls and better than those with Down syndrome on measures of visual inhibition (Go/No-Go, Stroop task). Thus, in this study RI seems to be spared in WS (Costanzo et al., 2013). Because syndrome and intellectual functioning were factors in performance in these studies and the interplay between the frontal lobe and other regions is still being investigated, additional research is needed to clarify the nature of frontal lobe involvement in RI.

Despite some indications of spared functioning, a substantial body of research exists which suggests that RI deficits are a key component of the WS behavioral phenotype and that the frontal lobe is a key player. Additionally, some research (i.e., Capitao et al., 2011; Meyer-Lindenberg et al., 2005) suggests a broader approach to conceptualizing RI difficulties in WS. In typically-developing individuals, prefrontal cortex white matter connections with the amygdala help to inhibit the amygdala. The prefrontal cortex and amygdala are suggested to be improperly connected in individuals with WS, as the integrity of white matter is compromised in the pathways between the prefrontal cortex – specifically, the orbitofrontal cortex - and the amygdala (Avery et al., 2012; Meyer Lindenberg et al., 2005). These structural impairments may give rise to anxieties and high levels of amygdala activity (Avery et al., 2012) and to the abnormal social behavior seen in WS (Meyer-Lindenberg et al., 2005). Perhaps the combination

of structural and connectivity differences in the prefrontal cortex and amygdala intensifies difficulties with RI that are more directly related to a single region.

Overall, neuroanatomical and neurofunctional differences exist in WS, some of which are suggested to be related to difficulties with inhibitory control. It is important to keep in mind that atypical use of particular neural connections, such as a failure to properly inhibit responses, may contribute to structural brain atypicalities; alternatively, structural differences in WS may contribute to areas of difficulty in the behavioral phenotype, including inhibitory difficulties. Regardless of the origin of the difficulties, research indicates that inhibition is a challenge in WS and that the frontal lobe is likely involved, making it a prime target for intervention.

Summary and limitations of the existing research. Research involving three key characteristics in WS – attention problems, hypersociability, and high anxiety – indicates that RI may be a common underlying factor that ties together this cluster of difficulties. The literature is mixed with regard to which specific brain regions are most involved, but despite this ambiguity, RI problems are a likely component and deserve closer attention in the WS population. The existing research does not generally address relations between lab-based inhibition abilities and real-world behavior. For example, even if people with WS show unimpaired approachability ratings, their overt behavior may not match what they identify in the lab setting as appropriate. The mixed nature of research findings also complicates choosing the best targets for intervention in order to address difficulties experienced by individuals with WS.

However, based on the potential role of RI in these difficulties, it is important to continue research that helps elucidate the nature of RI in WS and ways in which RI could be affected by intervention targeting processes in various brain regions. Poor inhibitory ability has the potential to impact a wide range of behaviors in WS; for example, attention problems may affect a child's

ability to learn and understand academic material, and the characteristic hypersociability understandably heightens parental concerns that children could be taken advantage of due to an overfriendly personality (Jones et al., 2000). Therefore, understanding inhibition in WS will provide additional knowledge about functioning in other domains of life as well (Little et al., 2013).

Researchers in the field have called for explorations of inhibition in WS across the lifespan (i.e., Greer et al., 2013). Neuroimaging work in WS has expanded impressively of late, but there are virtually no interventions targeting RI in WS to date to the author's knowledge, let alone interventions aimed at the adolescent WS population. Childhood and adolescence are crucial periods for attending to academic work and learning boundary-setting and appropriateness of interaction with strangers, and those with WS are at even further increased vulnerability due to a psychosocial profile so strongly characterized by inattentiveness, overfriendliness, and lack of inhibition (see Jawaid, Riby, Owens, White, Tarar, & Schulz, 2012). As children move into adolescence, the development of social peer interactions takes a more important role as individuals learn to navigate the social world on their own, but the lack of proper inhibitory skills in social situations may leave individuals with WS at risk for bullying, rejection, isolation (Jawaid et al., 2012), or sexual abuse (Rosner, Hodapp, Fidler, Sagun, & Dykens, 2004). For these reasons, it is compelling to target RI in the critical period of emerging adolescence and adolescence; however, no research has yet attempted to improve this ability in youth with WS.

Cognitive Training

Cognitive training involves attempting to improve the basic processes involved in cognition, such as attention, memory, or executive functions. Cognitive training programs may

offer promise for individuals with WS, particularly if these programs are able to target processes in areas of the WS brain that are suspected to be compromised. A training program may use tasks that tap into RI in order to target the areas that are thought to be involved, such as the orbitofrontal cortex.

There is mixed research regarding the efficacy of cognitive training to improve or modify cognitive processes in other populations, with some indications that results are generally positive but largely nonspecific (Karch, Albers, Renner, Lichtenauer, & von Kries, 2013) and other research suggesting training is highly promising. In adults, some targets for intervention have been processing speed, attention, learning, language, memory, visual abilities, concentration, and attention training to decrease social anxiety (Amir et al., 2009; Cicerone et al., 2000, Klonoff et al., 2007). In children, cognitive training (e.g., direct instruction, reinforcement, verbal self-instruction, and strategy training) has been effective in reducing errors, increasing response latency, and increasing inhibition of impulsive actions in typically-developing populations (Arnold & Forehand, 1978; Bender, 1976; Coats, 1979; Cole & Hartley, 1978; Ghatala, Levin, Pressley, & Lodico, 1985) and in children with ADHD (Baer & Nietzel 1991), intellectual disabilities (Duckworth, Ragland, Sommerfeld, & Wyne, 1974), and learning disabilities (Duckworth et al., 1974; Finch & Spirito 1980; Graybill, Jamison, & Swerdlik, 1984). Thus, the possibility of modification of cognitive processes is encouraged by research.

An exciting recent trend has been the use of computerized intervention programs to modify cognitive processes. This method is attractive because of relatively easy dissemination and the ability to more efficiently reach families in their home environment (potentially increasing generalizability of lab-based results). Computerized cognitive training has shown positive results in improving the skills of adults and children in both typically developing and

clinical populations. Significant cognitive improvement after training has been documented in adults with traumatic brain injuries, attention problems, psychiatric disorders, cognitive impairment, and some areas of mental decline associated with aging. Computerized training has improved the skills of children with ADHD, HIV, Nonverbal Learning Disorder, and autism spectrum disorder. Areas of improvement in adults and children include memory and attention (Boivin et al., 2010; Filippopoulos, 2005; Gagnon & Belleville, 2012; Loosli, Buschkuehl, Perrig, & Jaeggi, 2012; Herrera, Chambon, Michel, Paban, & Alescio-Lautier, 2012; Mahncke et al., 2006; Walton, Kavanagh, Downey, Lomas, Camfield, & Stough, 2015), anxious symptoms (Amir et al., 2009), processing speed, response time (Simpson, Camfield, Pipingas, Macpherson, & Stough, 2012; Vance et al., 2007), executive function (Gagnon & Belleville, 2012), response control, impulsiveness, spatial skills, hyperactivity (Slate, Meyer, Burns, & Montgomery, 1998), and emotion recognition (Silver & Oakes, 2001). Findings conflict regarding the effectiveness of computerized training for executive tasks, as some unpublished work indicates that children with ADHD and a comorbid disorder were not found to improve in executive functioning after training (Lomas, 2002).

Though findings are mixed, computerized cognitive training effects have also been documented to transfer to improvement in non-trained skills. For example, some recent results support that gains in one cognitive domain result in improvement on other tasks within that domain but not in different (non-trained) cognitive domains (Walton et al., 2015). Thorell, Lindqvist, Nutley, Bohlin, & Klingberg (2009) found that improvements on a trained inhibition task did not generalize to non-trained tasks; on the other hand, improvements on a computerized working memory task transferred to improved reading processes in school-aged children (Loosli et al., 2012), and to non-trained tasks such as attention (Thorell et al., 2009). Furthermore,

despite nonsignificant improvement in attentional bias as measured by a computerized training program for individuals with health anxiety, overall significant reductions in anxiety-related symptoms and other symptom domains were noted, indicating that there may be aspects of training that are therapeutic for real-world functioning (Lee, Goetz, Turkel, & Siwiec, 2015). Given these mixed findings, the computerized method of delivery is arguably promising and further investigation is needed. Importantly, there seem to be key factors to improvement when computerized training is employed, such as adherence to the training program (Owen et al., 2010).

Computerized training in the study of RI in clinical populations is limited. However, a recent series of clinical trials studies has utilized a computerized RI training program (Lee, preliminary data, 2015) to test effects on improving this ability in people with disorders characterized by poor RI, such as trichotillomania and OCD (Chamberlain et al., 2006). Promising effects are noted in the subject populations, including those with OCD, tic disorders, and trichotillomania (Lee, 2015). Specifically, RI training: 1) results in significant improvement on severity scales and more treatment responders compared to waitlist in children with trichotillomania; 2) shows promise as an adjunct to habit reversal training in children with Tourette syndrome, and 3) shows preliminary data demonstrating a notable reduction in obsessive-compulsive symptoms in adults with OCD, with the trend of maintenance or continued improvement to follow-up in these populations (Lee, 2015). These favorable results warrant the examination of the effects of RI training for children with Williams syndrome in an attempt to improve response inhibition and related general functioning. This pilot study investigated the effectiveness of an experimental online computer training program targeting RI in active training and waitlist crossover groups of children with Williams syndrome, based on the experimental

measure of RI and a related parent-report clinical outcome measure of child everyday functioning.

Summary of rationale for computerized intervention. Given the evidence for RI difficulties that seem to underlie particular challenges in Williams syndrome, the lack of intervention research for RI in this population to date, and the promising effects of computerized intervention on RI in other populations, online training to improve RI is an innovative approach for individuals with Williams syndrome. This intervention presents several advantages compared to traditional in-person intervention, though it comes with some limitations. First, this intervention is advantageous in that it targets populations with RI difficulties, representing a gain for individuals with rare neurodevelopmental conditions (such as the WS population) who show RI deficits but are rarely the focus of treatment. Computerized intervention is easy to disseminate (which is especially beneficial for populations with rare disorders who are spread across the country) and is cost-effective, using free video conferencing services and requiring minimal staff, space, and travel. The game-like nature of the tasks appeals to children, and the contextual similarity to computer games may boost enjoyment and adherence to the training schedule.

Limitations include the difficulty of ensuring that participants receive the optimal level and quality of treatment; previous research has found that it is important to adjust RI intervention to promote optimal levels of exposure (Klingberg et al., 2005). While the schedule and dosage of training is intended to be standardized, it is difficult to enforce a training schedule remotely, and families often have busy schedules that make coordination of a regular training schedule impossible. Especially when developing the intervention protocol for a new population, it is challenging to judge the optimal amount of training (session length, session number) and intensity of training (difficulty of levels, number of levels per session, passing criteria). The

average cognitive ability and common comorbidities in WS present a challenge when adjusting training in order to improve functioning and yet not overwhelm participants. Finally, it is difficult to predict generalizability of findings from experimental measures to real-world performance. Nonetheless, findings provide helpful knowledge about an effective, cost-efficient therapeutic option to improve psychosocial functioning in WS.

Aims and Hypotheses

Aim 1. Using a randomized controlled trial with waitlist crossover, explore the effects of a lab-administered, computerized response inhibition training program on inhibitory control in children with Williams syndrome.

Aim 2. Examine changes in parent-reported inhibition-related clinical outcomes after computerized response inhibition training and describe response to treatment.

Hypothesis 1. Based on results using a similar RI training program in other populations, it is expected that inhibitory ability will improve after training, as indicated by reduction in commission errors on the Go/No-Go task. Parents will also report reduction in RI-related symptoms on the Conners 3-P(S).

Hypothesis 1a. There may be potential therapeutic mechanisms of the computerized RI training such that error reduction on the lab-based task is correlated with symptom reduction on the clinical outcome measure.

Hypothesis 2. At Time 2, there will be more error reduction and symptom reduction in the active training group than in the waitlist group.

Hypothesis 3. The waitlist crossover group will show more error reduction on the computerized measure of RI and parental report of clinical outcomes after crossover training.

Hypothesis 4. Based on preliminary results in other populations (Lee, 2015), participants will exhibit maintenance or further improvement in RI at follow- up.

Aim 3. Examine potential predictors of treatment response.

Descriptive approach. Due to the small sample size and the pilot nature of the study, Aim 3 was formulated in order to provide largely descriptive results that may warrant further investigation in future higher-powered studies. For example, given that ADHD and RI appear to be highly interrelated (i.e., Hart et al., 2014), the severity of ADHD symptomatology may be associated with error reduction on the Go/No-Go Task or reduction in symptoms on the clinical outcome measure. However, it is difficult to hypothesize whether more ADHD-related symptoms will pose challenges to the level of engagement or will instead provide more 'room for improvement' than for children with less severe symptoms. Higher anxiety may predict poorer outcome on the lab-based task, as the training program involves switching between relevant target stimuli, and anxiety has been found to impair switching ability (Derakshan, Smyth, & Eysenck, 2009). Given that higher IQ has been a significant predictor of lower commission errors on Go/No-Go tasks in prior research (i.e., Horn et al., 2001), cognitive ability may appear to be related in some way to changes in commission errors during or after treatment.

Method

Participants

Participants were 20 children and adolescents with WS, aged 10-17, and parents. Children were diagnosed with Williams syndrome (confirmed by genetic testing), the first and main language spoken in the home was English, and families possessed a computer with internet access as well as a second electronic device capable of video conferencing. Exclusion criteria were a major surgery in the past six months, a comorbid disability that may interfere with

interpretation of results (e.g., autism spectrum disorder), and four or more sessions of previous inhibition training. No minimum IQ was required, as it was hoped that a representative sample of children with WS would be used in this study, and there was no indication that those with higher IQ, even if the error rates were lower overall, would benefit from training more than those with lower IQ. Fliers announcing the study were mailed to families seen previously at the Child Neurodevelopment Research Lab. Fliers were also e-mailed to the Williams Syndrome Association for distribution to attendees of the Williams syndrome conference and to families within driving distance of Milwaukee, Chicago, Minneapolis, St. Louis, Louisville, Des Moines, and Omaha metro areas. A description of the study was posted on the Williams syndrome Research Registry. The study was submitted to the online registry of Clinical Trials. Interested families were instructed to contact the Child Neurodevelopment Research Lab to complete a screening form and arrange participation in the study. See Table 1 for a characterization of the sample and the Treatment and Waitlist groups.

Measures

Measures administered in the current study were appropriate for use with children aged 10-17 years. The baseline assessment measures are widely used in populations with and without developmental disabilities and demonstrate strong psychometric properties. Experimental measures, including the computerized lab-based measure of response inhibition and the RI training program, were adjusted to what was thought to be manageable for children with WS based on preliminary trials and feedback from a child with WS.

Kaufman Brief Intelligence Test, Second Edition (KBIT-II; Kaufman & Kaufman, 2004). The KBIT-II was administered within a battery of measures assessing the child's cognitive ability, working memory, executive function, and attention. The KBIT-II is a highly

regarded measure of verbal and nonverbal intelligence, assessing verbal ability (Vocabulary and Riddles subtests) and nonverbal ability (Matrices subtest: ability to perceive relationships). It can be administered in a brief amount of time and is designed for individuals aged 4-90 years. This measure has strong psychometric properties and produces reliable and valid results. Internal consistency reliability is high, with mean split-half reliability coefficients for the Verbal Scale at .91, for the Nonverbal scale slightly lower but acceptable, between .80-.90, and for the Composite IQ score at .93. Test-retest reliability data is similar, with mean reliability at .91 for the Verbal scale, .83 for the Nonverbal scale, and .90 for the Composite IQ. Concurrent validity with other respected measures of cognitive ability ranges from .76-.90 (Bain & Jaspers, 2010). The Composite IQ standard score was used as a measure of intellectual functioning.

Conners 3rd Edition – Parent Short form [Conners 3-P(S); Conners, 2008]. The Conners 3 was administered to a primary caregiver. It is a 43-item questionnaire that provides a full assessment of ADHD-related symptoms. Parents rate their child's behavior over the past month; each item is rated on a 0-3 scale. Relations to subscales related to RI were explored; subscales of interest include Inattention, Hyperactivity/Impulsivity, Executive Functioning, and Defiance/Aggression. The Inattention scale reflects difficulties with attention, concentration, distraction, and careless mistakes. Difficulty on this scale may reflect a poor ability to inhibit the responses to distractions. The Hyperactivity/Impulsivity scale reflects the child's level of restlessness and impulsivity, providing a reflection of poor response inhibition in the inability to suppress unwanted or impulsive actions. The Executive Functioning scale reflects difficulty with organization or initiation of work; the frontal lobe's executive role in planning or organizing may relate to inhibition of pre-potent responses. The Defiance/Aggression scale reflects the child's

ability to manage anger and control aggression. Difficulty inhibiting an angry response may manifest as the exhibition of higher levels of defiant or aggressive behavior.

Progress reports are available to assess change over time. The Conners 3 has good test-retest reliability, with significant correlations ($p<.001$) for all coefficients, which range from .71-.98. It also has good internal consistency reliability, with coefficients ranging from .77-97, and good inter-rater reliability, with coefficients ranging from .52-94. Furthermore, it has strong factorial, construct, and predictive validity. It shows good convergent and divergent validity with other measures. It can differentiate children with and without ADHD, as well as identify children with ADHD from others in the general population and discriminate between those with ADHD and those with other clinical diagnoses, such as Disruptive Behavior Disorders and Learning Disorders (Conners, 2008). T-scores from the subscales of interest were used in analysis to describe changes in overall score over time.

Go/No-Go Task (Lee, 2014). The 8-minute computerized Go/No-Go task (Menon, Adleman, White, Glover, & Reiss, 2001), adapted for this study (Dr. Hanjoo Lee, University of Wisconsin-Milwaukee), assesses response inhibition abilities. It consists of two 120-item blocks of letters (P, Q, R, T, W, X), presented one at a time for 1000ms each. The participant is told to press the space bar for each letter except the letter "X." Letters other than "X" represent go trials, while each "X" represents a no-go trial. 25% of trials are no-go trials, during which the participant must inhibit the response (refrain from pressing the space bar) when the distractor ("X," the no-go trial) appears. The index of RI is the number of commission errors (CE; responses to a non-target) and was the primary outcome variable for this study. Omission errors (OE; failure to respond to a target within 1 second of presentation) are a measure of attention to the task and were also reported. Accuracy was recorded to reflect the child's attention and

alertness at each time point. Reaction time, or the speed with which participants respond to go trials, was investigated to describe change over time and compare to findings from prior research (e.g., Menghini et al., 2010). Pre- and post-training data and follow-up data were analyzed.

The Go/No-Go task was selected because, unlike a motor stroop task or stop-signal task, the Go/No-Go task did not introduce concern about understanding directionality given the visuospatial difficulties characteristic in individuals with WS. Additionally, Go/No-Go tasks have been used in the past with individuals with WS and are suggested to be manageable despite differences in brain function. Mobbs and colleagues (2007) state that "despite the anomalies previously observed in the [anterior cingulate cortex], the current study suggests that attentional processes in WS may function at a level sufficient to perform our simple Go/No-Go task" (p. 260). To facilitate participant understanding, our Go/No-Go task was first introduced to one child with WS and adjusted based on observation and feedback from the volunteer. Adaptations to increase participant understanding, given the average lowered IQ of this population, included the addition of detailed instructions presented visually with accompanying audio, teaching of correct responding through the requirement of correct button-presses during the instruction phase, and a several sets of practice trials. Study participants were administered this standardized 'practice' during the in-person baseline assessment to ensure that instructions were understood. All participants completed up to 15 eight-trial practice blocks, divided into three sets of five, before each administration of the Go/No-Go task. The passing criterion for each set of five was eight correct responses in a row (one entire block with no errors). If the participant did not achieve this goal, the maximum number of practice blocks was still 15. In allowing for a supervised, standardized practice for all participants, we hoped to help participants become familiar with the task and reduce effects of misunderstanding or forgetting instructions, given

that intellectual functioning in this population falls in the mildly to moderately delayed range. All participants were supervised in completing the practice tasks until they demonstrated an understanding of the goal of the task, and behavioral observations (including mood and practice progression) were recorded for each child.

Response Inhibition Training Program (Lee, 2014). The computerized training program developed by and adapted for this study (Dr. Hanjoo Lee, University of Wisconsin-Milwaukee) is a game-like computer program tapping into motor inhibition and interference control while incorporating an engaging story line. Because the number of sessions and length of each training session was standardized, all participants receive the same 'dosage' of training. (Training was intended to be spread across ten bi-weekly sessions, and families were asked to complete within seven weeks maximum; nearly all participants completed the training within 7 weeks.) An introduction and 'practice level' is administered before the first level is completed, and a passing criterion must be met on the practice level in order to progress. Levels are designed to reduce impulsive responses and improve inhibitory control. Stimuli consist of smiling characters of various shape/color combinations (circle vs. square; red vs. blue). Participants complete three 5-minute "levels" per session and are provided with a target color and shape combination, which changes 3-4 times within each level. Participants respond to stimuli by pressing the mouse button for the target combination, inhibiting the response to non-target stimuli. Feedback is built into the program such that hits and correct inhibition are rewarded, while misses and commission errors are followed by negative feedback. Occasionally a stop signal is included within a trial, and the participant must inhibit the response to a target stimulus.

Participants progress to more difficult levels provided a passing criterion is met. As levels progress, training becomes harder with regard to the rate of no-go trials, latency of the stop

signal, switch in response set, interfering distracter density, and level of stimulus incompatibility. Thus, participants must increase their response time for better accuracy and to avoid a miss. The stop signal sound becomes more delayed after presentation of the stimulus, and waiting for a stop signal is ineffective. Training is complete when participants have finished all ten sessions.

This RI training allows practice of 1) suppression of the pre-potent association between stimulus and response; 2) inhibition on the ongoing response; 3) selective inhibition of the response to nontarget stimuli; 4) cognitive flexibility in response to a change in target; and 5) maintenance of a goal-directed response while disregarding distracters. Adaptations to this program were designed with consideration of the lowered IQ present in WS and the potential for frustration stemming from inability to meet passing criterion. The main adaptation was a lower passing criterion for the first several levels. The level difficulty remained stationary with respect to targets and distracters, but the passing criterion was raised only very slightly each time so that the child was more likely to pass the first few levels to gain motivation. When the child demonstrated an ability to move to a more challenging set of training tasks, passing criteria increased to normal levels used in the original version. The highest level achieved at the final session (out of 40 possible levels) was used as a measure of progress on the RI training game.

Dimensional Change Card Sort (DCCS; Zelazo, 2006). The DCCS is a widely-used measure of cognitive flexibility; it assesses executive function (specifically, set-shifting). In this study the online version was used (recently made available through the National Institutes of Health Toolbox (NIH-TB) online; for ages 3-85; administration time 4 minutes). Participants are presented with a series of bivalent pictures (40 trials) and match according to one dimension and then another (i.e., shape and color), followed by several trials requiring a "switch" from one dimension to another after varying numbers of trials, which taps into cognitive flexibility. The

measure demonstrates strong test-retest reliability (intraclass correlation coefficient = .92). Convergent validity (0.51) and discriminant construct validity (0.14) are reported to be appropriate (Weintraub, Dikmen, Heaton, et al., 2013). The age-adjusted standard score was used as a baseline estimate of executive functioning ability when characterizing the sample.

Spence Children's Anxiety Scale, Parent Version (SCAS-P; Spence, 1999). The SCAS is a commonly-used screening measure for child anxiety problems. It consists of 38 items and was normed on children ages 6-18. It can reliably distinguish between children with and without anxiety disorders, as well as between different types of anxiety disorders. Reliability of subscales is satisfactory to excellent, with very high internal consistency reliability for the total scale (.93). Test-retest reliability is good (.60-.63 depending on age range). The measure demonstrates convergent, divergent, and discriminant validity. T-scores are not available for the Parent Version; thus, the raw total score was used as a basic indication of overall anxiety.

MINI International Neuropsychiatric Interview (MINI) – Kid, Parent Version 6.0 (Sheehan, 2010). The MINI-Kid Parent 6.0 is a well-established, clinician-administered structured diagnostic interview covering a wide range of psychiatric disorders. It demonstrates good sensitivity and specificity, excellent interrater and test-retest reliability (.64-1.00), and good discriminant and concurrent validity (Sheehan et al., 2010). For this study, the total number of symptoms endorsed on the ADHD section provided a basic indication of ADHD severity by which to compare individuals on a single attention-related variable.

Procedure

Baseline. Participants completed a screening form and gave informed consent and assent. Trained study staff met in person with participants to administer the measure of cognitive functioning (KBIT-II) and a battery of experimental measures of inhibition and executive

function. Participants completed the supervised "practice" of the computerized RI tasks, including the task instructions and all practice trials of the Go/No-Go task, on a study computer. Parents completed a diagnostic interview in person or online through videoconferencing equipment and completed the online Conners 3-P(S) within a questionnaire battery assessing the child's mood, behavior, attention, and anxiety. Study staff assisted parents in computer setup for the study either in person or with supervision via videoconferencing equipment to ensure proper technology was in place. Participants then completed the baseline computerized RI pre-intervention tasks, including the Go/No-Go task, remotely via online software during a staff-supervised videoconferencing session. After this Baseline was completed, participants were assigned to Treatment (immediate training) or Waitlist (wait followed by crossover) training condition. Block randomization stratifying by overall intellectual functioning was employed to make conditions comparable. As can be seen in Table 1, most characteristics were equivalent or nearly equivalent between the groups. Participants were yoked across conditions such that a participant in the immediate treatment condition completed training as a yoked participant completed the wait.

Treatment or Waitlist Crossover. Participants in the Treatment condition began the ten sessions of online RI training, approximately twice per week over 5-7 weeks, as soon as possible after Baseline. The Waitlist group waited 5-7 weeks after Baseline and were offered crossover treatment at the completion of the wait. The first two training sessions were supervised by study staff via videoconferencing equipment to ensure proper understanding and delivery of treatment. All videoconferencing activity was securely recorded to ensure proper administration of online components. Parents supervised the child at all times but were instructed not to assist the child in responding to targets or inhibiting a response. After treatment or wait, participants repeated the

Go/No-Go task after being provided with the computerized instructions and standardized practice. Parents repeated portions of the diagnostic interview endorsed at baseline, as well as questionnaire measures of psychosocial functioning and attention, including the Conners 3-P(S). Waitlist participants completed computerized RI tasks and parent questionnaires an additional time (both after the wait and after crossover treatment). For all sessions supervised by study staff, instructions were explained additionally as needed, and comprehension was checked and rules repeated when necessary to ensure understanding. Breaks were allowed as needed. For cases in which participants stopped following program-generated email prompts to complete training sessions, study staff reached out to families via phone to troubleshoot barriers.

Follow-up. Three months after completion of treatment, each participant completed a Follow-up assessment in which they were again administered the Go/No-Go task. Parents again completed portions of the diagnostic interview and the questionnaire battery, including the Conners 3-P(S). Noted is that the 3-month Follow-up session occurred as the final phase of the study for all participants, after Waitlist participants completed crossover training, to assess the long-term effects of treatment. See Figure 1 for a study flow visual.

Analytic Strategy

Given the pilot nature of this study and the small sample size, examination of results includes both statistical analyses as well as descriptive results and effect sizes. SPSS 23.0 was used for statistical analyses. The presence or absence of significant statistical differences is noted for key variables in tables below and in the text when significant. A p-value of .05 was used to indicate significance, given the small sample size. Trends were noted at $p<0.1$. Effect sizes for t-tests are interpreted according to Cohen (1988) as follows: small effect for d=.2-.3, medium effect for d=about .5, and large effect for d=.8. Effect sizes for Spearman correlations are

interpreted as follows: $p<.1$=small; $p<.3$=medium; $p<.5$=large. Residual scores were used for correlations between Go/No-Go and Conners 3 variables. Refer to Figure 2 as a schematic reference.

Results

To examine whether improvement in RI follows intervention, hypotheses were approached in multiple ways. First, change was explored for all research questions using statistical analyses and the aid of figures and charts detailing the pattern of mean scores. Next, given the small sample and pilot nature of the study, post hoc investigation focused on changes that were seen at the group level in an attempt to explore potential predictors of treatment response. One participant dropped out before Follow-up and was a visual and statistical outlier for the omissions error (OE) variable at all time points. Analyses including OE are reported with and without this participant, and any influence on interpretation is noted in the text.

Hypothesis 1

Based on results using a similar RI training program in other populations, it is expected that inhibitory ability will improve after training, as measured by reduction in commission errors (CE) on the Go/No-Go task. Parents will also report reduction in RI-related symptoms on the Conners 3 –P(S).

CE at immediate pre-training was compared to CE at immediate post-training for the sample as a whole. See Figure 3. Paired t-tests indicated that there was no significant reduction in CE or OE from immediate Pre-treatment to Post-treatment. Effect sizes for CE and OE were negligible to small (see Table 2).

Conners 3-P(S) (hereafter, Conners 3). To gauge the translation of lab-based improvement to real-world experience, paired sample t-tests were used to examine whether there

was reduction from Pre- to Post-treatment on Conners 3 subscales of interest. Reduction on the Conners 3 after treatment was not significant for any subscale, and effect sizes were negligible to small (see Table 2).

Hypothesis 1a

There may be potential therapeutic mechanisms of the computerized response inhibition training such that error reduction on the lab-based task is correlated with symptom reduction on the clinical outcome measure.

Spearman rank-order correlations were used to examine whether reduction in errors on the Go/No-Go Task (for both CE and OE) was related to reduction on Conners 3 scales (Inattention, Hyperactivity/Impulsivity, Executive Functioning, and Defiance/Aggression) from Pre- to Post-treatment. Residual scores were used to help account for variance in the pre-treatment scores. While many correlations returned weak effect sizes, large effect sizes were noted between reduction in OE and reduction in symptoms on both the Executive Functioning and Defiance/Aggression scales (significant at $p<.05$). Analyses without the OE outlier reduced the effect size for interrelations between OE and these two Conners 3 scales, though medium effect sizes were still noted (see Table 3).

Hypothesis 2

At Time 2, there will be more error reduction and symptom reduction in the Treatment group than in the Waitlist group.

Although no treatment effect was found, differences in Treatment and Waitlist groups were still assessed for the Go/No-Go task. Again, CE was the primary outcome variable. Baseline CE was compared to CE at Time 2 (Post Tx/Post Wait) to explore group differences. See Figure 4.

One-way ANCOVAs were performed with group as the independent variable and errors at Time 2 as the dependent variable, controlling for baseline errors. Assumptions of normality and homescedasticity were fulfilled (except for the Defiance/Aggression scale on the Conners 3, for which there was not equal variance across groups). Hypothesis 2 was not supported; the Treatment group did not show significantly greater reduction than the Waitlist group in CE at Time 2. Results were similar for OE. Effect sizes were small. In the treatment group, CE remained steady (t[9]=.21, p=.84), and there was an average reduction of 2 errors in OE (not significant, but with a medium effect size; t[9]=1.20, p=.25). In the WL group, average CE reduction was 2 errors, which was not significant (t[9]=.51, p=.62), and OE remained steady (t[9]=.022, p=.98). There were no significant group differences in reduction on any subscales of the Conners 3, and effect sizes were negligible to small. See Table 4 for group comparisons.

Hypothesis 3

The Waitlist Crossover group will show more error reduction on the computerized measure of response inhibition and parental report of clinical outcomes after Crossover training.

Though no treatment effect was seen for the sample, CE at Post Wait (directly before training) was compared to CE at Post (Crossover) Treatment to assess whether any reduction after treatment occurred specifically in the Waitlist group (see Figure 5). Paired sample t-tests indicated that there was no significant difference in CE or OE from Post-wait to Crossover, and effect sizes were negligible. Group means indicated a slight non-significant decrease in CE and no change OE after the crossover training. Furthermore, compared to Baseline, there was no significant reduction in errors after Crossover treatment (see Table 2). On the Conners 3, paired t-tests indicated a non-significant increase in symptoms on the Inattention scale and a statistically significant increase in symptoms on the Executive Functioning scale after Crossover training.

However, this T-score increase would not be considered clinically significant based on interpretation guidelines, as it was a less than 5 point increase (Conners, 2008).

Hypothesis 4

Based on preliminary results in other populations (Lee, 2015), participants will exhibit maintenance or further improvement in response inhibition at follow- up.

CE from Post-treatment and Follow-up was compared across the sample (see Figure 6). Paired sample t-tests indicated that there was no significant reduction in CE from Post-treatment to Follow-up, and the effect size was small. There was a significant reduction in OE from Post-treatment to Follow-up, and a large effect size was noted (Table 2). Graphically, these continued reductions are visually evident for both variables, though not statistically significant for CE. The standard deviation for change in CE score (15.62) was much larger than the standard deviation for change in OE score (3.26), resulting in a small effect for CE reduction. (See Figure 7 for a visual representation of change in errors over time for the sample, excluding the outlier for OE.) Change in scores on the Conners 3 was also investigated from Post-treatment to Follow-up for the sample as a whole. Reduction from Post-treatment to Follow-up was not significant on any subscale (see Table 2). (Figure 8 displays the mean change in Conners 3 scores over time.)

Given the reduction in errors on the Go/No-Go task at Follow-up, the prior analysis was followed with investigation of performance in individual groups (see Table 5). Continued reduction in mean CE and OE over time was visually noted in both Treatment and Waitlist groups. See Figure 9 for a visual representation of change in errors over time between groups, excluding the outlier for OE. Both groups showed significantly reduced OE from Post-treatment to Follow-up (T3), with large effect sizes. Reduction in CE was not significant in either group, and small effect sizes were noted, given the high degree of variability of scores.

Post Hoc Analyses

Correlations between Go/No-Go and Conners 3 at Follow-up. Notable error reductions were found on the Go/No-Go task at Follow-Up. Therefore, Spearman rank-order correlations between residual change scores on the Go/No-Go task and Conners 3 were conducted from Baseline to Follow-up to explore potential therapeutic effects of treatment. While there were no significant relations between Go/No-Go (CE or OE) and subscales of the Conners 3 for the sample, medium effect sizes were noted for the correlation between reduction in both CE and OE and reduction in Executive Functioning difficulties on the Conners 3, as well as between reduction in CE and reduction on the Hyperactivity scale (Table 6).

Investigation of Potential Predictors. Post-hoc analyses explored potential predictors of the change that was seen in scores from Baseline to Follow-up in errors on the Go/No-Go task. Cognitive ability, age, gender, baseline cognitive flexibility/executive function (as measured by the DCCS), baseline number of ADHD symptoms (as reported on the MINI), and baseline number of anxiety symptoms (as reported on the SCAS) were examined for their role as potential predictors. Additionally, progress on the training game and change in response time from Baseline to Follow-up were used as independent variables.

Baseline number of ADHD symptoms predicted improvement over time (higher ADHD symptoms predicted less error reduction). There was a negative correlation between progress on the game and reduction in CE (i.e., attaining a higher game level predicted less reduction in CE). While the negative correlations with CE were not significant for these variables, medium effect sizes were noted. Finally, there was a significant negative correlation between reduction in response time and reduction in CE (i.e., slower response time predicted greater CE reduction).

No other variables significantly predicted change in CE or OE from Baseline to Follow-up, and effect sizes were negligible to small. See Table 7.

Discussion

This study aimed to explore the effects of a computerized training program on response inhibition (RI) in children with WS using both a lab-based task and a parental questionnaire as outcome measures. Overall, the RI training program was not found to be effective immediately following treatment based on performance on the lab-based task or parent ratings, and the treatment group did not outperform the waitlist group. Both groups showed error reduction at the 3-month follow-up assessment, suggesting that any treatment effect observed may be delayed. While parents did not report significant reduction in everyday RI-related symptoms, there were some associations between change on the lab-based measure and change in clinical outcomes. Baseline level of ADHD symptomatology appeared to predict the level of improvement follow-up.

Overall Treatment Effect (Hypothesis 1)

The hypothesis that RI training would result in improvement on the Go/No-Go task immediately following intervention was not supported. The treatment was not found to be effective at immediate post-treatment based on changes in the main index of RI (commission errors) on the computerized Go/No-Go task, or the Conners 3-P(S) subscales related to RI (Inattention, Hyperactivity/Impulsivity, Executive Functioning, and Defiance/Aggression). While preliminary results in related research suggest therapeutic effects of RI training on clinical outcome measures (Lee, 2015), parents of children in this WS sample reported minimal changes across time. In general, there are mixed results regarding transfer effects of computerized

cognitive training (e.g., Loosli et al., 2012; Thorell et al., 2009; Walton et al., 2015). Several factors may have influenced the absence of a treatment effect.

First, it is possible that the treatment is ineffective for children with Williams syndrome because of some aspect of the behavioral phenotype of Williams syndrome. Promising effects were seen in other child populations with disorders characterized by poor RI (tic disorders; trichotillomania), although none of these populations had the degree of cognitive impairment together with the pervasiveness of attention difficulties found in this sample (80% diagnosed with ADHD), and computerized cognitive training for ADHD has yielded inconsistent findings (Sonuge-Barke, Brandeis, Holtmann, & Cortese, 2014). Previous research has suggested that despite improvement on computerized cognitive tasks (including inhibition) for individuals with ADHD, there is not a clear transfer to untrained executive functioning tasks and behaviors (Dovis, Van der Oord, Wiers, & Prins, 2015). Adequate attentional focus is crucial to the task; a training effect is unlikely to occur if a child cannot first establish proper attention.

Additionally, the adaptations to the training program to accommodate the lowered IQ and attention difficulties in WS may have affected its potency. Based on feedback from a pilot participant, adaptations included an extended introduction with accompanying audio and pictures, practice before each administration, deviation from the established number and length of sessions (from eight 5-level sessions to ten 3-level sessions), with live supervision, instruction, and redirection. However, the extended practice may have contaminated naïve baseline scores, and adaptations that were intended to support optimal learning and promote attention and perseverance may have worked counterproductively (e.g., perhaps instruction and practice length exhausted an already-compromised attention span). The amount of practice and session length needed were yet uncharted and may have affected effort.

Finally, participants' scores were highly variable at each assessment, with large standard deviations for change scores. While variable test-retest scores are not uncommon for Go/No-Go tasks, it is possible that the measure of RI either does not produce reliable results for some children with WS, or that it is difficult for them to understand. They may need more exposure than was anticipated before the task is truly learned.

Relations between Conners and Go/No-Go Task (Hypothesis 1a).

Despite the lack of overall treatment effect, there were some interrelations between effects of the intervention on the lab-based task and effects of the intervention on parent-reported behavior immediately after treatment. Relations were significant between reduction in omission errors and reduction in executive functioning difficulties and defiant/aggressive behavior after treatment, with a large effect. Given that the target of the training program was inhibitory ability (commission errors) and not necessarily attention-related variables (omission errors), it is particularly difficult to hypothesize about the directionality of these associations. Overall, without a treatment effect, the changes on either measure cannot be assumed a result of treatment.

Group Differences: Treatment vs. Waitlist Performance at Time 2 (Hypothesis 2)

There was no significant difference in errors between the two groups after treatment vs. wait. A slight reduction in omission errors, not significant but with a medium effect size, was seen in the treatment group alone, perhaps reflecting an effect of treatment on attention. There were no group differences in clinical outcomes. Results were dissimilar from findings for children with trichotillomania, in which nearly half of the RI treatment group responded on a clinical outcome measure after treatment, whereas only about 10% of the waitlist participants responded. In previous research, participants with Tourette syndrome or OCD who completed RI

training showed more symptom reduction on a clinical outcome measure at the follow-up assessment (which took place before the crossover training), compared to placebo. These results prompt discussion about the contrasting outcome in the WS sample.

First, very few of the waitlist participants in the WS sample produced stable scores across baseline and post-wait assessments. Variability is to be expected; however, some participants improved or declined by double or triple their previous score. Improvement after a wait may be attributed to practice effects, but decline after the wait may indicate that a subset of children lose persistence or lose sustained attention to a task over time. Given the difficulties with sustained attention in the WS population (ADHD rates of 65%, primarily inattentive-type, and 80% ADHD rate in the current sample), the highly variable repeat scores were likely influenced by changes in attention. It is possible that this measure as it was presented to this WS sample was too difficult or was presented within a battery that was too lengthy and exhausted attention or promoted ambivalence, and pervasive attention difficulties may have affected the task's ability to reliably gauge RI for some participants.

Another possible explanation is that for a sample with mean cognitive ability in the impaired range, completing 5-7 weeks of the engaging, cartoonlike training program and then returning to the more standardized, less engaging Go/No-Go task resulted in decreased engagement in the task. However, a strength of this study is the trained supervision at every assessment, which provided the opportunity to eliminate as much child ambivalence as possible. There is likely another factor at play, whether individual (e.g., becoming more familiar with and less anxious about the task) or, more broadly, a certain characteristic/combination of characteristics (i.e., IQ and attention).

Effect of Crossover Training for the Waitlist Group (Hypothesis 3)

Given that no treatment effect for the treatment group was observed, it is not surprising that the hypothesis that the waitlist group would improve after crossover was not supported. Crossover training did not result in significant commission or omission error reduction in the waitlist group; mean performance was similar from across all three assessments. These clinical findings after crossover treatment differ from the effects seen in children with trichotillomania, where about 50 to 60% responded on clinical outcome measures after the crossover. In the present study repeat exposure did not appear to greatly influence mean errors, but again there was high variability within individual patterns on the Go/No-Go task, which emphasizes the variability of the sample in attention, understanding, or persistence. If steadier individual results had been produced after the wait, the crossover results would have been more telling about the effects of practice versus crossover training.

Maintenance of Improvement at Three Month Follow-up (Hypothesis 4)

The purpose of exploring effects after three months was to examine whether improvement, if present, was maintained for a longer term than has been studied using similar training programs. The WS sample exhibited mean reductions in commission and omission errors from immediately after treatment to the follow-up assessment (Table 2), as did the two groups separately (see Figure 9). This is likely indicative of more than a practice effect, since after treatment, the groups had shown little change over nearly the same amount of time. Because of high variability, the visually-evident reduction in commission errors was not significant; a more stable baseline may have resulted in a clearer effect.

It does appear that there is an association between the intervention and reduction in omission errors (supporting findings by Thorell and colleagues, 2009) over time, even though this variable was not the target of treatment. The large effect for this reduction in the treatment

group was replicated in the waitlist group. With the very high rate of ADHD in this sample, it is likely that the attentional component of the intervention affected performance on the attention-related variable. This is important in understanding why no effect was seen for the RI-specific variable, commission errors. Adequate attention to the task is a prerequisite for the ability of the task to measure response inhibition. Based on the significant improvement in attention over time, the sample as a whole likely did not exhibit adequate attention to the task at earlier points in the study. Finally, results suggest that effects of computerized intervention on attention-related variables may take time.

Maintenance or further improvement at follow-up on the lab-based task is interesting in light of the promising results seen on clinical outcome measures in other populations (i.e., Lee, 2015), and together the results build support for a delayed effect of treatment. Notably, in the current sample no reductions were evident on parent ratings of behavior even at the follow-up assessment. This is not surprising given that there was no effect for commission errors in the WS sample across time points, indicating that as a group the children did not show improved response inhibition. Finally, though the sample showed large reductions in omission errors, this improvement does not appear to signify that the sample will also show reductions in real-world ADHD-related symptoms.

In the present study's design, the follow-up took place three months after training/crossover training, rather than before crossover training as in the studies by Lee (2015). Follow-up scores would have been more informative if the immediate treatment response had occurred as expected. Since the follow-up took place after both groups had received training, it cannot be concluded whether the maintenance seen for the WS sample was due to long-term treatment effects or to repeated exposure. Still, the current model provides some evidence for a

long-term treatment effect rather than a practice effect. Finally, there is some indication of a relation between improvement on the lab-based task and reduction in symptoms of hyperactivity and executive functioning difficulties over a longer period of time.

Potential Predictors of Improvement at Follow-up

Attention. A lower baseline number of ADHD symptoms predicted greater reduction in commission errors from baseline to follow-up. This builds upon prior research indicating relations between higher ADHD symptomatology and more commission errors (Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014) and provides evidence that more severe ADHD could interfere with the effectiveness of the RI training program. Recalling that ADHD and RI are interrelated (Hart et al., 2014) is important in understanding the reasons that sample did not show a treatment response and that, even at the follow-up, the sample showed incredibly variable error rates. Most of the sample was diagnosed with ADHD, and the mean scores on the parental measure of attention difficulties fell in the at-risk or clinical range. Therefore, this sample of children likely shows a higher level of attention-related difficulties than most other samples who have undergone computerized training. In past research with children who have ADHD and a comorbid condition, executive functioning improvements were not seen after computerized training on executive tasks (Lomas, 2002). It is possible that for children with ADHD and WS, the syndrome plus attention difficulties interfere with the potential to benefit from this intervention.

Other predictors and moderators. Longer response time was associated with greater reduction in commission errors from baseline to follow-up. It is possible that, although many participants did not exercise enough inhibition to significantly reduce errors, they learned that they were more effective if they slowed down. Additionally, participants who did not progress as

far within the RI training program actually showed greater reduction in commissions at follow-up, which may suggest that children who struggle most with inhibition-related tasks have more "room for improvement" and experience the greatest amount of delayed benefits on a lab-based task. No other associations (e.g., IQ, executive ability) with the improvement noted at follow-up were found. It was originally suspected that IQ may be related to commission errors, based on past research using a Go/No-Go task (i.e., Horn et al., 2001). The present results are more in line with findings that cognitive ability was not the driving factor in differences in brain functioning when individuals with WS were engaged in a Go/No-Go task (Mobbs et al., 2007). This could be promising for the future of cognitive training in individuals with intellectual disability and/or very low executive abilities, as it suggests that decrements in IQ do not interfere with the benefits associated with treatment.

Innovation, Limitations, and Future Directions

Computerized RI intervention for WS. This study was the first of its kind in a sample of children and adolescents with Williams syndrome. RI difficulties have been broadly described in the Williams syndrome population, but no research to date has specifically targeted these difficulties. Further, the use of technology to extend computerized cognitive training programs to clinical populations is in its infancy. Developments in this area represent an effort to improve cost-efficiency and dissemination of interventions for populations with rare disorders. All assessments were observed live via videoconferencing equipment, allowing staff to promote understanding and motivation while noting attention, behavior, environment/distractions, and technical difficulties. Without this supervision component, it would be difficult to confidently view data as representative of the sample's abilities on the tasks as currently presented.

Score patterns were extremely variable, and it is still unclear whether children with Williams syndrome benefit from computerized training for RI or other cognitive processes. It will be important to determine whether this program can be further adapted to produce a stable baseline for children with WS so as to effectively evaluate the impact of treatment on trained tasks and the generalizability of improvement to daily life. Nonetheless, this study has provided insight for future research involving the delivery of computerized cognitive retraining programs to individuals with Williams syndrome.

Study design. A major limitation of this study is that because a treatment response was not seen at post-treatment as anticipated, the placement of the 3-month follow-up after waitlist crossover training does not allow for a comparison of treatment vs. non-treatment over time. A model that instead allows for collection of follow-up data for separate groups *before* the waitlist participants receive crossover training would provide more robust evidence for a long-term effect of training. The advantage to the current study's extended follow-up is the suggestion that, if present, treatment effects may be long-lasting (previous studies performed a 1-month follow-up).

The small sample is also a limitation. It is difficult to gather a substantial group of children and adolescents from a population with a rare developmental disability. Power is low, and results can become skewed by a few participants' scores or through attrition. High variability in a small sample increases difficulties in identifying potential outliers. It would be helpful to work with a small number of participants to determine how to establish a baseline and how to ensure that instructions are clear, simple, and easily understood. Single-subject design would be useful if this is the approach.

A typically-developing control group would have provided a comparison for error rates, practice effects, effects on attention, and perhaps response to treatment. Some research (Capitao

et al., 2011; Costanzo et al., 2013) indicates that individuals with WS do not show deficits in RI on lab-based RI tasks. A typically-developing control group would have helped support the present study's contrasting results, as the sample demonstrated high rates of errors which would be grounds for exclusion from studies in the other populations that have received this RI training. The lack of a placebo training condition could also be considered a limitation, but since this was a pilot study, the main focus was whether a treatment effect is detectable compared to waitlist.

Training in individuals with low IQ. There have been very few cognitive training programs targeting specific processes in populations with developmental disabilities or low intellectual functioning. While representative of the population, the large range in IQ certainly introduces difficulties interpreting the reliability of this measure. Improvement has been seen after cognitive training in individuals with mild cognitive impairments (Herrera et al, 2012), and Mobbs and colleagues (2007) suggested that individuals with WS can understand a simple Go/No-Go task. However, it is possible that our lab-based measure was too difficult for some participants to understand and complete outside of the lab setting. Further, given the cognitive deficits and potential to forget instructions, perhaps larger effects would be seen if participants completed the entire training program in a shorter amount of time.

Piloting a novel response inhibition intervention in new population with high rates of comorbid disorders also brings forth major limitations. There are no guidelines about optimal training levels or effectiveness of an RI intervention in WS, and study procedures were based on what has appeared promising for other populations. Participants did improve on the training game, but perhaps this was not captured by the Go/No-Go task because time intervals between training sessions and pre/post assessments were not optimally spaced.

Even with positive feedback from a pilot participant, it was difficult to predict how a larger sample of individuals with WS would respond, as the population ranges widely in terms of IQ, ADHD severity, and other comorbidities. A more detailed look at the contribution of potential moderators (i.e., attention difficulties) would be helpful. It is possible that with a larger sample, combinations of characteristics could be explored (e.g. IQ + ADHD status). Predictors that can be assessed at baseline (such as performance on an abbreviated practice) should be explored in order to promote efficiency in selecting participants likely to benefit.

Conclusion

Overall, the computerized response inhibition treatment as delivered does not appear to be effective for the majority of children and adolescents with Williams syndrome. Some preliminary evidence of a possible delayed effect was noted, in line with results from research using a similar intervention. The absence of an immediate treatment effect on lab-based or clinical outcome measures may reflect the influence of a combination of characteristics of this population (in particular, high rates of clinical-range attention problems, as well as variable IQ), the difficulty of the task, and trouble remembering instructions. Differences were not seen when comparing treatment and waitlist group performance or when examining changes after crossover treatment. However, error reduction was noted for the treatment group at follow-up, which was replicated in the waitlist group. This suggests that the effects of the training program may be most evident after time has passed, but changes to the study design will be necessary to further explore this possibility. No reductions in clinical outcomes were reported by parents at the sample level. Reduction in errors was related to reduction in some symptom domains on the clinical outcome measure immediately after treatment and at follow-up. For those with WS, receiving a treatment with an attentional component appeared to promote improved attention to

the trained lab-based task. Baseline ADHD symptomatology and slowing of response time appear to be associated with longer-term improvement on the lab-based response inhibition task. Overall, given the improvements seen at follow-up, it is possible that with a modification of current response inhibition training program and the establishment of appropriate attention to the task necessary to obtain a stable baseline, this intervention could result in improved response inhibition on lab-based tasks in some children with Williams syndrome. Further research will be needed to assess the translation of improvement to inhibition-related daily functioning.

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Table 1

Participants and Descriptives at Baseline

	Sample (N=20)	Tx Group (n=10)	WL Group (n=10)
Gender	12 Male, 8 Female	6 Male, 4 Female	6 Male, 4 Female
ADHD Status			
n Inattentive Type	13 (65%)	7	6
n Combined Type	3 (15%)	1	1
Descriptives	*M* (*SD*), Range	*M* (*SD*), Range	*M* (*SD*), Range
Age	14.42 (1.92), 10-17	13.86 (1.46,) 10-16	14.98 (2.23), 11-17
IQ (SS)	67.40 (16.13), 44-97	69.80 (13.40), 45-97	65.00 (18.89), 44-94
DCCS (SS)	76.06 (12.23), 58-96	78.47 (11.41), 63-94	73.66 (13.19), 58-96
Conners 3 Subscale	*M* (*SD*), Range; #at risk/clinical	*M* (*SD*), Range	*M* (*SD*), Range
Inattention	76.15 (10.63), 58-90; 18	73.90 (11.46), 58-89	78.40 (9.80), 60-90
Hyperactivity	60.85 (14.84), 44-90; 9	58.60 (13.10), 44-90	63.10 (16.80), 44-90
Executive Function	71.53 (11.07), 46-90; 16	68.11 (12.55), 46-87	74.60 (9.10), 66-90
Defiance/Aggress	53.42 (12.93), 44-84; 3	51.78 (13.05), 44-84	54.90 (13.35), 45-81

Note. SS=Standard Score; DCCS(SS) = Dimensional Change Card Sort age-adjusted Standard Score; MINI ADHD = Mini International Neuropsychiatric Interview ADHD section; SCAS = Spence Children's Anxiety Scale

Table 2

T-tests for Hypotheses 1, 3, 4

Hypothesis 1: Pre-Post Treatment for Sample					
Variable, *n*	**Pre-Treatment Mean (SD)**	**Post-Treatment Mean (SD)**	**t(df)**	***p***	**Effect Size**
CE, *20*	25.35 (15.53)	24.45 (15.71)	t(19)= 0.36	.72	0.081
OE, *20*	11.83 (14.12)	10.69 (15.01)	t(19)= 0.53	.60	0.12
(OE°, *19)*	10.16 (10.47)	8.42 (6.77)	t (18)=1.25	.23	0.29
Inatt, *19*	74.25 (11.22)	75.53 (10.99)	t(18)=-0.30	.77	0.069
Hyp/Impuls, *19*	60.35 (13.48)	60.95 (13.96)	t(18)=-0.059	.95	0.014
ExF, *18*	68.53 (10.70)	69.89 (10.90)	t(17)=-0.63	.53	0.15
Def/Agg, *18*	54.42 (13.04)	52.11 (10.32)	t(17)= 1.08	.30	0.25
Hypothesis 3: Waitlist Group, Pre-Post Treatment and Baseline to Post Tx					
Variable, *n*	**Post Wait Mean (SD)**	**Post Tx Mean (SD)**	**t(df)**	***p***	**Effect Size**
CE, *10*	22.33 (17.94)	20.67 (15.65)	t(9)= .29	.78	0.092
OE, *10*	13.60 (11.65)	13.40 (20.64)	t(9)= -.38	.71	0.12
(OE°, *9)*	8.00 (9.32)	7.22 (7.05)	t(8)= .41	.69	0.14
Inatt, *9*	76.33 (10.82)	80.78 (6.69)	t(8)= -1.74	.12	0.58
Hyp/Impuls, *9*	63.33 (15.62)	63.89 (14.74)	t(8)= -.19	.86	0.063
ExF, *9*	69.78 (9.52)	73.56 (7.92)	t(8)= -3.21	.012*	1.07*
Def/Agg, *9*	56.67 (14.04)	55.44 (13.41)	t(8)= .50	.63	0.17
Variable, *n*	**Baseline (SD)**	**Post Tx Mean (SD)**	**t(df)**	***p***	**Effect Size**
CE, *10*	23.11 (13.78)	20.67 (15.65)	t(9)= .85	.42	0.27
OE, 10	13.36 (15.44)	13.40 (20.64)	t(9)= -.13	.90	0.041
(OE°, *9)*	11.11 (15.54)	7.22 (7.05)	t(8)= .91	.39	0.30
Hypothesis 4: Post-Treatment to Follow-Up (Time 3) for Sample					
Variable, *n*	**Post-Treatment Mean (SD)**	**Follow-Up Mean (SD)**	**t(df)**	***p***	**Effect Size**
CE, *19*	24.45 (15.71)	19.74 (13.54)	t(18)= 1.25	.23	0.29
OE, *19*	8.42 (6.77)	5.43 (5.45)	t(18)= 3.58	.002**	0.82**
Inatt, *18*	75.53 (10.99)	75.42 (2.97)	t(17)= -.69	.50	0.12
Hyp/Impuls, *18*	60.95 (13.96)	62.21 (13.25)	t(17)= -1.60	.13	0.38
ExF, *17*	69.89 (10.90)	70.37 (12.53)	t(16)= -.39	.70	0.095
Def/Agg, *17*	52.11 (10.32)	54.00 (12.43)	t(16)= -2.22	.041*	0.54*

Note . CE=Commission Errors; OE=Omission Errors; Inatt=Inattention; Hyp/Impuls= Hyperactivity/Impulsivity; ExF=Executive Function; Def/Agg=Defiance/Aggression. Data was incomplete for 3 participants at various time points.

*p<. 05; **p <.01; °=excluding one outlier

Table 3

Spearman Correlations: Reduction in Errors and Symptoms, Pre-Post Treatment

		Conners 3 Subscale			
Go/No-Go Variable		**Inattention (N=19)**	**Hyperactivity (N=19)**	**Executive Function (N=18)**	**Defiance/ Aggression (N=18)**
CE	**rs**	- .26	- .25	- .36	.08
	p	.28	.30	.14	.76
	Effect	Small	Small	Medium	Negligible
OE	**rs**	.018	.013	.52*	.55*
	p	.94	.96	.027	.017
	Effect	Negligible	Negligible	Large	Large
(OE, *19°*)	**rs**	.12	-.060	.44	.47
	p	.63	.81	.074	.058
	Effect	Small	Negligible	Medium	Medium

Note: CE=Commission Errors; OE = Omission Errors. Residual change scores used.

+$p < .1$; *$p < .05$

°=excluding one outlier

Table 4

ANCOVA for Treatment vs. Waitlist Groups, Time 2

Go/No-Go	**F (1,18)**	***p***	**Effect Size**
CE	0.12	.73	.16
OE	0.36	.56	.28
(OE°)	F (1,17)=0.69	.42	.28
Conners 3	**F (1,17)**	***p***	**Effect Size**
Inatt	0.028	.87	.079
Hyp/Impuls	0.005	.95	.033
ExF	0.26	.62	.25
Def/Agg×	3.13	.096	×

Note . CE=Commission Errors; OE=Omission Errors; Inatt=Inattention; Hyp/Impuls=Hyperactivity/Impulsivity; ExF=Executive Function; Def/Agg=Defiance/Aggression.

× *Data not normal; error variance was not distributed equally across groups*

°=excluding one outlier

Table 5: Post Hoc Analyses

Additional t-tests: Treatment and Waitlist Groups from Post-Treatment to Follow-up

Variable, *n*	**Post-Treatment Mean (SD)**	**Follow-Up Mean (SD)**	**t(df)**	***p***	**Effect Size**
Waitlist					
CE, *9*	20.67 (15.65)	18.44 (13.16)	0.50 (8)	.63	0.17
OE, *9*	7.22 (7.05)	4.78 (5.78)	2.59 (8)	.032*	0.86
Treatment					
CE, *10*	26.50 (16.05)	20.90 (14.46)	1.19 (9)	.27	0.38
OE, *10*	9.50 (6.69)	6.40 (5.32)	2.48 (9)	.035*	0.78

Note : CE=Commission Errors; OE=Omission Errors

Table 6

Spearman Correlations: Reduction in Errors and Symptoms at Follow-Up

Go/No-Go Variable		Conners 3 Subscale			
		Inattention (N=18)	**Hyperactivity (N=18)**	**Executive Function (N=17)**	**Defiance/ Aggression (N=17)**
CE (N=19)	**rs**	.10	.30	.37	.17
	p	.69	.22	.14	.50
	Effect	Small	Medium	Medium	Small
OE (N=19)	**rs**	.14	.27	.44	.16
	p	.57	.26	.069	.52
	Effect	Small	Small	Medium	Small

Note: CE=Commission Errors; OE = Omission Errors
Residual change scores used.

Table 7

Spearman Correlations: Predictors of Improvement from Baseline to Follow-Up

Go/No-Go Variable		IQ	Age	DCCS	ADHD	SCAS	RT	Game Level
CE (N=19)	rs	.12	.22	.16	- .31	- .092	- .64	- .32
	p	.61	.35	.54	.18	.70	.004**	.17
	Effect	Small	Small	Small	Medium	Negligible	Large	Medium
OE (N=19)	rs	.20	.21	.083	- .088	.23	- .12	- .014
	p	.42	.40	.74	.72	.34	.63	.96
	Effect	Small	Small	Negligible	Negligible	Small	Small	Negligible

Note: CE=Commission Errors; OE = Omission Errors

+p <.1; *p< .05; **p< .01

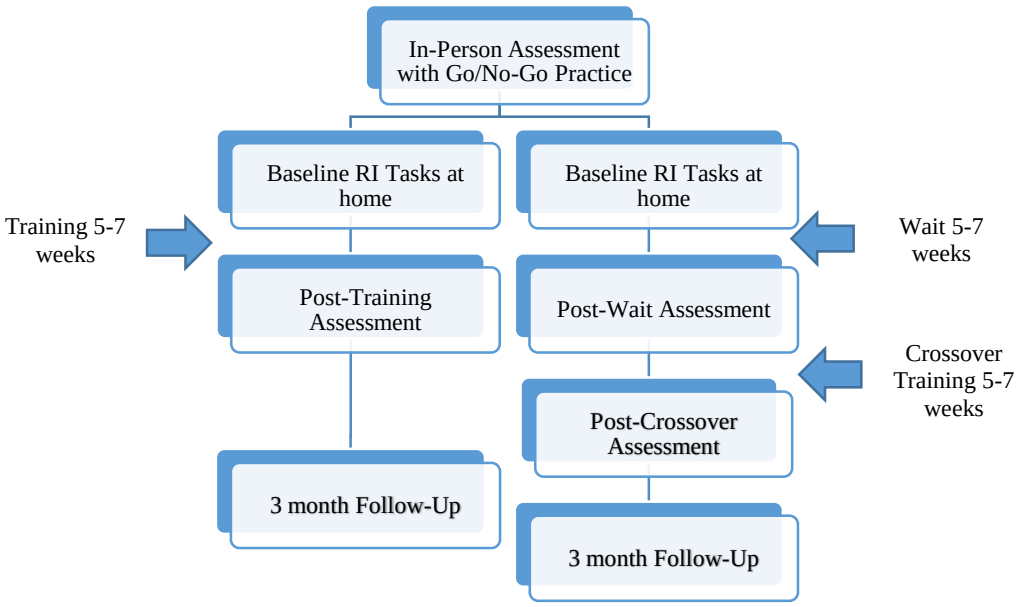

Figure 1. Study Flow Chart
Note: Go/No-Go Task and Conners 3-P(S) were administered at each assessment.

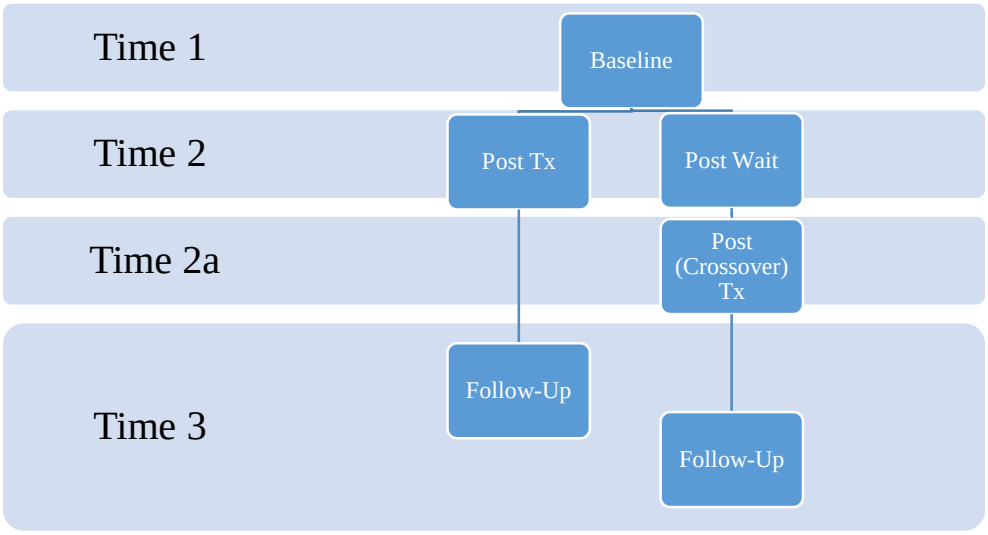

Figure 2. Study Schematic and Time Points at which Go/No-Go and Conners 3-P(S) Administered.

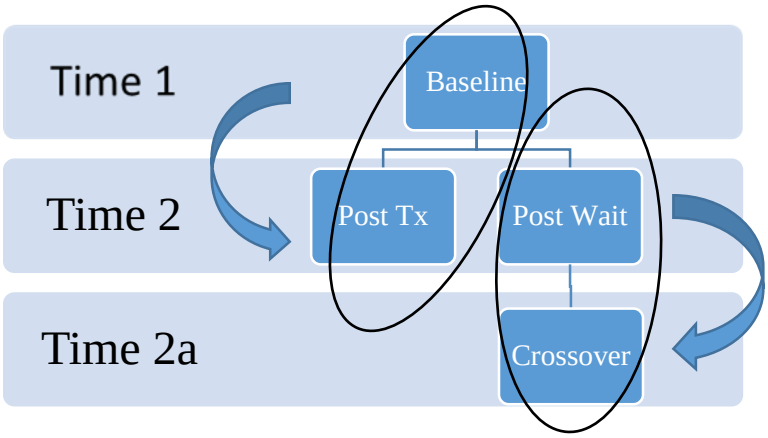

Figure3. Hypothesis 1 Strategy: Immediate Pre- to Post-training T-tests for Sample.

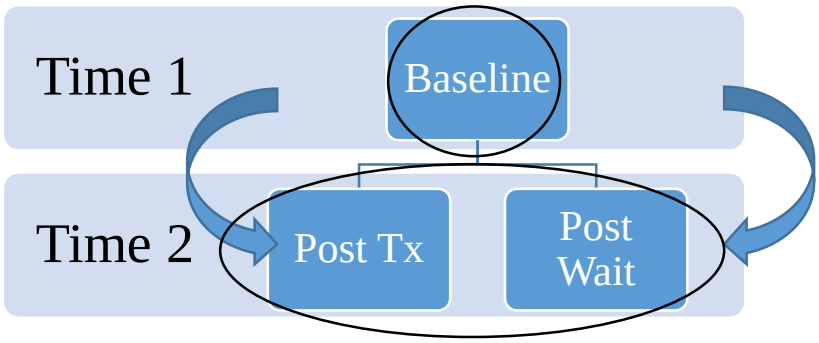

Figure 4. Hypothesis 2 Strategy: ANCOVA Controlling for Baseline Performance.

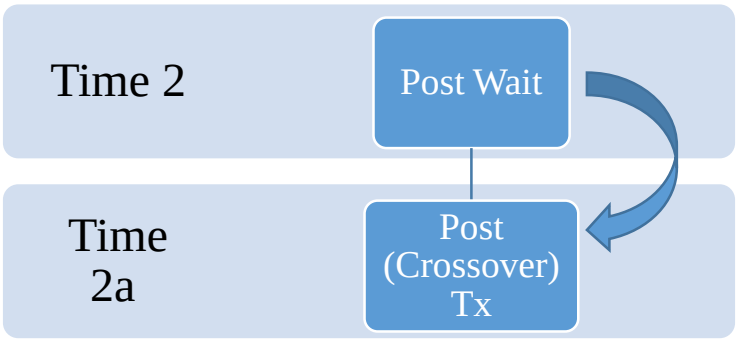

Figure 5. Hypothesis 3 Strategy: Examination of Change after Crossover.

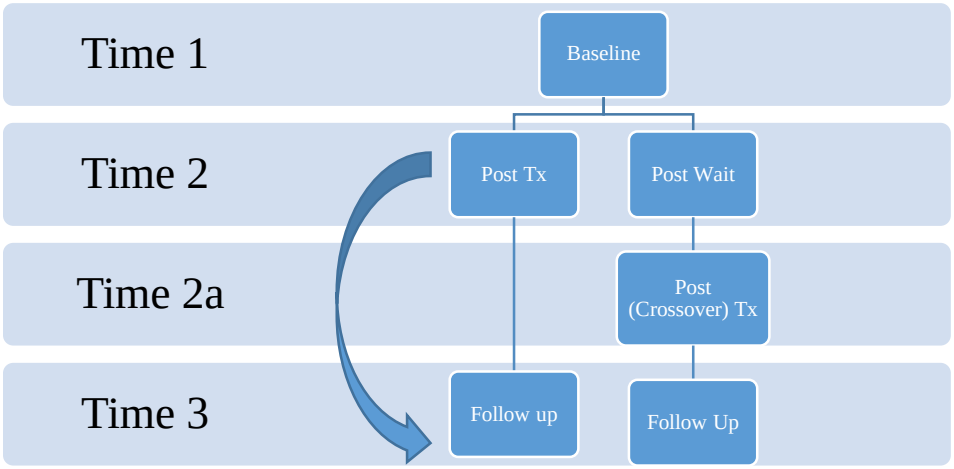

Figure 6. Hypothesis 4 Strategy: Maintenance at Follow-up.

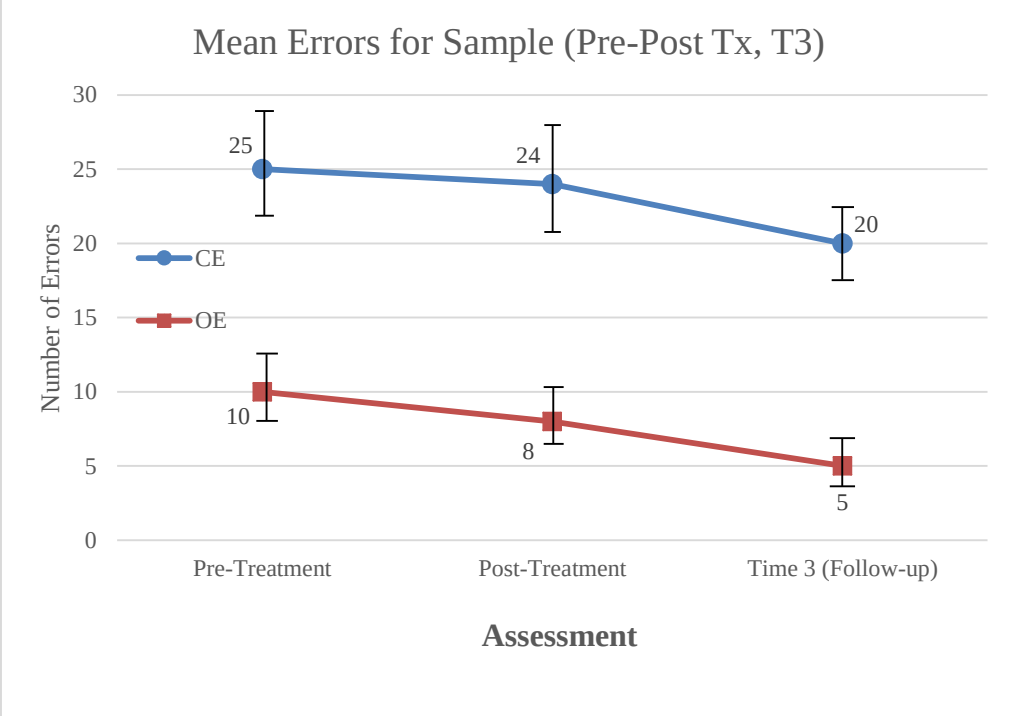

Figure 7. Mean Errors for the Sample from Pre-treatment to Follow-up.
Note: Excludes the outlier for OE. Standard Error bars shown at each data point.
CE=Commission Errors; OE=Omission Errors

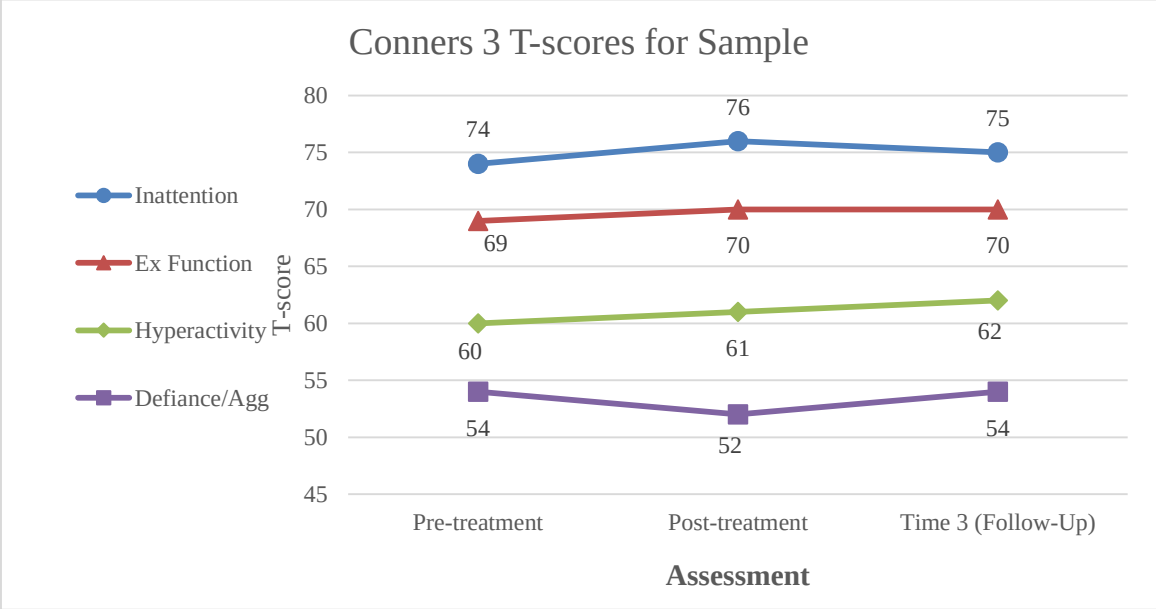

Figure 8. Mean Conners 3 Subscale t-scores for the Sample from Pre-treatment to Follow-up.
Note: Ex Function = Executive Functioning; Defiance/Agg = Defiance/Aggression

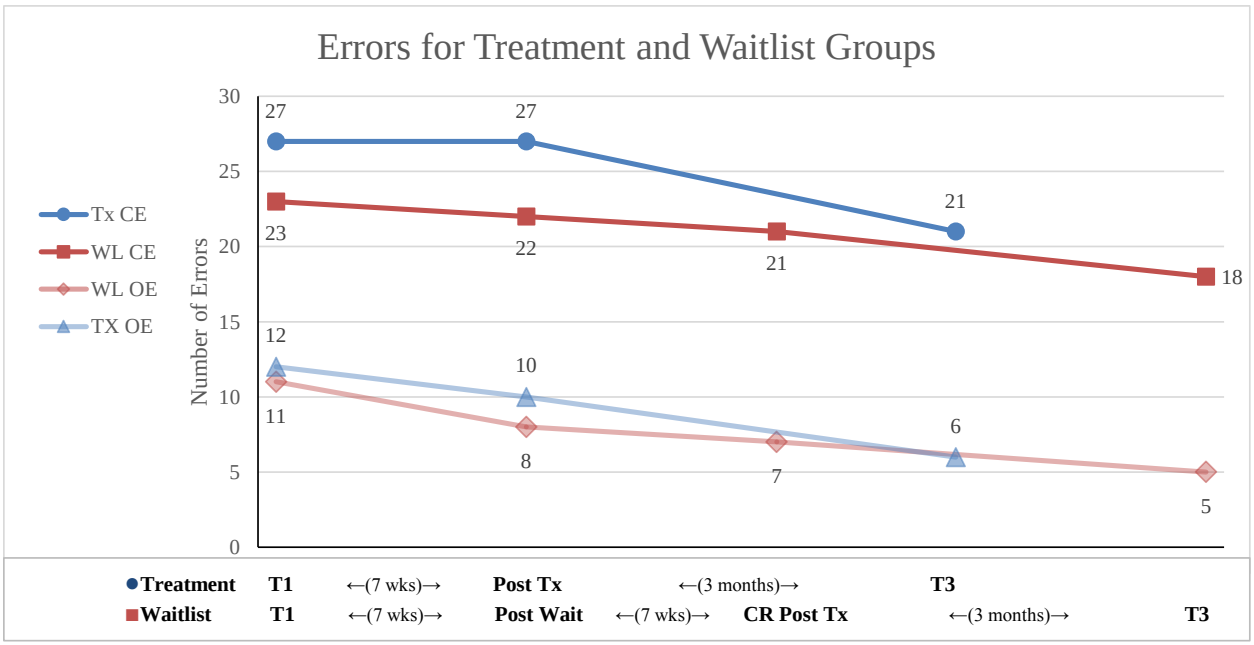

Figure 9. Mean Errors from Baseline to Follow-up for Groups.
Note: Excludes the outlier for OE. Tx=Treatment; WL=Waitlist; CE=Commission Errors; OE=Omission Errors
T1=Baseline; Post Tx=Post-treatment; CR PostTx=Crossover Post-Treatment; T3=Time 3 (Follow-Up)

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Curriculum Vitae

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Education

Expected Ph.D. University of Wisconsin - Milwaukee, *Milwaukee, WI*
Program: Clinical Psychology
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Dissertation defended: 6/23/2016
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Major: Psychology; Minor: Individualized Program - Autism Spectrum Disorders
Degree Awarded: May 2011
GPA: 3.98; Psychology GPA: 4.0
Honors Thesis title: *Cognitive Flexibility in Preschool Children: A Longitudinal Perspective*
Honors Thesis Mentors: Kimberly Andrews Espy, Ph.D.; Jennifer Nelson, Ph.D.

Honors and Awards

University of Wisconsin-Milwaukee

- UWM Graduate School Distinguished Dissertation Fellowship, (2015-16)
- UWM Summer Research Fellowship (2015)
- Williams Syndrome Association Professional Conference Student Travel Award (2014)
- Sigma Xi Grant-in-Aid of Research Award (2013-14)
- UWM Chancellor's Fellowship (2011-13)

University of Nebraska-Lincoln

- College of Arts and Sciences Dean's Scholars Society (2010-11)
- Bachelor of Arts Graduation with Highest Distinction (2011)
- National Residence Hall Honorary (2010-11)
- National Merit Scholarship (2007-11)
- Honors Program (2007-11)
- Dean's List (2007-11)

Memberships and Leadership

- Society of Pediatric Psychology APA Division 54
- Association for Psychological Science
- Sigma Xi, Chapter 682 University of Wisconsin-Milwaukee (2011-16)
- Association of Graduate Students in Psychology: Member (2011-16)
- Association of Neuropsychology Students in Training, UWM Chapter (2012-14)
- Association of Graduate Students in Psychology: Vice President (2012-13)
- Association of Graduate Students in Psychology: Secretary (2011-12)

Professional Activity

- Ad hoc journal reviewer
    - *Research in Developmental Disabilities* (2014)
    - *Journal of Childhood & Developmental Disorders* (2016)

Clinical Experience

Graduate Assistant: (2011-16)
Child Neuropsychology Clinic, University of Wisconsin - Milwaukee
Supervisor: Bonita Klein-Tasman, PhD

Pediatric Psychology Intern (2014-16)
Children's Hospital of Wisconsin, Department of Psychiatry and Behavioral Medicine

- Asthma Plus Multidisciplinary Clinic (2015-16)
  Supervisors: Jacquelyn Smith, PhD; Patricia Marik, PsyD
- General Child Clinical Outpatient Rotation (2014-15)
  Supervisor: Matthew Jandrisevits, PhD
- Pediatric Kidney Transplant Multidisciplinary Clinic; Pediatric Outpatient (2014-15)
  Supervisor: KristiLynn Cedars, PhD
- Consultation & Liaison Rotation (March 2015, March 2016)
  Supervisor: Patricia Marik, PsyD
- Student practicum weekly didactics - Children's Hospital of Wisconsin. (2014-16)

Student Therapist (2012-16)
University of Wisconsin-Milwaukee

- Behavioral Activation Clinic for Adults with Depression (2013-16)
  Supervisor: Christopher Martell, PhD

- Tic Disorders Specialty Clinic (2012-14)
  Supervisors: Douglas Woods, PhD; Bonita Klein-Tasman, PhD; Flint Espil, MA

Practicum Student
Psychology Clinic, University of Wisconsin-Milwaukee
- Empirically Supported Interventions (2012-13)
  Supervisors: Jonathan Kanter, Ph.D.; Shawn Cahill, Ph.D.
- Clinical Psychology Assessment (2012-13)
  Supervisors: Bonita Klein-Tasman, PhD; Han Joo Lee, PhD

Clinical Psychology Practicum Student (2012)
Children's Hospital of Wisconsin, Department of Psychiatry and Behavioral Medicine
Constipation Clinic
Supervisors: Hobart Davies, PhD; Alan Silverman; PhD

Clinical Psychology Practicum Student (2011-12)
Learning Disabilities Clinic, University of Wisconsin - Milwaukee
Supervisors: Bonita Klein-Tasman, PhD, David Osmon, PhD

Supportive Home Care Provider and Paraprofessional (2011)
Developmental Services of Northwest Kansas – Hays, Kansas

One-on-One Paraeducator (2010)
Hays Area Children's Center – Hays, Kansas
Supervisor: Doug Greer, Director

Family-Employed ABA Trainee/Therapist (2009)
Lincoln, Nebraska
Supervisor: Ginger Buhl-Jorgensen, Senior ABA Therapist

Research Experience

Child Neurodevelopment Research Lab, University of Wisconsin-Milwaukee
Research Advisor: Bonita Klein-Tasman, PhD
Studies include:
Response Inhibition Training in Children with Williams Syndrome (2014-16)
Development of Replays for Children with Williams Syndrome (2014-16)
Early Indicators of Emotional, Learning, and Cognitive Difficulties in Neurofibromatosis-1 (2011-15)
Emotion Regulation and Dysregulation in Children and Adolescents with Williams Syndrome (2011-15)
Patience and Planning in Typically Developing Children (2011-2012)

University of Wisconsin-Milwaukee, Psychology Clinic
Voice over Internet Protocol - Delivered Behavior Therapy (CBIT) for Pediatric Tic Disorders
Project Director: Douglas Woods, PhD
Role: Research Therapist (2013)

Developmental Cognitive Neuroscience Lab, University of Nebraska-Lincoln

Project Director: Kimberly Andrews-Espy; PhD; Supervisor: Doran Hadan
Role: Undergraduate Research Assistant (2009-11)

Publications

Peer-Reviewed Publications

Defenderfer, E. K., Davies, W. H., Raicu, A., **Brei, N.,** & Klein-Tasman, B. P. (In press). History of toilet fears in early childhood as a predictor of childhood anxiety disorders. *Children's Health Care.*

Brei, N., Schwarz, N., & Klein-Tasman, B.P. (2015). Predictors of parenting stress in children referred for an autism spectrum disorder diagnostic evaluation. *Journal of Developmental and Physical Disabilities*, doi: 10.1007/s10882-015-9439-z

Ricketts, E., Goetz, A., Capriotti, M., Bauer, C.; **Brei, N**., … Woods, D. (2015). A randomized waitlist-controlled pilot trial of voice over internet protocol-delivered behavior therapy for youth with chronic tic disorders. *Journal of Telemedicine and Telecare.* doi: 10.1177/1357633X15593192

Klein-Tasman, B. P., Lira, E., Li-Barber, K. T., Gallo, F., & **Brei, N.** (2015). Parent and teacher perspectives about problem behavior in children with Williams syndrome. *American Journal on Intellectual and Developmental Disabilities, 120* (1), 72-86. doi: 10.1352/1944-7558-120.1.72

Casnar, C. L., Janke, K., van der Fluit, F., **Brei, N**., & Klein-Tasman, B. P. (2014). Relations between fine motor skill and parental reports of attention in young children with neurofibromatosis-1. *Journal of Experimental and Clinical Psychology, 6*(9). doi: 10.1080/13803395.2014.957166

Brei, N., Klein-Tasman, B. P., Schwarz, N., & Casnar, C. L. (2014). Language in young children with neurofibromatosis-1: Relations to functional communication, attention, and social functioning. *Research in Developmental Disabilities, 35* (10), 2495-2504. doi: 10.1016/j.ridd.2014.06.016

Klein-Tasman, B. P., Colon, A., **Brei N**., van der Fluit, F., Casnar C., … Walker, J. (2013). Adaptive behavior in young children with Neurofibromatosis type 1. *International Journal of Pediatrics*, Vol. 2013. doi:10.1155/2013/690432

Book Chapters/Reviews

Klein-Tasman, B. P., & Brei, N.G. (In press). Williams syndrome. In B. Caplan, J. DeLuca, & J.S. Kreutzer (Eds.), *Encyclopedia of Clinical Neuropsychology.* New York, NY: Springer

Paper Presentations

Klein-Tasman, B. P., Lira, E., Li-Barber, K. T., Gallo, F. J., & **Brei, N.** (2014, July). *Parent and teacher perspectives about problem behavior in children with Williams syndrome.* Paper presented by B. P. Klein-Tasman at the Professional Williams Syndrome Conference, Anaheim, CA.

Brei, N., Klein-Tasman, B. P., Schwarz, N., & Casnar, C. L. (2014, April). *Language in young children with neurofibromatosis-1: Relations to functional communication, attention, and social functioning.* Paper presented by **N. Brei** at the 16th Annual Graduate Student Research Symposium: Milwaukee, WI.

Poster Presentations

Brei, N., Lee, H., Basche, K., & Klein-Tasman, B.P. (2016, May). Web-based response inhibition training in children with Williams syndrome. Poster presented at the 28th Annual Association for Psychological Science Convention, Chicago, IL.

Defenderfer, E. K., Davies, W. H., Raicu, A., **Brei, N**., & Klein-Tasman, B. (2016, April). *History of toilet fears in early childhood as a predictor of childhood anxiety disorders.* Poster presented at the Society of Pediatric Psychology 2016 Annual Conference, Atlanta, GA.

Raicu, A., Lesch, L., **Brei, N**., Lee, H., Schwarz, N., & Klein-Tasman, B.P. (2016, April). *Acceptability of web-based response inhibition training in children with Williams syndrome.* Poster presented at the 30th Annual National Conference for Undergraduate Research, University of North Carolina, Asheville, NC, and at the UW-Milwaukee Undergraduate Research Symposium, Milwaukee, WI.

Hayward, A. M., Fiscus, E. A. H., **Brei, N**., Lee., H., & Klein-Tasman, B.P. (2016, April). *Online response inhibition training for children with Williams syndrome: Patterns of practice performance*. Poster presented at the National Conference of Undergraduate Research, University of North Carolina, Asheville, NC, and at the UW-Milwaukee Undergraduate Research Symposium, Milwaukee, WI.

Wilson, A., **Brei, N. G**., Rivera, K., Basche, K., Lee, H., & Klein-Tasman, B. P. (2015, April). *Pilot Study of Response Inhibition in Adolescents with Williams Syndrome using a Go/No-Go Task*. Poster presented at the 14th Annual UW-System Symposium for Undergraduate Research and Creative Activity, Milwaukee, WI.

Raicu, A.M., **Brei, N. G**., Klein-Tasman, B. P., & Levine, K.L. (2015, April). *Improving Psychosocial Functioning in Children with Williams Syndrome: The Manual Development Process*. Poster presented at the UW-System Symposium for Undergraduate Research and Creative Activity, Milwaukee, WI.

Rivera, K. M., Helms, M. I., Casnar, C. L., **Brei, N. G**., Schwarz, G. N., & Klein-Tasman, B.P. (2014, April). *Examination of BASC-II Content Scales in Young Children with Neurofibromatosis-1*. Poster presented at the UWM 6th annual Undergraduate Research Symposium: Milwaukee, WI.

Anglin, T., Basche, K., Casnar, C. L., **Brei, N. G**., Schwarz, G. N., & Klein-Tasman, B. P. (2014, April). *Social Skills of Young Children with NF1: Relations to Attention Problems and Cognitive Functioning.* Poster presented at the UWM Undergraduate Research Symposium, Milwaukee, WI.

Brei, N.G., Casnar, C., van der Fluit, F., Mambwe, C., Waldron, S., Hunter, S.J., Tonsgard, J., & Klein-Tasman, B.P. (2014, February). *Relations of language functioning to attention, functional communication, and social skills in young children with NF1.* Poster presented at the 42nd Annual Meeting of the International Neuropsychological Society, Seattle, Washington.

Casnar, C., Janke, K., van der Fluit, F., Haberman, D., **Brei, N**., Solomon, M., Hunter, S., Tonsgard, J., & Klein-Tasman, B.P. (2013, October). *Relations between fine motor skills and parental report of*

attention in young children with neurofibromatosis - type 1. Poster presented at the 33rd Annual Conference of the National Academy of Neuropsychology, San Diego, California.

Janke, K. M., Casnar, C., van der Fluit, F., Haberman, D.A., **Brei, N. G**., Hunter, S. J., & Klein-Tasman, B. P. (2013, February). *Concurrent relations between early neuropsychological and academic skills in young children with NF1 and typically developing peers.* Poster presented at the 41st Annual Meeting of the International Neuropsychological Society, Waikoloa, Hawaii.

Colon, A., Walker, J., **Brei, N**., Casnar, C., Van der Fluit, F., & Klein-Tasman, B. P. (2013, April). *Adaptive Behavior in Children with NF1: Considering the Role of Intellectual Functioning.* Poster presented at the 27th National Conference on Undergraduate Research: LaCrosse, WI.

Schultz., C., Casnar, C. L., **Brei, N. G**., & Klein-Tasman, B. P. (2013, April). *Attention in Young Children with NF-1: Comparison to Unaffected Children.* Poster presented at UWM's 5th annual Undergraduate Research Symposium: Milwaukee, WI.

Mambwe, C., Waldron, S. L., **Brei, N. G**., & Klein-Tasman, B. P. (2013, April). *Early Language Development in Children with NF1.* Poster presented at 27th National Conference on Undergraduate Research: LaCrosse, WI.

Bennett, D, Janke, K. M., Casnar, C. L., **Brei, N. G.**, & Klein-Tasman, B. P. (2013, April). *"Hot" and "Cool" executive functioning in children with neurofibromatosis type 1.* Poster presented at the 27th National Conference for Undergraduate Research: La Crosse, WI.

Heimann, N. G., Nelson, J., Sheffield, T., & Espy, K. A. (2011, April). *Cognitive flexibility in preschool children.* Poster presented at University of Nebraska-Lincoln Undergraduate Research Conference, Lincoln, NE.

Teaching and Assistantship Experience

University of Wisconsin-Milwaukee:

- Teaching Assistant: Child Psychology (Fall 2011, Fall 2012)
- Teaching Assistant: Online Child Psychology (Spring 2012, Spring 2013, Fall 2013, Spring 2014)
- Research Assistantship: Child Neurodevelopment Research Lab (Fall 2014, Spring 2015)

Volunteer Activities

- Big Brothers Big Sisters of Metro Milwaukee (2012-16): Community-based mentor
- Saints Peter and Paul Meal Delivery Program - Milwaukee, WI (2014-16)
- Heartland Big Brothers Big Sisters - Lincoln, NE (2008-11): School-based mentor
- Prayer & Action Summer Mission Program – Rural Kansas (June-Aug. 2009): Staff

References upon request