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Validating and Applying the CSBS-ITC in Neurogenetic Syndromes

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Abstract

Although social communication skills are commonly delayed in children with neurogenetic syndromes, skill profiles in very young children are largely under-characterized, in part due to the lack of validated assessment measures appropriate for these populations. We addressed this gap by validating and applying a popular early social communication screening measure, the Communication and Symbolic Behavior Scales Developmental Profile – Infant-Toddler Checklist (CSBS-ITC) in three previously understudied neurogenetic groups: Angelman, Prader-Willi, and Williams syndromes. Our results suggest that when used within the appropriate scope of screening and surveillance, the CSBS-ITC detects meaningful variability in skills across ages in young children with neurogenetic syndromes and may provide useful information about both individual- and population-level social communication profiles in these populations.

Keywords

Angelman; measure validation; neurogenetic syndrome; Prader-Willi; social communication; Williams syndrome

Social communication skills, such as gesture use, eye contact, and early vocalizations, are commonly delayed in individuals with neurogenetic syndromes, triggering cascading effects on later language and communication development. Early and targeted treatment may be the key to circumventing or preventing challenges related to these obstacles; however, given the extremely low prevalence rates of some neurogenetic syndromes, in addition to the commonly late age of diagnosis, very little is known about early social and communicative development in these populations. This problem may be exacerbated by the paucity of measures validated to assess abilities in individuals with cognitive impairments, particularly in early childhood. The present study aims to address these challenges by first characterizing the utility of a popular early social communication screening measure in populations with neurogenetic syndromes, which we then apply to present preliminary information regarding early social communication profiles of young children with Angelman, Prader-Willi, and Williams syndromes.

Effectively screening and monitoring early social communication skills is critical to routing children to efficient, targeted interventions. Early social communication skills are particularly important because they form the building blocks for the mastery of later language and communication skills. Individuals with neurogenetic syndromes often experience deficits in these types of early social communication skills, and therefore are at risk for resulting language delays and communication deficits (Abbeduto, Brady, & Kover, 2007; Jolleff & Ryan, 1993; Singer Harris, Bellugi, Bates, Jones, & Rossen, 1997). Importantly, interventions targeting pre-linguistic skills have proven effective in improving later communication outcomes (Fey et al., 2006; Warren et al., 2008; Yoder, Woynaroski, Fey, & Warren, 2014) and in reducing problem behaviors related to the inability to communicate needs to others (Chow & Wehby, 2016; Sigafoos, 1997). Therefore, screeners that can adequately detect social communication deficits can enable targeted social communication interventions, which in turn may facilitate cascading positive effects across multiple functional domains.

The Communication and Symbolic Behavior Scales – Infant-Toddler Checklist (CSBS-ITC).

The CSBS-ITC (Wetherby & Prizant, 2003) is a popular brief screening measure used to identify delays in early social communication that may be indicative of atypical developmental outcomes such as autism spectrum disorder (ASD) and language delays later in life. The 24-item measure can be used with children ages 6 to 24 months and can be extended to children as old as 5 or 6 years of age whose functional communication levels are 24 months or younger. Because of its brevity, the CSBS-ITC can be used by pediatricians as part of routine early developmental well-visit screening to detect early signs of ASD and language delays that may warrant further evaluation. For example, in a study using the CSBS-ITC for systematic screening at routine 12-month well-visits, about 75% of the infants who failed the CSBS-ITC at 12 months were ultimately diagnosed with ASD, a language delay or other developmental delay at a later time point (Pierce et al., 2011). Furthermore, the CSBS-ITC has been shown to differentiate children with ASD from typically developing children at 12 months, and from typically developing children and children with specific language impairments at 24 months (Veness et al., 2012). Although a number of well-validated, comprehensive measures are available for in-depth evaluations of social communication development, the CSBS-ITC provides an efficient method for large-scale screening, making the measure particularly useful in time- or resource-limited settings.

CSBS-ITC in special populations.

As a screening measure, the CSBS-ITC is intended to be applied broadly with the goal of detecting children at increased risk for ASD and language delays amongst heterogeneous populations. In the original standardization sample, the CSBS-ITC was administered to the parents of 2,188 children with no previously-identified developmental delays to create normative data, with an additional 60 children identified as at-risk for communication and language delays added for validation analyses (Wetherby & Prizant, 2003). More recently, the CSBS-ITC has been used to characterize populations at increased risk for developing ASD and language delays (Pierce et al., 2011; Wetherby, Brosnan-Maddox, Peace, & Newton, 2008), and has also been applied to characterize delays associated with cerebral palsy (Coleman, Weir, Ware, & Boyd, 2015; Lipscombe et al., 2016). However, the utility of

the CSBS-ITC has rarely been evaluated in populations with neurogenetic syndromes, with the exception of a single study in children with 22q11 deletion syndrome (Muldoon et al., 2015). Based on evidence that the CSBS-ITC meaningfully discriminates developmental skills in a subset of neurodevelopmental disorders (Veness et al., 2012), we sought to further apply the CSBS-ITC to characterize early social communication in three understudied neurogenetic syndromes. Examining the range of scores outputted by the CSBS-ITC and profile features across these three syndromes will both inform the validity of the CSBS-ITC across three groups with variable cognitive and developmental profiles, as well as address the paucity of information on early social communication development in these groups.

Validating Screening Measures for Children with Neurogenetic Syndromes

Although screening measures do not provide the depth of information afforded by gold-standard diagnostic measures, screening tools offer a number of practical benefits including lower cost, reduced time burden for patients and their families, and the capacity to be administered remotely. Furthermore, measures that screen for deficits in specific areas of development may help quickly identify which areas to prioritize in targeted treatment. These benefits are particularly relevant to understanding development in rare neurogenetic syndromes, as patients often demonstrate broad developmental delays that can obscure individual differences in strengths and needs. Patients with rare syndromes also may not have access to local specialists who can interpret these developmental nuances via in-person diagnostic assessments. Thus, screeners may be used to quickly identify areas of relative weakness to be targeted first in treatment, as well as to characterize population-based data that would be difficult or financially prohibitive to collect locally. For example, screening measures routinely used in pediatric settings may be retrospectively aggregated to permit “big data” approaches to populations that are typically restricted to small-sample research. Thus, determining the validity of screening measures – particularly those routinely used in clinical settings – may facilitate opportunities for more comprehensive profiling of early developmental phenotypes.

Screening measures are also being used more frequently in neurogenetic syndrome research as a method of monitoring development and progress of skills over the course of pharmaceutical and behavioral clinical trials. It is crucial that measures used for these purposes are sensitive to improvements in skills to ensure that clinical trial results are representing the efficacy of the treatment rather than limitations in measurement (Berry-Kravis, Knox, & Hervey, 2011). Indeed, limited options for appropriate outcome measurement tools has been cited as a potential reason for failed clinical trials in neurogenetic syndromes (Berry-Kravis et al., 2013; Braat & Kooy, 2014; Jacquemont et al., 2014). This need has motivated efforts to both create new measures and validate existing measures appropriate to clinical trials for neurogenetic syndromes (Berry-Kravis et al., 2013; Hessel et al., 2009, 2016). Notably, existing measure development for clinical trials in neurogenetic syndromes has largely focused on school-aged and adult populations, despite the need for clinical trials to soon extend to early childhood groups (Berry-Kravis et al., 2013). Thus, there is a particular need to validate brief early childhood measures that may be well-suited for clinical trials research.

As part of this validation process, there are several specific considerations that must be addressed to ensure screening measures are effective and appropriate for neurogenetic syndromes. One consideration is whether the screening measure is sensitive to specific weaknesses relative to the broad global delays often present in neurogenetic syndromes, and whether these deficits are meaningful in a way that can predict abnormal development over and above the presence of a global developmental delay. One method for addressing this consideration is to use cross-syndrome comparisons, which permit determination of whether features emerge across multiple groups, therefore potentially reflecting global developmental delay, or vary across multiple groups, which suggests features are not emerging secondary to developmental delay (e.g. Abel & Tonnsen, 2017). Furthermore, there is evidence that a broad developmental screener created specifically for use in populations with intellectual disability can detect syndrome-specific profiles at both the item and subscale levels (Steinhausen et al., 2002), suggesting the possibility of detecting nuanced differences in skills among individuals who demonstrate broad cognitive deficits. Another consideration is whether the screener accurately characterizes the developmental trajectories of behaviors in neurogenetic syndromes, and if it is sensitive to the rate of skill acquisition within these populations (Harris, 2010). Individuals with neurogenetic syndromes often acquire skills at slower rates than their typically developing peers, and normative data often capture the increasing deviance from typical development as opposed to small advances in skills over time (Fisch et al., 2010). Thus, longitudinal studies that explore sensitivity to change are particularly important for screeners being used as measures of treatment efficacy, as the measure must capture acute, meaningful change in skills. Longitudinal studies may also inform optimal options for tracking change over time. For example, depending on the skill being assessed, the use of raw scores for tracking change over time may be preferable to normative scores, which provide important population-level information about the child's skills but may not be sensitive enough to capture small but meaningful within-individual growth over time. In fact, because standard scores use normative data to compare a child's abilities to other similarly-aged children, it is possible that a child who is gaining skills at a slower rate than typically developing children will demonstrate *decreasing* normative scores over time, reflecting the increasing deviance from typical development as opposed to the gradual increase in skills over time.

Social Communication in Neurogenetic Syndromes

Given emerging evidence that the CSBS-ITC may offer a useful, brief screening measure of social communication in children with ASD, cerebral palsy, and 22q11 deletion syndrome (Lipscombe et al., 2016; Muldoon et al., 2015; Veness et al., 2012), we sought to validate and apply this measure to three understudied neurogenetic syndromes: Angelman, Prader-Willi, and Williams syndromes. These groups were selected due to the currently limited characterization of social communication profiles, likely reflecting the challenges of amassing sufficient participant samples for in-person diagnostic assessments in rare syndromes. The range of skills present across these disorders also provides an opportunity to assess the applicability of the CSBS-ITC to individuals with mild to severe developmental impairments. Here, we briefly review the genetic and developmental features of each of these syndromes, including extant literature on early social communication development.

Angelman syndrome.

Angelman syndrome (AS) affects approximately 1 in 10,000 to 12,000 individuals and is caused by reduced expression of the *UBE3A* gene found on the maternally-inherited chromosome 15 at q11-q13 (Kyllerman, 1995; Petersen, Brøndum-Nielsen, Hansen, & Wulff, 1995). The majority of cases are caused by a genetic deletion at 15q11-q13 (75%), with the remaining caused by a mutation of the *UBE3A* allele on 15q11-q13 (15%), paternal uniparental disomy (7%; inheritance of both copies of chromosome 15 from one parent, here the father), or a microdeletion affecting the imprinting center on chromosome 15 (2–4%; Mabb, Judson, Zylka, & Philpot, 2011). The *UBE3A* gene is associated with synaptic development and neural plasticity, and its reduced expression in AS is associated with severe cognitive and motor impairments and limited or absent speech (Thibert, Larson, Hsieh, Raby, & Thiele, 2013). Most individuals with AS do not master more than one or two meaningful words, and many exhibit difficulties with other forms of social communication, such as gestures (Jolleff & Ryan, 1993). Furthermore, prevalence estimates of ASD in AS range from 34–81% (Richards, Jones, Groves, Moss, & Oliver, 2015; Trillingsgaard & Østergaard, 2004), potentially reflecting the challenge of differentiating ASD-specific behaviors in AS from behaviors related to the severe developmental delays often present in this population. Receptive language abilities are often a relative strength compared to expressive language abilities (Gentile et al., 2010). Individuals with AS most frequently communicate with others for the purposes of making their wants or needs known and less frequently communicate to label or imitate, relative to other groups with severe intellectual disabilities (Didden, Korzilius, Duker, & Curfs, 2004). Despite these communication challenges, individuals with AS are known for their generally happy demeanor and frequent smiling and laughing in social situations, particularly during interactions with adults (Horsler & Oliver, 2006; Oliver, Demetriades, & Hall, 2002).

Prader-Willi syndrome.

Prader-Willi syndrome (PWS) affects 1 in 10,000 to 30,000 individuals and is caused by unexpressed genes on the paternally-inherited chromosome 15q11-q13 (Cassidy, Schwartz, Miller, & Driscoll, 2012). Approximately 70% of PWS cases are caused by genetic deletion, 28% are caused by maternal uniparental disomy, and the remaining 2% are caused by imprinting defects (Everman & Cassidy, 2000). Phenotypic characteristics across PWS subtypes include distinctive physical features, low muscle tone in infancy, mild to moderate intellectual disability, and an elevated appetite starting in early childhood (Cassidy, 1997). Both expressive and receptive language development have been shown to be impaired in this population beyond delays that are expected based on cognitive ability alone (Dimitropoulos, Ferranti, & Lemler, 2013; Lewis, Freebairn, Heeger, & Cassidy, 2002), with some variation in language profiles based on genetic subtype (Roof et al., 2000; Whittington et al., 2004). Rates of ASD are also slightly higher in individuals with PWS caused by the mUPD than those with the DEL subtype (35.3% vs. 18.5%; Bennett, Germani, Haqq, & Zwaigenbaum, 2015). Relative strengths in PWS include reading and puzzle-solving skills (Hansen & Rogers, 2012; Ho & Dimitropoulos, 2010), which could potentially be leveraged during treatment to emphasize social communication during these activities and to maximize treatment effectiveness.

Williams syndrome.

Williams syndrome (WS) has an estimated prevalence of 1 in 7,500 to 20,000 and is caused by a deletion on chromosome 7q11.23 (Schubert, 2009). The WS phenotype often involves mild to moderate intellectual disability, cardiovascular problems, visual-spatial deficits and hypersociability (Schubert, 2009). Early receptive and expressive language development is often delayed, but not more than would be expected based on mental age (Brock, 2007; Paterson, Brown, Gsodl, Johnson, & Karmiloff-Smith, 1999). However, individuals with WS may demonstrate abnormalities in other types of early social communication skills relative to their language skills. For example, gesture use has been shown to be impaired in WS compared to individuals with Down syndrome with comparable language abilities (Singer Harris et al., 1997). Similarly, in a study of toddlers with WS aged 17 to 55 months, Laing et al. (2002) noted limited use of instrumental and declarative gestures as well as difficulties initiating and responding to joint attention. A recent meta-analysis estimates the prevalence of ASD in WS at approximately 12% and suggests that populations with NGS, WS represents one of the least likely syndromes to have a comorbid diagnosis of ASD (Richards et al., 2015). Notably, use of eye contact is a strength for individuals with WS (Riby & Hancock, 2008), as is the strong affinity for social interaction that often characterizes this population (Jones et al., 2000).

The Present Study

Information on early social communication in individuals with Angelman, Prader-Willi, and Williams syndromes is still relatively scarce, particularly in the first few years of life, limiting parents' and providers' knowledge of syndrome-specific patterns of typical and atypical development. Population-based screening measures such as the CSBS-ITC, provide an efficient, low cost, and accessible option for characterizing early initial profiles and change in social communication in children with neurogenetic syndromes who are underrepresented in the current literature base. This information may assist in preparing earlier and more targeted treatment plans for individuals with neurogenetic syndromes, ultimately promoting more positive social communication outcomes in these populations. However, given that most developmental screening measures have not been designed for use in these populations, measures such as the CSBS-ITC must first be carefully examined to ensure the instrument is capable of capturing diverse patterns of individual differences and longitudinal change among individuals with neurogenetic syndromes.

The present study addresses these needs through two interrelated studies. In Study 1, we examine whether the CSBS-ITC is sensitive to the range of social communication skills in children with neurogenetic syndromes by comparing syndrome-specific profiles to age-matched typically developing (TD) controls. Integrating multiple syndrome groups provides information about whether group differences are likely to be driven by developmental delays broadly (e.g. all syndrome groups display similarly atypical profiles) versus syndrome-specific variability that may inform more nuanced assessment and treatment planning (e.g. variable profiles across neurogenetic groups). In Study 2, we assess whether the CSBS-ITC is sensitive to within-individual change over time in neurogenetic groups, again integrating a TD comparison group to give perspective to patterns observed in the NGS groups. Together,

these studies aimed to both validate and characterize CSBS-ITC profiles in young children with neurogenetic syndromes, laying the foundation for improved characterization and measurement of skills in these populations.

Method

Participants

Across studies, participants included 92 children with neurogenetic syndromes (NGS; 33 AS, 26 PWS, 33 WS) and 57 typically developing (TD) children (total $n=149$) ages 6 to 57 months. Mothers were recruited to participate in [MASKED], an ongoing longitudinal study of early development in NGS. Families were recruited through social networks, the Angelman Syndrome Foundation and Registry (www.angelman.org), and the Williams Syndrome Association and Registry (www.williams-syndrome.org/registry). TD participants were recruited through paid advertisements on Facebook targeting a national sample of mothers with young children. Study procedures were approved by the [MASKED] Institutional Review Board.

To be included in the study, families had to reside in the United States with English as the primary language spoken in the home. TD exclusion criteria included premature birth (< 37 weeks gestation), speech delay, and having a first-degree family member diagnosed with autism. Genetic status was confirmed by medical report for 72% of the NGS participants (AS 65%, PWS 87%, WS 64%). AS subtypes were reported for 94% of AS participants and included maternal deletion (76%, $n = 25$), *UBE3A* mutation (9%, $n = 3$), and uniparental disomy (9%, $n = 3$). PWS subtypes were reported for 93% of PWS participants and included paternal deletion (62%; $n=16$) and maternal uniparental disomy (31%, $n = 8$). Norm-based scores for NGS participants born prematurely (< 37 weeks; $n = 12$) were calculated based on corrected age for children younger than 24 months. All surveys were completed by the child's biological mother. Demographic information is presented in Table 1.

Measures

Communication and Symbolic Behavior Scales Developmental Profile – Infant-Toddler Checklist (CSBS-ITC; Wetherby and Prizant, 2003).—The CSBS-ITC is a 24-item parent-report checklist used to detect delays in early social communication and symbolic skills in infants 6 to 24 months of age, as well as children up to 5 or 6 years of age who have functional developmental levels younger than 24 months. Items on the CSBS-ITC are grouped into seven Clusters, which further combine into three Composites: Social (Emotion and Eye Gaze, Communication, Gestures), Speech (Sounds, Words), and Symbolic (Understanding, Object Use). All items are summed to calculate a Total score, which ranges from 0 to 57. For children within the normative age range (6–24 months), the Total raw score and Composite raw scores are converted to standardized scores and percentile ranks using age-based norms. The Total standard score ranges from 65 to 135, and standard scores for each composite range from 3 to 17. Total and Composite standard scores with percentile ranks 10% are considered to fall within the range of concern. As per measure guidelines, the CSBS-ITC can be collected on children who are older than 24 months of age; for these children, only raw score data are available.

Publisher-reported Cronbach's alphas for the Composites and Total raw scores range from .87 to .93 and all Composites and Total normative scores had Cronbach's alphas of .95 (Wetherby & Prizant, 2003). Good test-retest reliability across a four month interval was also reported, ranging from .65 to .88 for raw scores and normative scores across domains (Wetherby & Prizant, 2003). The CSBS-ITC has been compared to the Mullen Scales of Early Learning (MSEL; Mullen, 1995) to determine sensitivity, specificity and predictive power. Sensitivity of the CSBS-ITC to detect children who "failed" the MSEL (i.e. score <10th percentile on at least two MSEL scales or <2nd percentile on at least one MSEL scale) at a 3-year follow up assessment was .84, while specificity of correctly identifying children who did not "fail" the MSEL was .73. Positive predictive power was .44 and negative predictive power was .95. The CSBS-ITC has been applied to ASD (Veness et al., 2012), cerebral palsy (Lipscombe et al., 2016), and 22q11 deletion syndrome (Muldoon et al., 2015) populations, but has not been broadly validated for use in neurogenetic syndromes.

Vineland Adaptive Behavior Scales – Third Edition (VL-3; Sparrow, Cicchetti and Saulnier, 2016).—The VL-3 is a semi-structured interview of adaptive skills for individuals aged birth through 89 years. Mothers answered questions about their child's adaptive behavior across four domains: Communication, Daily Living Skills, Socialization, and Motor Skills. Internal, test-retest, and inter-rater reliability coefficients for the four VL-3 domains are all in the good to excellent range (Sparrow et al., 2016). Previous versions of the VL-3 have been commonly applied to neurogenetic syndrome groups, including in clinical trials (Budimirovic et al., 2017).

Procedure

Participants' biological mothers contacted the lab and completed screening questions to determine eligibility. Mothers were then sent the link to a password-protected online survey, which included the CSBS-ITC. Mothers were contacted with a link to the second online survey (also including the CSBS-ITC) approximately six months after completing the first survey (or twelve months after completing the first survey for children older than 36 months), and were additionally asked to complete a phone interview during which the VL-3 was administered.

Preliminary Analyses

We included the full sample of participants ($n = 149$) for raw score analyses in Study 1. Analyses of normative scores and longitudinal data required subsetting of the full sample based on participants who had the necessary data available. Specifically, standard score analyses in Study 1 required a subset of participants with a CSBS-ITC collected between the ages of 6 and 24 months when normative data is available, and analyses of longitudinal data in Study 2 require participants with a 2nd CSBS-ITC available from a follow-up assessment conducted 6–12 months after the initial assessment). Both the full sample and the subsamples were matched on standardized mean differences in age using standards set by Kover and Atwood (2013). These procedures determine group equivalence based on the effect sizes and variance ratios, both of which are less influenced by sample size than p -values. Effect sizes and variance ratios for each sample are presented in Table 2, and summary data about each sample is included in Table 3. As these data demonstrate, effect

sizes provided evidence of appropriate matching across both full sample and cross-group comparisons. Variance ratios were within the acceptable range for the full sample; however, due to the more restrictive nature of the normative range and longitudinal subsamples, the variances by group in these samples were not as closely matched.

Data were evaluated for non-normal distributions and outliers. Raw scores and normative scores (Study 1), and difference scores (Study 2) were relatively normally distributed (skew < 1.96 and kurtosis < 2) for all samples; thus, scores were not transformed. Models adjusting age for prematurity produced identical results to models using chronological age; therefore, chronological age was used in all models to maximize interpretability.

Study 1: Broad Profiles and Age Effects

Our first study examined the utility of the CSBS-ITC in measuring social communication skills in NGS populations by examining whether the CSBS-ITC is sensitive to syndrome-specific profiles and age-related changes in NGS compared to TD populations. This study included 92 individuals with NGS (33 AS, 26 PWS, 33 WS) and 57 TD participants for primary raw scores analyses, with normative score analyses available for a subsample of 51 NGS (17 AS, 17 PWS, 17 WS) and 35 TD participants. TD and syndromic groups were matched on age and sex in the full sample (age: Kruskal-Wallis $\chi^2 = 0.62$, $p = .891$; sex: Pearson's $\chi^2 = 3.85$, $p = .278$) and the normative range subsample (age: Kruskal-Wallis $\chi^2 = 0.53$, $p = .912$; sex: Pearson's $\chi^2 = 1.31$, $p = .726$) per matching guidelines outlined in Table 2.

We hypothesized that despite increased rates of floor effects in NGS groups, the CSBS-ITC would detect syndrome-specific profiles that both differentiate the NGS groups from the TD group as well as characterize differences across specific NGS groups. First, we hypothesized that the NGS groups would demonstrate higher rates of floor effects and scores in the range of concern than the TD group, and that the AS group would demonstrate the highest rates among the NGS groups. Next, we predicted that raw scores and normative scores would be lower in the NGS groups than in the TD group and that the AS group would exhibit lower scores than the PWS and WS groups. We also hypothesized that despite the NGS groups displaying lower scores than the TD group overall, CSBS-ITC raw scores and normative scores would demonstrate similar relationships with age in both the TD and the NGS groups (i.e. age associated with higher raw scores, while normative scores demonstrate more stable relationships with age).

To test these hypotheses, we first descriptively characterized percentages of normative scores in the range of concern (%ile rank ≥ 10), normative scores at the measure floor (Total SS = 65; Composite SS = 3), and raw scores at the measure floor (Total/Composite RS = 0) for each group across all CSBS-ITC domains. Next, we ran regressions of CSBS-ITC Total and Composite scores on group status, child, and an interaction of group and age. We conducted separate models for raw scores and normative scores in each CSBS-ITC domain (Total, Social, Speech, Symbolic). The TD group was coded as the reference group in primary models, which were repeated with each of the NGS groups as the reference group to acquire estimates of pairwise NGS contrasts and estimates of the age coefficient for each NGS

group. For each regression, we accounted for multiple comparisons using the Holm-Bonferroni Sequential correction.

Results

Cutoff Profiles and Floor Effects.—Figure 1 depicts the percentage of scores at the measure floor and in the range of concern across groups. As predicted, the NGS groups tended to demonstrate higher rates of scores in the range of concern (29–100%) and normative score floor effects (0–88%) than the TD group (9–20% range of concern; 0–9% normative floor effects) across CSBS-ITC domains. However, while floor effects were present in normative scores across all CSBS-ITC domains for most NGS groups, floor effects were nearly absent for raw scores across NGS groups, with only the AS demonstrating raw score floor effects in the Speech Composite (24%). Thus, as expected, raw scores showed the most potential for representing the range of social communication skills present among NGS participants.

Among the NGS groups, the AS group exhibited the least variability in scores across metrics, with all participants scoring in the range of concern and the majority exhibiting floor effects in normative scores of each CSBS domain. However, only 8 of 33 participants (24%) in the AS group received raw scores of 0 on the CSBS-ITC Speech Composite, and none received raw scores of 0 on any other domain. Thus, at the raw score level, the CSBS-ITC does appear to measure some skills that children with AS attain in early childhood. Scores for the PWS and WS groups were less affected by floor effects across metrics relative to the AS group, with WS slightly more affected than PWS. Whereas 29–59% of participants with PWS scored in the range of concern across domains, 71–94% of participants with WS received scores in the range of concern, with particularly high rates in Total (88%) and Social (94%) domains. Normative score floor effects were lower in PWS and WS compared to AS, ranging from 0–24% in PWS and 24–35% in WS. No PWS or WS participants received raw scores at the measure floor on any domain. Additionally, the PWS group was the only NGS group that demonstrated a lack of normative score floor effects on any CSBS-ITC domain, with 0% of PWS participants scoring at the normative score floor on the Symbolic Composite. Thus, raw scores demonstrated variability across all syndrome groups, and normative scores demonstrated variability in PWS and WS only.

Group Differences and Age-Related Change.—Results of linear regressions of age, group and the interaction of age*group onto each CSBS-ITC domain are presented in Table 4 and Figure 2. As expected, all NGS groups demonstrated significantly lower raw and normative scores than the TD group across all CSBS-ITC domains. CSBS-ITC Total raw scores in the NGS groups tended to be on average about 11 to 28 points lower than the TD group (Total RS Group $B_{ASvsTD} = -27.97$, $SE = 2.23$, $p < .001$; Total RS Group $B_{PWSvsTD} = -11.51$, $SE = 2.47$, $p < .001$; Total RS Group $B_{WSvsTD} = -14.62$, $SE = 2.21$, $p < .001$), and Total standard scores in the NGS groups were on average about 22 to 36 points lower than the TD group (Total SS Group $B_{ASvsTD} = -36.70$, $SE = 3.54$, $p < .001$; Total SS Group $B_{PWSvsTD} = -22.20$, $SE = 3.54$, $p < .001$; Total SS Group $B_{WSvsTD} = -30.39$, $SE = 3.53$, $p < .001$).

Raw score and standard scores generally demonstrated the expected relationship with age across groups. Raw scores were significantly positively associated with age across all CSBS-ITC domains in the TD, WS and PWS groups, with the exception of the Social Composite in the PWS group. The AS group demonstrated non-significant associations of raw scores with age on all CSBS-ITC domains except the Symbolic Composite, on which raw scores demonstrated a significant positive association with age. As predicted, standard scores tended to demonstrate a more stable association with age across groups. Standard scores were not significantly associated with age on any CSBS-ITC domain across NGS groups; however, the TD group did demonstrate significant positive associations of the Total SS and Symbolic SS with age.

Interaction coefficients provide information about whether CSBS-ITC domains demonstrate significantly different associations with age across groups. As reported in Table 4, interaction coefficients were significant for AS vs. TD for Speech RS and for WS vs. TD on Symbolic SS. The Speech RS interaction coefficient for AS vs. TD indicates that the AS group acquired skills in this domain at a lower rate than the TD group, reflecting the fact that the Speech raw scores were positively associated with age in the TD group but not the AS group. The Symbolic SS interaction coefficient for WS vs. TD suggests that the WS group acquired skills in this domain at a lower rate than the TD group. While Symbolic SS significantly increased with age in the TD group, the WS group demonstrated a non-significant, but slightly negative association of Symbolic SS with age. All other NGS raw and standard scores demonstrated similar associations with age as the TD group (Table 1). Thus, the CSBS-ITC generally detected similar relationships in the TD and NGS groups between age and CSBS-ITC scores for both raw scores (which generally increased with age in both groups) and normative scores (which generally remained stable over time in both groups). Importantly, while stable normative scores in the NGS group may indicate stable relationships of normative scores with age similar to those observed in the TD group, this stability may also reflect the high rates of floor effects in the NGS normative CSBS-ITC scores. Thus, it is possible that the rate of skill acquisition in the NGS group may be increasing or decreasing with age relative to the normative population, but that the CSBS-ITC is not sensitive enough to capture these patterns at the very low end of developmental skills.

In addition to capturing broad differences between the TD and NGS groups, The CSBS-ITC also detected several significant syndrome-specific profiles, particularly at mean level scores. Specifically, the CSBS-ITC captured robust differences in social communication skills between the AS and PWS groups, with the AS group demonstrating significantly lower raw and standard scores than the PWS group across all CSBS-ITC domains. Furthermore, while CSBS-ITC normative scores did not capture differences between the WS and AS or the WS and PWS groups, raw scores did capture these more nuanced profiles. In particular, the AS group had lower raw scores than the WS group across all CSBS-ITC domains, and the PWS group demonstrated higher Total RS than the WS group. Thus, while normative scores may be able to detect robust syndromic profiles, it appears that raw scores are more sensitive to nuanced differences in phenotypic social communication profiles.

Summary.

As expected, raw and normative scores in the NGS groups reflected deficits in early social communication skills compared to the TD group. However, despite high rates of scores in the range of concern and floor effects in NGS CSBS-ITC normative scores, raw scores across all CSBS-ITC domains captured significant age-related growth in the NGS groups, as well as nuanced syndrome-specific profiles of social communication skills. This suggests that the range of social communication skills measured by the CSBS-ITC is sufficient to detect meaningful variability in skills across ages, despite the tendency for individuals with NGS to demonstrate fewer early social communication skills than TD controls overall. In particular, raw scores provided more robust measurement of skills, given the much lower rates of floor effects observed in raw scores compared to normative scores.

Study 2: Individual Growth

Based on the results of Study 1, which indicated that CSBS-ITC raw scores generally increased with age in both TD and NGS groups, we next explored the sensitivity of CSBS-ITC raw scores to detect within-individual change over time. We did not analyze normative scores given our previous findings that normative scores in NGS groups are generally stable across age (Study 1). Participants included 60 individuals with NGS (15 AS, 21 PWS, 24 WS) and 49 TD children who completed 2 time points, with a second follow-up assessment completed 3 to 20 months ($M = 7.26$, $SD = 2.84$) after their initial assessment. TD and syndromic groups were matched on age and sex (age: Kruskal-Wallis $\chi^2 = 0.25$, $p = .969$; sex: Pearson's $\chi^2 = 2.05$, $p = .563$) per matching guidelines outlined in Table 2.

We hypothesized that across groups, raw scores would be sensitive to within-individual change across development. To test this hypothesis, we first calculated a difference score for each CSBS-ITC domain ("Developmental Change" = follow-up raw score - initial raw score) and the amount of time between the initial and follow-up assessments ("Time Interval" = age at final assessment - age at initial assessment). Then, we regressed Developmental Change onto group and Time Interval for each CSBS-ITC domain (Total, Social, Speech, Symbolic), controlling for multiple comparisons using the Holm-Bonferroni correction. Time Interval was centered at 6 months so the intercept value would be interpreted as skills gained after a 6-month period. The TD group was coded as the reference group in primary models, which were repeated with each of the NGS groups as the reference group to acquire estimates of the intercept coefficient for each NGS group as well as pairwise comparisons between NGS groups.

Results

Results of linear regressions of group and Time Interval onto each CSBS-ITC raw score domain are presented in Table 5 and Figure 3. CSBS-ITC Total scores after a 6-month period were an average of 8 points higher than at the initial assessment in the TD group (Intercept $B_{TD} = 8.01$, $SE = 1.18$, $p < .001$), with similar patterns of significant gains observed among PWS (Intercept $B_{PWS} = 7.61$, $SE = 1.75$, $p < .001$) and WS (Intercept $B_{WS} = 9.54$, $SE = 1.79$, $p < .001$). The TD, PWS and WS groups similarly demonstrated significant gains over a 6-month period on all CSBS-ITC Composites as well (Table 5). The

AS group did not exhibit significant improvements over a 6-month interval in any CSBS-ITC domain. However, pairwise group comparisons of changes in CSBS-ITC raw scores over a 6-month interval indicated that changes in CSBS-ITC raw scores made by the NGS groups were not significantly different from those made by the TD group. Furthermore, pairwise comparisons between NGS groups also suggested similar gains made across NGS groups, with the exception of gains in Speech RS for the WS and AS groups, for which the WS gained significantly more skills on average over the 6-month interval than the AS group (Group $B_{WSvsAS} = 2.45$, $SE = 0.83$, $p = .004$). Notably, many older children in the TD group scored at or close to the measure ceiling at both assessments, resulting in small RS gains over the Time Interval due to reaching the upper limit of the RS range. This raises the point that the rate of skill acquisition at older ages may be different for TD children, who have generally acquired the maximum range of skills measured by the CSBS-ITC, compared to children with NGS who often acquire skills later and at slower rates than their TD peers. Thus, non-significant differences between the TD and NGS groups in the number of skills acquired over a predicted 6-month period could also be explained by differential rates of skill acquisition across ages.

Summary.

CSBS-ITC raw scores detected significant within-individual change in social communication skills over a predicted 6-month period, particularly in the TD, PWS and WS groups, suggesting the CSBS-ITC may be sensitive to acute gains in individual skills across a relatively narrow age window. Therefore, the CSBS-ITC may be useful for tracking individual growth in PWS and WS, though may have more limited utility in AS.

Discussion

Given the scarcity of information on early social communication in rare neurogenetic syndromes and the challenges linked with early treatment and intervention planning in these populations, establishing valid and efficient assessment measures is critical to informing and measuring clinical change. The present study aimed to explore the utility of a popular social communication screening measure in three understudied populations with rare neurogenetic syndromes. Our studies confirmed that the CSBS-ITC generally detects meaningful variability in skills across ages and produced preliminary social communication profiles of very young children with neurogenetic syndromes, adding to the relatively limited literature on early social communication and creating a foundation for future use of the CSBS-ITC in these populations. Together, these studies suggest that despite some limitations, the CSBS-ITC is a generally appropriate and applicable measure of early social-communication skills in neurogenetic syndromes.

Utility of the CSBS-ITC in NGS Populations

Findings across studies unveiled a number of strengths of the CSBS-ITC in its application within NGS populations. For the majority of individuals with neurogenetic syndromes, the CSBS-ITC was sensitive enough to capture social communication skills typically exhibited by individuals with these syndromes, particularly through the use of raw scores. Indeed, raw scores not only demonstrated low rates of floor effects, but also detected age-related growth

in social communication skills. CSBS-ITC raw scores tended to increase with age, and were also successful in detecting within-individual gains in skills over a predicted 6-month period, suggesting that the skills measured by the CSBS-ITC are acquired quickly enough in NGS populations that growth can be detected over the span of a few months. Therefore, despite generally low levels of social communication skills and overarching cognitive and developmental delays across all NGS groups, the CSBS-ITC still provides useful and meaningful information about social communication skills in NGS groups at the population level, and has the potential to capture variability in the rates of acquisition of these skills in NGS populations over time.

Despite these strengths, our study also illuminated some areas in which the utility of the CSBS-ITC may be limited in NGS populations. Normative scores, particularly the descriptive “range of concern,” were less variable among NGS participants and may provide limited utility in identifying specific areas of strengths or weaknesses apart from what might already be expected due to global developmental delays. Normative scores demonstrated high rates of floor effects in the NGS groups, indicating that the CSBS-ITC normative sample may not provide sufficient information about variability in skills at lower ability levels. This issue was particularly problematic in the AS group, where rates of floor effects and scores in the range of concern were highest. Although these findings are consistent with the well-documented speech and motor delays associated with AS, they also suggest that the CSBS-ITC normative data may have limited utility in AS and other NGS populations with very severe developmental delays. Any applications of the CSBS-ITC in these groups should instead focus on levels and change in raw scores over time.

Applications for Neurogenetic Syndrome Subgroups

The CSBS-ITC has the potential to address many of the difficulties encountered when studying early social communication in very young children with rare neurogenetic syndromes, as it can be administered with low burden on families, is appropriate for use in very young children, and is sensitive to some syndrome-specific differences in social communication profiles. Broadly, the CSBS-ITC captured the most dramatic differences between the AS group and PWS and WS groups, with the AS group performing significantly lower than the other two groups across most CSBS-ITC domains and displaying the highest rates of floor effects and scores in the range of concern. This suggests that the CSBS-ITC is able to detect pronounced differences between NGS groups that would be expected based on syndromic phenotypes.

In the AS group, the CSBS-ITC detected some patterns of social communication skills that are consistent with the AS phenotype. Rates of floor effects were highest in the Speech Composite (88%) and lowest in the Social Composite (71%) for the AS group, potentially reflecting the AS phenotypic profile of severe language difficulties with relative strengths in social interactions (Oliver et al., 2002; Thibert et al., 2013). Furthermore, the Symbolic raw score demonstrated a significant association with age in the AS group, suggesting that skills in this domain may continue to steadily increase over time, consistent with relative strengths in receptive language in AS (Gentile et al., 2010). However, every participant in the AS group had scores in the range of concern for all domains, and predicted gains in social

communication skills across 6 months as measured by CSBS-ITC raw scores were negligible across domains (estimated Total raw score gain of 3.51, and Composite raw scores gains ranging from 0.59 to 1.63). Therefore, this measure – particularly the Speech Composite and the cutoff scores provided for each domain – may have limited utility for individuals with AS or other severe delays and is likely not sensitive enough to detect individual differences in strengths and needs in these populations.

The CSBS-ITC showed more promise for use in PWS and WS populations. The majority of participants in each group were not scoring at the measure floor, and CSBS-ITC raw scores exhibited significant predicted growth over a 6-month period across all domains in both PWS and WS (estimated gains in Total raw scores ranging from 7 to 10, and predicted Composite raw score gains of 1 to 4 over a 6-month period). The PWS group demonstrated the lowest rates of floor effects and scores in the range of concern across CSBS-ITC domains, particularly in the Symbolic Composite. Zero PWS participants scored at the measure floor in this domain, which measures receptive language skills and various levels of pretend and symbolic play, suggesting that these skills may be relative strengths for the PWS group. This is somewhat inconsistent with previous literature suggesting that both expressive and receptive language development is impaired in PWS beyond what might be expected based on cognitive ability alone (Dimitropoulos et al., 2013; Lewis et al., 2002). Raw scores in the Speech Composite were more consistent with these previous findings, as they demonstrated the smallest growth over a predicted 6-month interval in the PWS group, suggesting that these skills may be acquired more slowly relative to other social communication skills in the PWS group.

Patterns of floor effects and scores in the range of concern were somewhat varied in the WS group. Interestingly, the highest rate of scores in the range of concern for the WS group was in the Social Composite (94%), seemingly inconsistent with the WS phenotype of hypersociability (Schubert, 2009). This suggests that the CSBS-ITC may not be capturing the types of skills that individuals with WS use most effectively in social situations. Alternatively, high rates of scores in the range of concern on the Social Composite may reflect that fact that gesture use, an area of known weakness in WS (Laing et al., 2002; Singer Harris et al., 1997) is measured in this Composite, in which the CSBS-ITC may be capturing early delays in these skills in this population. Scores in the Speech Composite for the WS group were least affected by floor effects and scores in the range of concern, potentially reflecting the less severe impairment in language skills relative to other social communication skills in the WS group (Brock, 2007; Paterson et al., 1999).

Limitations and Future Directions

This study presents a comprehensive analysis of the performance of a popular screening measure in NGS populations, providing a framework for establishing valid screening measures and adding to the sparse literature on early social communication in these populations. Despite these strengths, this study does also present some limitations and areas for further study. Our sample was fairly homogenous, and additional work is needed to validate this measure in a more representative sample. Similarly, while our study included a large overall sample size of participants in the NGS group relative to previously published

studies, our sample sizes were much smaller for our analyses of CSBS-ITC normative scores (Study 1) and those involving longitudinal analyses (Study 2). Future work with expanded samples is needed to replicate the findings in this study and further characterize the utility of this measure in NGS. In particular, further work is needed to test differential longitudinal functioning of the CSBS-ITC across ages in the NGS groups, as our restricted sample did not allow for more complex modeling of differential test performance across ages. Furthermore, while our sample did represent individuals with three rare neurogenetic syndromes to allow for cross-syndrome comparisons, it is unclear whether observed syndrome-specific profiles captured true phenotypic differences as opposed to variations in developmental delays. Additional work with NGS groups matched on developmental level will clarify this distinction. Notably, the CSBS-ITC is a screening measure that should not be used for communication-related diagnoses. Due to the online nature of this study, we did not have access to any in-person measures of developmental ability to determine the severity of cognitive impairment in our NGS groups. Future work may build on our findings by integrating standard clinical measures that assess outcomes related to social communication, such as autism or language delays. These data will allow for further confirmation of the ability of the CSBS-ITC to detect individuals who go on to have specific social communication deficits as opposed to broad developmental delays. Relatedly, while there are numerous advantages of using a brief screening measure in NGS populations, it is possible that other brief social communication measures that provide added detail (e.g., the 41-item CSBS Caregiver Questionnaire; Wetherby & Prizant, 2003) may be similarly- or better-suited to characterize social communication profiles in NGS populations.

Summary

Overall, the CSBS-ITC has the potential to be a useful, brief screening measure of social communication in NGS populations. Our findings suggest this measure can meaningfully characterize and capture age-related growth in early social communication skills among individuals with syndromes generally associated with moderate levels of cognitive impairment, and skills measured by the CSBS-ITC converge with other well-validated measures of adaptive functioning. These findings support the potential of the CSBS-ITC to provide much-needed information about early social communication development in generally understudied populations. Given our findings that the CSBS-ITC is sensitive to natural developmental growth over a relatively short period of time (6 months), an important next step will be to evaluate whether the CSBS-ITC can detect clinically-meaningful change over the course of treatment. These findings suggest that, when used within the appropriate scope of screening and surveillance, the CSBS-ITC may offer a valid metric for informing individual level and population-level profiles and trajectories of early social communication skills, made even more accessible by the relatively low time and monetary burden to researchers and families.

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Figure 1.
Percent of Sample with Normative Scores in the Range of Concern, Normative Scores at the Measure Floor, and Raw Scores at the Measure Floor by Group

Figure 2.
Linear Regressions of Age, Group, and Age*Group for each CSBS-ITC Domain

Figure 3.
Regressions of Time Interval and Group onto Change in CSBS-ITC Raw Scores

Table 1.

Demographic Information for Full Sample by Diagnostic Group

	AS (n=33)		PWS (n=26)		WS (n=33)		TD (n=57)	
	n	%	n	%	n	%	n	%
Race/Ethnicity								
American Indian	0	0%	0	0%	0	0%	0	0%
Asian	1	3%	1	4%	0	0%	0	0%
Black	0	0%	0	0%	0	0%	0	0%
Pacific Islander	0	0%	0	0%	1	3%	0	0%
White	26	79%	19	73%	26	79%	51	89%
Multiple Races	1	3%	1	4%	1	3%	1	2%
Not Reported	5	15%	5	19%	5	15%	5	9%
Income	n	%	n	%	n	%	n	%
\$0-\$49,000	4	12%	5	19%	6	18%	12	21%
\$50,000-\$99,999	11	33%	11	42%	14	42%	19	33%
\$100,000-\$149,999	10	31%	2	8%	7	21%	12	21%
\$150,000+	8	24%	7	27%	4	12%	14	25%
Not Reported	0	0%	1	4%	2	6%	0	0%
Maternal Education	n	%	n	%	n	%	n	%
HS Diploma or Less	4	12%	0	0%	1	3%	1	2%
Some College/Associate Degree	8	24%	6	23%	10	30%	7	12%
Bachelor's Degree	8	24%	13	50%	11	33%	21	37%
Advanced Degree	13	39%	7	27%	11	33%	28	49%
Maternal Marital Status	n	%	n	%	n	%	n	%
Single, Never Married	2	6%	0	0%	4	12%	1	2%
Married	29	88%	24	92%	27	82%	56	98%
Divorced	0	0%	1	4%	2	6%	0	0%
Separated	1	3%	0	0%	0	0%	0	0%
Engaged	1	3%	1	4%	0	0%	0	0%
	AS (n=15)		PWS (n=18)		WS (n=21)		TD (n=40)	
	M	SD	M	SD	M	SD	M	SD
Vineland ABC	51.40	7.76	69.17	10.93	69.33	14.12	95.75	12.42
Communication Domain	34.07	11.62	67.00	16.26	67.95	20.14	100.93	11.68
Socialization Domain	63.40	7.54	73.44	14.30	74.67	13.97	93.05	12.20
Motor Skills Domain	38.20	18.06	58.94	16.55	66.67	18.76	99.75	12.58
Age in Months at Vineland	32.37	13.090	26.11	12.38	31.86	12.05	24.68	14.46

Note. ABC = Adaptive Behavior Composite. Vineland data are only available for a subset of participants in each group who have completed a follow-up assessment when the Vineland is administered.

Table 2.

Effect Sizes (*d*) for Standardized Mean Differences and Variance Ratios (var) of Chronological Age Calculated for Matching the Full Sample and Subsamples on Chronological Age

	AS vs. TD		PWS vs. TD		WS vs. TD		AS vs. PWS		PWS vs. WS		WS vs. AS	
	<i>d</i>	var	<i>d</i>	var	<i>d</i>	var	<i>d</i>	var	<i>d</i>	var	<i>d</i>	var
Full sample	.00	1.11	.18	1.11	.03	1.30	.18	1.00	.03	1.17	.17	1.17
Normative Range subsample	.14	1.81	.14	1.49	.04	1.12	.03	2.69	.10	1.62	.10	1.66
Longitudinal subsample	.06	1.47	.12	2.91	.01	1.60	.23	4.28	.07	2.35	.13	1.82

Note: The Full sample was used for analyses of raw scores in Study 1. The Normative Range and Longitudinal subsamples are subsets from the Full Sample. The Normative Range subsample was used for analyses of normative scores in Study 1, and the Longitudinal subsample was used for analyses of longitudinal data in Study 2. As per thresholds reported in Kover & Atwood (2013), groups with a standardized mean difference with a Cohen's *d* of less than .20 and a variance ratio less than 1.33 are considered adequately matched.

Table 3.
Means and Standard Deviations of Relevant Study Variables for the Full Sample and Subsamples by Diagnostic Group

Full Sample	AS (n=33)		PWS (n=26)		WS (n=33)		TD (n=57)	
	M	SD	M	SD	M	SD	M	SD
Chronological Age	26.97	13.43	24.51	13.41	26.62	12.40	26.95	14.16
Total Raw Score	18.81	9.28	33.28	14.16	32.06	13.90	46.60	12.66
Social Raw Score	10.48	4.70	16.12	6.97	15.58	6.29	21.45	5.24
Speech Raw Score	2.33	2.29	6.80	3.91	7.36	4.29	11.11	3.91
Symbolic Raw Score	5.88	3.61	10.62	4.84	9.12	4.18	14.18	4.20
Normative Range Subsample (Study 1)								
	AS (n=17)		PWS (n=17)		WS (n=17)		TD (n=35)	
	M	SD	M	SD	M	SD	M	SD
Chronological Age	16.49	3.96	16.36	6.49	16.89	5.04	17.09	5.32
Total Standard Score	65.53	1.50	79.82	9.59	71.82	9.38	102.69	17.79
Social Standard Score	3.47	0.87	7.18	3.86	4.82	2.40	10.63	3.57
Speech Standard Score	3.18	0.53	6.35	2.50	5.76	2.73	10.51	4.18
Symbolic Standard Score	3.35	0.86	7.06	1.71	4.94	2.16	11.60	3.39
Longitudinal Subsample (Study 2)								
	AS (n=15)		PWS (n=21)		WS (n=24)		TD (n=49)	
	M	SD	M	SD	M	SD	M	SD
Chronological Age at Time 1	23.29	14.63	21.69	7.07	22.62	9.54	22.52	12.05
Chronological Age at Time 2	30.23	15.33	28.74	9.31	31.09	11.13	29.39	12.83
Time Interval	6.94	2.36	7.04	3.59	8.47	3.24	6.87	2.26
Total Raw Score at Time 1	18.29	8.94	33.14	11.82	29.21	12.72	42.76	13.65
Social Raw Score at Time 1	9.80	4.41	16.24	6.29	14.17	5.78	19.59	5.59
Speech Raw Score at Time 1	2.27	1.94	6.43	2.91	6.67	4.09	10.27	4.11
Symbolic Raw Score at Time 1	5.79	3.75	10.48	3.80	8.38	3.81	12.90	4.84
Total Raw Score Change	3.50	3.66	7.60	6.84	9.52	6.03	8.00	9.29
Social Raw Score Change	1.60	2.16	2.57	3.74	3.26	3.17	3.28	4.77
Speech Raw Score Change	0.57	2.10	1.95	2.72	3.00	2.31	1.88	2.40
Symbolic Raw Score Change	1.00	1.08	2.81	2.32	2.96	2.16	2.69	3.39

Note: The Full sample was used for analyses of raw scores in Study 1. The Normative Range and Longitudinal subsamples are subsets from the Full Sample. The Normative Range subsample was used for analyses of normative scores in Study 1, and the Longitudinal subsample was used for analyses of longitudinal data in Study 2.

Table 4.

Linear Regressions of Age, Group, and Age*Group on Each CSBS-ITC Domain

	Age			Group ^a						Age*Group ^a						
	AS	PWS	ws	TD	AS vs. TD	PWS vs. TD	WS vs. TD	AS vs. PWS	PWS vs. WS	WS vs. AS	AS vs. TD	PWS vs. TD	WS vs. TD	AS vs. PWS	PWS vs. WS	WS vs. AS
	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)
Total Raw Score ^b	0.36 ^h (0.13)	0.59 (0.16)	0.79 (0.14)	0.56 (0.10)	-27.97 (2.23)	-11.51 (2.47)	-14.62 (2.21)	-16.46 (2.73)	3.11 (2.71)	13.35 (2.49)	-0.20 (0.16)	0.04 (0.19)	0.23 (0.17)	-0.24 (0.21)	-0.19 (0.22)	0.43 ^h (0.20)
Social Raw Score ^c	0.16 ^h (0.07)	0.18 ^h (0.08)	0.31 (0.07)	0.18 (0.05)	-10.99 (1.11)	-4.94 (1.21)	-5.87 (1.11)	-6.05 (1.34)	0.93 (1.33)	5.12 (1.25)	-0.02 (0.08)	0.00 (0.09)	0.14 (0.09)	-0.02 (0.10)	-0.14 (0.10)	0.15 (0.10)
Speech Raw Score ^d	0.06 (0.04)	0.15 (0.05)	0.23 (0.04)	0.19 (0.03)	-8.71 (0.64)	-3.76 (0.72)	-3.68 (0.64)	-4.94 (0.79)	-0.08 ^h (0.79)	5.02 (0.72)	-0.13 (0.05)	-0.04 (0.05)	0.04 (0.05)	-0.09 (0.06)	-0.08 (0.06)	0.17 (0.06)
Symbolic Raw Score ^e	0.14 (0.04)	0.24 (0.05)	0.24 (0.05)	0.19 (0.03)	-8.34 (0.72)	-3.04 (0.78)	-5.04 (0.71)	-5.29 (0.86)	2.00 (0.86)	3.30 (0.81)	-0.05 (0.05)	0.05 (0.06)	0.05 (0.06)	-0.10 (0.06)	0.00 (0.07)	0.10 (0.06)
Total Standard Score ^f	-0.08 (0.75)	0.44 (0.46)	0.00 (0.59)	1.58 (0.39)	-36.70 (3.54)	-22.20 (3.54)	-30.39 (3.53)	-14.51 (4.11)	8.19 ^h (4.10)	6.32 (4.10)	-1.66 (0.85)	-1.14 (0.60)	-1.58 ^h (0.71)	-0.52 (0.88)	0.44 (0.75)	0.08 (0.96)
Social Standard Score ^g	-0.10 (0.19)	0.15 (0.12)	-0.02 (0.15)	0.23 ^h (0.19)	-7.12 (0.89)	-3.32 (0.89)	-5.73 (0.89)	-3.80 (1.04)	2.41 ^h (1.03)	1.38 (1.04)	-0.32 (0.21)	-0.08 (0.15)	-0.25 (0.18)	-0.24 (0.22)	0.17 (0.19)	0.07 (0.24)
Speech Standard Score ^g	-0.05 (0.20)	-0.09 (0.12)	0.00 (0.15)	0.26 ^h (0.10)	-7.27 (0.92)	-4.12 (0.92)	-4.67 (0.91)	-3.15 (1.06)	0.55 (1.06)	2.60 ^h (1.06)	-0.31 (0.22)	-0.3511 (0.16)	-0.26 (0.18)	0.04 (0.23)	-0.09 (0.19)	0.05 (0.25)
Symbolic Standard Score ^g	-0.04 (0.14)	0.07 (0.09)	-0.21 (0.11)	0.35 (0.07)	-8.15 (0.66)	-4.40 (0.66)	-6.53 (0.66)	-3.75 (0.76)	2.13 ^h (0.76)	1.62 (0.76)	-0.39 ^h (0.16)	-0.2811 (0.11)	-0.56 (0.13)	-0.11 (0.16)	0.29 ^h (0.14)	-0.17 (0.18)

Note. **Bolded values** indicate significant findings after correcting for multiple comparisons.

^aCoefficients represent difference of scores of the first group listed scores from scores of the second group listed.

^bRange for CSBS-ITC Total Raw Score is 0–57.

^cRange for CSBS-ITC Social Composite Raw Score is 0–26.

^dRange for CSBS-ITC Speech Composite Raw Score is 0–14.

^eRange for CSBS-ITC Symbolic Composite Raw Score is 0–17.

^fRange for CSBS-ITC Total Standard Score is 65–135.

^gRange for CSBS-ITC Composite Scaled Scores is 3–17.

^hValue becomes non-significant when using the Holm-Bonferroni Sequential Correction.

Table 5.

Regressions of Time Interval and Group onto Change in CSBS-ITC Raw Scores

	Intercept				Group ^a							
	AS	PWS	WS	TD	AS vs. TD	PWS vs. TD	WS vs. TD	AS vs. TD	PWS vs. WS	WS vs. AS		
	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)	β (SE)		
Total Raw Score ^b	3.51 (2.25)	7.61 (1.75)	9.54 (1.79)	8.01 (1.18)	-4.50 (2.51)	-0.40 (2.08)	1.54 (2.07)	-4.10 (2.82)	-1.94 (2.44)	6.03 (2.81) ^f		
Social Raw Score ^c	1.63 (1.04)	2.61 (0.88)	3.35 (0.91)	3.31 (0.60)	-1.68 (1.19)	-0.70 (1.05)	0.04 (1.05)	-0.97 (1.35)	-0.74 (1.22)	1.71 (1.34)		
Speech Raw Score ^d	0.59 (0.65)	1.96 (0.55)	3.03 (0.55)	1.89 (0.35)	-1.30 (0.73)	0.07 (0.64)	1.14 (0.63)	-1.38 (0.84)	-1.07 (0.76)	2.45 (0.83)		
Symbolic Raw Score ^e	1.02 (0.77)	2.83 (0.61)	3.00 (0.61)	2.70 (0.41)	-1.69 (0.86)	0.12 (0.72)	0.30 (0.71)	-1.81 (0.97)	-0.17 (0.84)	1.98 (0.96) ^f		

Note. **Bolded values** indicate significant findings after correcting for multiple comparisons.

^a Coefficients represent difference of scores of the first group listed scores from scores of the second group listed.

^b Range for CSBS-ITC Total Raw Score is 0–57.

^c Range for CSBS-ITC Social Composite Raw Score is 0–26.

^d Range for CSBS-ITC Speech Composite Raw Score is 0–14.

^e Range for CSBS-ITC Symbolic Composite Raw Score is 0–17.

^f Value becomes non-significant when using the Holm-Bonferroni Sequential Correction.