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Illuminating the neglected end of the spectrum: Identifying subgroups of minimally verbal children with ASD and their differential response to intervention

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Illuminating the neglected end of the spectrum:

Identifying subgroups of minimally verbal children with ASD and their differential response to intervention

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Education

by

Maria Santina Pizzano

2020

ABSTRACT OF THE DISSERTATION

Illuminating the neglected end of the spectrum:

Identifying subgroups of minimally verbal children with ASD and their differential response to intervention

by

Maria Santina Pizzano

Doctor of Philosophy in Education

University of California, Los Angeles, 2020

Professor Connie L. Kasari, Chair

The past thirty years have seen a proliferation in intervention development and testing for autism spectrum disorders (ASD). As a result, there are evidence-based approaches effective at improving the lives of individuals with ASD and their families. However, these approaches frequently have small effects, largely due to the wide heterogeneity that is characteristic of ASD. As those with ASD have a range of cognitive, social, and language characteristics, one-size-fits-all intervention approaches may not best meet the varied needs of this population. Additionally, little intervention research has included or focused on those most in need of effective interventions: those with little to no language. The present examination consists of three studies with the overall aim to characterize heterogeneity in minimally verbal children with ASD and determine whether response to naturalistic versus structured interventions are different depending on child profile. This aim was achieved via secondary data analysis of three separate minimally verbal intervention samples. All included participants had 30 different words or less but in one sample were school-age and received intervention (naturalistic v. structured) for 6 weeks and in another study were preschool-age and received intervention (naturalistic v. structured) for 6 months. Subgroup profiles identified in Study 1 were used as predictors of intervention response in Studies 2 and 3. Results suggest that minimally verbal children with ASD are heterogeneous and can be characterized based on nonverbal versus verbal measures into subgroups, with patterns that emerge in preschool and persist through early childhood. Furthermore, profile subgroups are suggested to account for much of the variability in response to intervention. In particular, having one word on a naturalistic language sample at entry made a difference in subgroup by intervention interactions. For some of the language outcomes, subgroup by intervention interactions suggest that, at least initially, a more structured intervention approach may be more beneficial for those participants with at least one word and the lowest nonverbal and verbal scores across measures while those children with higher scores across measures may benefit from a more naturalistic approach. Implications for future interventions and details are discussed.

The dissertation of Maria Santina Pizzano is approved.

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2020

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Pizzano, M., Shire, S., & Kasari, C. Creating a simple fidelity tool for implementation of autism intervention in the community. Poster presented at the University of California Center for Research in Special Education, Disabilities, & Developmental Risk (SPEDDR) Conference, Davis, CA, January 2019.

Pizzano, M., & Kasari, C. Parent perspectives of a parent-teacher communication app after use in a classroom for preschoolers with ASD. Poster presented at the International Society for Autism Research (INSAR) Conference, Rotterdam, Netherlands, May 2018.

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PREFACE

Autism spectrum disorder (ASD) affects 1 in 54 individuals, nearly 2% of the population, and emerges in early childhood (CDC, Maenner, Shaw, & Baio, 2020). Characterized by challenges in social communication and increased repetitive behavior (American Psychological Association, 2014), early signs of ASD can be reliably detected as early as age 2 with noticeable differences from typical development such as lack of eye contact, reduced orienting to name, and delayed emergence of vocalizations (Landa, Holman, & Garret-Mayer, 2007).

ASD is referred to as a spectrum due to wide variability in phenotype (Lombroso, et al., 2009). Cognitive levels range from far above average, as is the case in savants, to far below average, as is the case in those with severe intellectual disability (Rimland, 1978; Matson & Shoemaker, 2009). Verbal language ability also ranges from being indistinguishable from typically developing individuals to having fewer than five spoken words (Tager-Flusberg, Paul, & Lord, 2005; Lord, et al., 2006).

ASD carries economic and personal repercussions as well. A conservative estimate of the economic costs of an individual with ASD is $3.2 million over the course of a lifetime (Ganz, 2007). Parents of children with ASD have noted that it affects their personal well-being in the areas of work, marriage, feelings of social isolation, stigma, and guilt (Myers, Mackintosh, & Goin-Kochel, 2009; Kuhlthau, 2014). Considering the heterogeneity and impact of ASD as well as the importance of language, it is imperative to ensure that interventions are meeting the varied needs of each individual with ASD, to optimize their opportunity to develop spoken language and achieve an optimal outcome, or the "best possible outcome considering a child's history" (Costello & Maughan 2015, Georgiades & Kasari, 2018).

1. Introduction

1.1. Interventions for ASD: Where are we after 30 years of research?

Many interventions have been developed over the last thirty years to improve the lives of individuals and families affected by ASD, with an increase in rigorous design methods across the last decade. A recent review of all randomized controlled trials (RCTs) testing intervention for children under 6 with ASD identified a total of 48 that have been published, with 40 published since 2010 (French & Kennedy, 2018). Of these 48 RCTs, no less than 32 different intervention models were used. Additionally, 27 evidence-based practices could be identified across interventions (Wong, et al., 2015). This represents a massive increase in variety of approaches since the initial intervention for children with ASD was developed by Ivar Lovaas in 1987, with little consensus about which approaches to apply at what time for what individuals. Intervention models tend to fall into one of two theoretical perspectives, though there are other models with independent origins.

Early Intensive Behavioral Intervention (EIBI). Intervention approaches target the core deficit of social communication in ASD differently. One approach is comprehensive, targeting a wide range of behavior and cognitive skills in addition to social communication. The most common comprehensive intervention package in the field of ASD is referred to as Early Intensive Behavioral Intervention (EIBI), and draws largely from the work pioneered by Ivar Lovaas (1987). Lovaas used a method of intervention referred to as discrete trial teaching (DTT). DTT is based on the science of applied behavior analysis (ABA) and uses the repeated delivery of a stimulus-response-consequence to the child to teach specific skills. Discrete trials are based in Skinner's operant conditioning theory, and include methods of shaping, chaining, discrimination training, and establishing contingencies. While ABA refers to an umbrella of strategies used to individualize instruction based on principles of behavior theory, DTT is probably the most common and widely accepted method of ABA. EIBI is the closest to being the standard of intervention in the community setting and is often the most commonly recommended method of intervention for individuals with ASD (NRC, 2001). A 2010 review found that EIBI interventions delivered to preschool-aged children for at least 20 hours per week effectively improved children's developmental outcomes (Virues-Ortega, 2010). While comprehensive intervention programs are appealing given the broad developmental needs of children with ASD, current models are limited to positive effects on overall cognition, with unknown or limited effects on social communication, and unknown or limited information about their effect on those who are minimally verbal.

Naturalistic Developmental Behavioral Intervention (NDBI). Another method for targeting skills in individuals with ASD is via a more natural, developmentally informed approach. NDBI refers to interventions that are implemented in natural contexts, are more child versus adult centered, use natural reinforcements, create naturally occurring learning opportunities, and target developmentally anchored skills in an appropriate sequence. NDBIs have some overlap with ABA methods in using a number of behavioral strategies, in particular to manage child behavior. The goal of these interventions is to reduce prompt dependence, promote motivating exchanges, ensure generalization of skills, and teach meaningful and relevant language. Several NDBIs were derived primarily from principles of ABA (e.g., Pivotal Response Training (PRT), Koegel, O'Dell, & Koegel, 1987) and others from developmental principles (e.g., Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER), Kasari, Freeman, & Paparella, 2006), but all models use a mixture of strategies combining developmental and behavioral theories. Although some NDBIs can be considered comprehensive packages (e.g., PRT), most are research tested as targeted interventions.

Recent reviews have examined the landscape of interventions for children with ASD and concluded that treatments that are found to offer significant benefits have only small effects (French & Kennedy, 2018). On average, children with ASD have increases in spoken language following early intervention with no differential effect of comprehensive versus targeted treatment approach (Hampton & Kaiser, 2016). Anywhere from 30-50% of children with ASD continue to enter school without fluent language and show impairments in core deficits (social communication and restricted, repetitive behaviors (RRBs)) (Anderson et al, 2007), so there continues to be room for innovation in intervention design and analysis. Autism intervention research, having established the effectiveness of early individualized programs, needs to begin to develop personalized courses of intervention to address the heterogeneous needs of the spectrum.

1.2. Tailoring Treatment: Toward a personalized approach to intervention for ASD

Personalized approaches to intervention address heterogeneity to optimize effectiveness for all individuals. This idea comes from the framework of personalized, or precision, medicine. Rather than treat a disorder uniformly with a single approach for all patients, treatment is tailored to an individual's specific presentation of a disorder (Jameson & Longo, 2015; Collins & Vermus, 2015). It is a growing trend in the biological sciences and medical field that has only recently been applied to mental health disorders and ASD (Almirall & Chronis-Tuscano, 2016). In the medical field, personalized medicine began with advances in genomics that allowed treatment to be matched with a patient's genome (Okimoto & Bivona, 2014; Dawood & Broglio, 2010). The approach made its way to psychological therapy, where some work has been done to tailor modular treatment programs to a patient's individual phenotype (e.g. Weisz, et al., 2012). Autism intervention approaches have not yet bridged the gap between studies that determine intervention effectiveness and studies that determine which interventions work best for certain individuals. The Interagency Autism Coordinating Committee (IACC) 2013 strategic plan for ASD notes the importance of moving toward a personalized approach to intervention and calls for additional research in this area (IACC, 2013). To begin to personalize intervention for those with ASD, it is necessary to understand predictors of response, mediators and moderators of intervention, and identification of subgroups.

Heterogeneity. Heterogeneity is a well-established aspect of ASD that affects intervention outcome but remains inadequately addressed in intervention development (Howlin, Magiati, & Charman, 2009; Fernell & Gillberg, 2010). Multiple systematic reviews have noted heterogeneity in response to intervention as a limitation that makes it difficult to draw conclusions about an intervention's effectiveness (e.g. French & Kennedy, 2018; Zwaigenbaum, et al., 2015). Community providers recognize heterogeneity in intervention response and as a result do not choose just one intervention but use a combination of evidence-based and non-evidence-based interventions in unique ways (Stahmer, Collings, & Palinkas, 2005). Across all evidence-based approaches, 50% of children make substantial gains while 50% make variable or limited progress (Stahmer, Schreibman, & Cunningham, 2011).

Such variability in response is likely due to individual differences. Individual differences within ASD have been characterized based on personality, neurocognitive profile, symptom severity, cognitive scores, verbal ability, joint attention skills, and peer engagement, but these characterizations are not yet systematically organized (Tager- Flusberg & Joseph, 2003;

Schwartzman, Wood, & Kapp, 2016; Georgiades, et al., 2013; Scherer & Schreibman, 2005; Anderson et al., 2007; Shih et al., 2016).

Predictors of Outcome. Predictors of outcome and responses to intervention are just beginning to be investigated for children with ASD. When it comes to intervention response, having few spoken words, low social motivation, and less joint attention initiation is linked to a decreased response to intervention, independent of IQ scores (Kasari et al., 2008; Bopp et al., 2009). Sherer & Schreibman (2005) found that response to PRT may be related to higher levels of toy play and lower levels of avoidance. A follow-up found that improving toy play can lead to an improved PRT response (Schreibman, Stahmer, Barlett, & Dufek, 2009). Other investigations have shown improved treatment response with higher IQ at entry, stronger language and social communication ability, adaptive skills, and younger age at entry (Eldevik, et al., 2006; Sallows & Graupner, 2005; Flanagan, et al., 2012).

Other groups have found some inconsistencies in predictors of response to intervention, particularly that higher autism severity may lead to greater response (Remington, et al., 2007), or that those with lower severity may actually have greater response to intervention (Makrygianni & Reed, 2010). These analyses are in comparison to a waitlist or treatment as usual control, as few studies have been reported that compare two different interventions to each other. However, two studies have reported on predictors of response when comparing active interventions: Yoder & Stone (2006) compared a picture exchange system (PECS) to a play-based language intervention (RPMT), and Paul, et al. (2013) compared two language interventions, a naturalistic approach and a discrete trial approach. In the PECS versus play-based intervention comparison, those who entered with more joint attention initiations improved more in generalizing joint attention initiations in the play-based intervention, while those with less joint attention gained greater requesting ability in the PECS intervention. In the naturalistic versus discrete trial language intervention comparison, those who entered with higher receptive language skills did better in the naturalistic intervention and those with lower receptive language skills did better with the discrete trial approach for number of parent reported words. These studies suggest that treatment approach may matter for children with varying characteristics.

The majority of investigations into predictors of outcome are related to language development. For typically developing children, those who use more joint attention skills gain language faster (Tomasello and Farrar, 1986). Similarly for children with ASD, response to joint attention and initiation of joint attention lead to the development of expressive language (Anderson, et al., 2007; Sigman & McGovern, 2005, Kasari, Paparella, Freeman, & Jahromi, 2008; Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012). Joint engagement differences in children with ASD also predict verbal language differences (Adamson, Bakeman, Deckner, & Romski, 2009). In addition, starting consonant inventory, motor imitation, and adaptive behavior are all linked to later language development (Yoder, Watson, & Lambert, 2015). Receptive language has been linked to receptive vocabulary, ASD severity, general cognitive level, joint attention, and nonverbal cognition (Yoder, Watson, & Lambert, 2015; Sigman & McGovern, 2005; Charman, et al., 2003; Luyster, Kadlec, Carter, & Tager-Flusberg, 2008). These are all important considerations and contributions, but the result is a cluttered landscape of potential individual predictors across multiple domains of development.

Identification of Subgroups. One solution that simplifies the web of singular predictors is to classify individuals into subgroups based on shared characteristics that may have a common response to intervention or a similar developmental trajectory. This idea has been previously applied to the autism spectrum and other neurodevelopmental disorders and provides a promising step towards creating personalized treatment approaches for individuals with ASD. Subgroups have been identified both by cluster analysis and latent class or profile analysis. Cluster analysis (e.g. Hartigan & Wong, 1979), is a data-driven approach that divides individual subjects into subgroups, where individuals are more similar to each other than to those in other subgroups. Individuals are categorized based on scores on multiple measures and clustering can therefore be used to identify subgroups within a heterogeneous sample. Various approaches exist for identification of clinically relevant subgroups within a sample of participants. Some commonly used approaches for cluster identification are hierarchial clustering, partitioning clustering, and latent variable mixture modeling (LVMM).

Partitioning clustering divides a sample into k groups, with k being the number of groups as determined by the researcher. Groups can be determined by the mean value of all data points in a cluster (K-Means Clustering) or by a single data point in the center of the cluster that has minimal dissimilarity with the other cluster data points (K-Medoid Clustering). Schwartzman, Wood, & Kapp (2015) applied K-means clustering with a group of 828 adults to reveal four subtypes within the five factor model of personality. Williams, Gulsrud, & Kasari (2018) also applied K-means cluster analysis, but in the context of a parent-mediated intervention for children with ASD.

Hierarchial clustering creates clusters also distinguished by similarity within versus between clusters but a key difference is the aim to create clusters that have a predetermined order. The clusters are created in a tree to create a meaningful taxonomy. Stevens, et al., (2000) applied a hierarchical cluster analysis approach to identify subgroups based on their cognitive function, social ability, and ASD severity scores in a group of 138 school-age children with

ASD. Results revealed two subgroups, one with scores consistently in the typical range and another with scores consistently below average.

Latent variable mixture modeling uses observed measures to identify groups based on latent characteristics (Oberski, 2016). Latent Profile Analysis (LPA) is used when the observed measures are continuous, while Latent Class Analysis (LCA) is used when the observed measures are categorical. LCA has been used, for example, to characterize baby siblings of children with ASD to identify subgroups (Landa, Gross, Stuart, & Bauman, 2012). The LCA identified four distinct classes with varying trajectories based on latent differences in cognitive profile. In this example, domains on the MSEL were used to identify classes with the outcome of diagnostic classification used to mark developmental trajectory. Four classes were identified, one representing accelerated development without ASD classification, one with normative development, one with delay in some of the subscales, and one with delay across all subscales.

Each of these clustering approaches has advantages and disadvantages, requiring the satisfaction of various assumptions. Partitioning clustering assumes that there are k clusters, variables have equal variance, clusters are grouped in spheres, and clusters are similar in size. Partitioning clustering cannot handle missing data and additional decisions must be made when data is missing. This type of clustering requires considerable experimenter decision-making and the resulting model may be overfit to a sample without any generalizability. Hierarchial clustering also assumes that variables have equal variance and also cannot handle missing data, with no unique assumptions. LPA identifies profiles without the assumption that subgroups exist and does so in a more rigorous and objective manner (Meyer, Stanley, & Vandenberg, 2013).

Application of these clustering methods is crucial to begin to understand heterogeneity in the autism spectrum and differential response to intervention. In 2001, NRC recommendations for ASD research included a recommendation for more investigation into personalization of intervention by identifying sub categories within the ASD spectrum, isolating specific strategies of interventions for specific aspects of ASD, and adequately comparing different interventions to combine them into a personalized program. The present study aims to begin to fill this gap for minimally verbal children with ASD.

1.3. Heterogeneity and minimally verbal children: More than just a label

Minimally verbal children with ASD exhibit a wide range of heterogeneity and do not share a single set of defining characteristics (Tager-Flusberg & Kasari, 2013), though less is known about this group due to continued exclusion from research studies (Dawson, et al., 2010; Russell, et al., 2019; Jack & Pelphrey, 2017). Assessing this group can pose additional challenges and there is no consensus about which measures to use (Tager-Flusberg & Kasari, 2013). A meta-analysis of all research published in 2016 identified a total of 100,245 participants across 301 studies, of which 94% reported no intellectual disability (Russell, et al., 2019). This lack of inclusion and relative lack of information points to the need for a focus on this group in autism research and is a reason that their development and response to intervention was highlighted in the IACC 2011 strategic plan (Tager-Flusberg & Kasari, 2013).

Nearly 30-50% of preverbal preschoolers with ASD are still only minimally verbal at six years of age, defined as using no more than 20 functional spontaneous words (NIH workshop, 2010). Having even one word prior to intervention is a predictor of treatment response, and verbal speech by age five is predictive of child adaptive functioning. As a result, the IACC identified a goal of ensuring that 90% of children with ASD have speech by school age (Stahmer, Schreibman, & Cunningham, 2011; IACC, 2011). There is an urgent need to focus on improving language as it is a powerful predictor of child outcomes and a critical component to developing independence later in life (Howlin, Mawhood, & Rutter, 2000).

This group also has variability in cognitive skill. Though they may share the common characteristic of limited expressive language compared to the typical population, the amount of functional words in the minimally verbal definition varies from less than 20 (Yoder & Stone, 2006) to fewer than five (Kasari, Paparella, Freeman, & Jahromi, 2008), to zero (Koegel, Shirotova, & Koegel, 2009). Additionally, while some have receptive language scores on par with their expressive language scores, others have receptive language scores that are higher than their expressive language scores (Skwerer, Jordan, Brukilacchio, & Tager-Flusberg, 2016; Rapin, Dunn, Allen, Stevens, & Fein, 2009). Their nonverbal cognitive level does not necessarily correlate with their low verbal cognitive level, as some have higher nonverbal cognition (NVIQ) than their expressive language may suggest, and some have cognitive abilities in the average range of intelligence (Bal, Katz, Bishop, & Krasileva, 2016; Munson, et al., 2008).

1.4. Aims

Heterogeneity within ASD is currently poorly characterized and even less is known about variability within the minimally verbal group. Gaining language is of utmost concern for these individuals, but not enough information is known about which interventions work best for who to ensure that all are able to attain functional spoken language. Moving from a one-treatment-for-all approach to an individualized approach is essential to meet the varied needs of this group and to give each individual the best opportunity to develop functional spoken language.

This dissertation is among the first to identify subgroups within a sample of minimally verbal children and relate heterogeneity in the sample to differential response to interventions targeting language and social communication outcomes. This goal is accomplished through three studies:

Study 1: Identify subgroups in a population of minimally verbal children with ASD, determined by cognition, ASD severity, adaptive behavior, receptive language, and play skills.

Study 2: Determine whether there is differential subgroup improvement in school-aged minimally verbal children with ASD for language and precursors to language in 6-week response to NDBI intervention (JASPER) versus an EIBI intervention (DTT).

Study 3: Determine whether there is differential subgroup improvement in preschool-aged minimally verbal children in language and precursors to spoken language- joint engagement, initiations of joint attention, and clinical ratings of improvement- in 6 month response to NDBI (JASPER) versus EIBI (DTT) interventions.

2. STUDY 1: Characterizing heterogeneity across early childhood in minimally verbal children with ASD

2.1 Aims

Study 1 presents a characterization of minimally verbal children with ASD, from preschool through early childhood. This is accomplished through examination of three separate samples of minimally verbal participants.

Aim 1- Identify subgroups in a sample of minimally verbal school-age children with ASD age 5-8.

Aim 2- Replicate subgroups within a separate minimally verbal school-age 5-8 sample, drawn from a different participant pool.

Aim 3- Identify subgroups in a preschool-aged sample of minimally verbal children with ASD age 2-5.

2.2 Method

Participants

Participants from three different randomized, controlled trial (RCT) projects comprise the sample of the current analysis. All three projects focused on exclusively minimally verbal children with ASD. The samples will be referred to as Sample 1, Sample 2, and Sample 3, with all data from the entry timepoint of each project. All projects had inclusion criteria to confirm diagnosis via the ADOS and enrollment in current or prior interventions. All projects also had exclusion criteria of major medical conditions, sensory or motor disabilities, and uncontrolled seizures. Samples will not be combined for analyses; rather each research question of the current investigation will address a distinct sample.

Sample 1 includes 193 children aged 5-8 years who expressed less than 30 spontaneous words on a natural language sample and nonverbal cognitive age equivalent of at least 12 months as measured by the Mullen Scales of Early Learning (MSEL, Mullen, 1997) or the Leiter International Performance Scale (Leiter-R; Roid & Millet, 1997) Sample 1 was recruited from local public schools near four different research centers. Sample 2 includes 49 children recruited from the community near three major research centers. Participants in Sample 2 were 5-8 years old and expressed less than 30 spontaneous words on a natural language sample and had a receptive language age equivalent of at least 24 months on two of three potential assessments- the Test of Early Language Development- Third Edition (TELD-3, Hreske, Wayne, Rein, & Hammill, 1999), Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4; Dunn & Dunn, 2007), or Leiter (Kasari, et al., 2014). Sample 3 includes 164 children aged 33-58 months who expressed less than 30 spontaneous words on a natural language sample and exhibited nonverbal cognitive age equivalent of at least 12 months as measured by the visual reception or receptive language scales on the MSEL. Sample 3 participants were recruited through local public schools near 3 different research centers.

Baseline data was used to address all three Study 1 aims. Aim 1 was addressed using Sample 1. Aim 2 was addressed using Sample 2. Aim 3 was addressed using Sample 3.

Measures

A breakdown of assessments and variables used for subgroup profiles can be found in Table 1-1. Clustering variables were all from baseline assessments. Assessments were conducted by research personnel blind to treatment condition and timepoint.

Participant Characteristics. A demographic questionnaire was used to obtain descriptive information about child and family characteristics. Demographic information pertaining to household income, parent education, and child age were used to characterize the samples.

Profile Assessments

*Autism Diagnostic Observation Scales (*ADOS; Lord, et al., 2012). The ADOS is a semi-structured observational assessment used in the present analysis for the purpose of eligibility and as a profile identification variable. Multiple modules are available and the administrator chooses the appropriate module based on child language level. For this population, a Module 1- designed for nonverbal or single-word communication- was administered. A standard set of materials and probes are used to observe a child's social behavior, communication, and repetitive behavior. These observations are translated to scores and are used to determine whether the behaviors are significant enough to warrant an autism classification based on established cutoffs. All samples had ADOS data at baseline. ADOS scores are categorized into two domains- social affect and restricted and repetitive behavior. Social affect and restricted and repetitive behavior scores are combined for an overall score. The social affect and restricted and repetitive behavior scores were used as subgroup identification variables in all analyses.

Vineland Adaptive Behavior Scales, 2nd edition (VABS-II; Sparrow, et al., 2005). The VABS-II is an interview conducted by a research professional with a parent or caregiver. The interview spans a wide range of domains, yielding both an overall score and scores for the domains of daily living skills, communication, and socialization. All samples had VABS-II data at baseline. These scores can be converted into standard scores and age equivalents. The total raw score for the subdomain of daily living was used as a subgroup clustering variable in all analyses.

Mullen Scales of Early Learning (MSEL; Mullen, 1997). The MSEL is a standardized test of visual reception, fine motor, gross motor, expressive language, and receptive language skills in infants and young children. MSEL scores are translated into age equivalents for each of these areas. In Samples 1 and 3, the MSEL was administered before randomization by blind, trained assessors and scaled mental age equivalent scores were used for eligibility to establish a child's mental age as being equal to or greater than 12 months. MSEL baseline data was gathered for Sample 1 (Aim 1) and Sample 3 (Aim 3). Visual reception and fine motor age equivalents were averaged to yield a nonverbal cognition age equivalent that was used for profile identification, as in Bishop, Guthrie, Coffing, & Lord (2011).

Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4; Dunn & Dunn, 2007). The PPVT-4 tests receptive language ability in children two years of age and older. Children are shown an array of four images and directed to select the image that corresponds to the instructor's spoken word. The PPVT-4 was used to measure receptive language ability at baseline in Samples 1 and 2. PPVT-4 raw scores were used as a profile identification variable in the Aim 1 and Aim 2 analyses.

Leiter International Performance Scale-Revised (Leiter-R; Roid & Millet, 1997). The Leiter-R is a nonverbal cognitive assessment that yields a nonverbal IQ score and age equivalent for individuals between the ages of 2 and 20 years. The Leiter-R was used to measure nonverbal cognitive ability at baseline in Sample 1 and Sample 2. Age equivalents were used as a clustering variable in Aim 1 and Aim 2 analyses.

Symbolic Play Assessment (SPA; Kasari, et al., 2006; Ungerer and Sigman, 1981). The SPA is a structured, naturalistic play-based assessment that lasts approximately 10-20 minutes. Administered by a treatment- and timepoint- blind examiner, the assessment consists of five standard sets of toys intended to encourage the child to play spontaneously. The assessor does not prompt the child to play in any way but presents the toy sets individually and allows the child to fully explore each item in the play set until it becomes clear that the child will not exhibit any new play acts. The videotaped assessment is then coded by a blinded team member for number and level of play acts. Total number of different play levels exhibited is summed to yield a functional play diversity variable. Functional play diversity is a clustering variable for Aim 1, 2, and 3 analyses.

Early Social Communication Scales (ESCS; Mundy, et al., 2003). The ESCS is a structured, videotaped play-based assessment. The assessor administers the assessment with a standard set of toys and with a standard set of opportunities for the child to exhibit social communication. The assessment lasts 15-20 minutes and is administered by a blinded staff member trained to above 80% fidelity. Total initiations of joint attention (IJA) and total initiations of behavior regulation (IBR) were used as profile indicator variables for Aim 1, 2, and 3.

Parent-Child Interaction (PCX; Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015). The PCX is a taped parent-child interaction. All participants are given a standard set of toys and instructed to play as they typically would for 10 minutes. For Sample 3, in Aim 3, the PCX was used to transcribe the child verbal language variables SCU and NDWR.

Coded Variables

All coding was completed by trained research staff and graduate students blind to treatment condition and timepoint. Coders were trained to reach reliability of 0.8 or higher via intraclass correlation analyses. Table 1-2 provides further reliability details.

Spontaneous Communicative Utterances (SCU; Kasari, et al., 2014). SCU refers to comments, requests, and other language that the child initiates spontaneously. SCU is derived from transcripts of the NLS (Samples 1 and 2/Aims 1 and 2) or the PCX (Sample 3/Aim 3). Treatment and timepoint-blind research study staff transcribed the videos using Systematic Analysis of Language Transcripts (SALT) conventions. Blinded raters coded and verified the transcripts to note whether each child utterance was spontaneous rather than scripted or prompted and whether the utterance functioned to comment, request, or serve another purpose. Raters are trained to a reliability above 80% as measured by intraclass correlation coefficients. Spontaneous utterances of all types are included in SCU. For Sample 3 (Aim 3), SCU was coded from the PCX. Raters were trained to transcribe the PCX to reach fidelity in both transcription and transcription coding. A reliable transcriber viewed each transcript a second time to verify the transcription and codes. The average ICC for coding the transcripts was 0.98 (range 0.96-0.99).

For Samples 1 and 2 (Aim 1 and 2), SCU was coded from the NLS. SCU is a subgroup identification variable in all aims.

Number of Different Word Roots (NDWR; Kasari, et al., 2014). NDWR refers to the number of unique words used by a child in either the NLS (Aims 1 and 2) or PCX (Aim 3). It is coded with SCU from transcripts according to the same conventions. NDWR is used in Aim 1, 2, and 3 as a profile identification variable.

Initiations of Joint Attention (IJA; Mundy, et al., 2003). IJA is coded from the ESCS videotapes. IJA refers to verbal and nonverbal spontaneous child communication to share with their social partner (IJA) For this study, total IJA frequencies were used as a profile identification variable for all three aims.

Initiations of Behavioral Requests (IBR; Mundy, et al., 2003). Coded according to the same conventions as IJA, total frequency of IBR refers to spontaneous verbal and nonverbal initiations of requests and was used in the present analysis to classify profiles in all three aims.

Functional Play Diversity (FPD; Chang, et al., 2016). The SPA is coded by blinded raters for functional, spontaneous play acts across and within play level. Raters maintain a reliability rate of 80% or higher as measured by intraclass correlation coefficients. FPD refers to the number of different functional play acts with toys within the same play level and across play levels. Play develops in increasingly complex sequential levels beginning with indiscriminate and culminating in thematic play (Lifter & Bloom, 1989). Each play level refers to a specific cognitive skill related to objects and play. FPD, a secondary outcome variable in the present analysis, captures a child's complexity of play as it refers to skill at playing across multiple levels and flexibility within a play level to engage in a variety of play acts (Chang, et al., 2016). FPD is used as a clustering variable for all Aim 1, 2 and 3 analyses.

Analysis

Identification of profile variables. Profile indicator variables were determined from previous literature that indicated powerful predictors of outcome. Potential profile variables were evaluated for latent profile definition ability via descriptive analysis of distribution and range, and via entropy analysis within latent profile models. Variables were identified in Aim 1 and then used in Aim 2 in a replication analysis. The same variables were used again in Aim 3.

Identification of subgroups. Latent Profile Analysis (LPA) is a data-driven mixture modeling method that uses continuous observed measures to identify groups based on latent characteristics (Oberski, 2016). This method groups individuals within a larger sample who have similar symptom presentations into smaller homogeneous profile groups. Latent Class Analysis (LCA) is a similar approach that uses categorical observed measures to identify classes of similar individuals within a sample. LPA offers a way to group individuals with varying levels of symptom severity on various measures into homogeneous groups with within-group similarities on symptom severity as measured by a latent group factor. LPA was used to identify subgroups for all aims- Aims 1, 2, and 3. LPA analyses were conducted using latent variable modeling software included in the Mplus 8 software (Muthen & Muthen, 2016). Mplus allows the presence of missing at random data and uses all available data to estimate the model (Muthen, 2004). An additional consideration for the use of LPA in Mplus is that of nonnormality. The LPA model allows for nonnormal indicator variables and operates under the assumption that even in nonnormal or skewed data, smaller groups of normal distributions likely exist (Titterington, Smith, & Makov, 1985; Masyn, 2013). Within- profiles, the model therefore assumes that variable distribution is normal (Masyn, 2013; Muthen 2003).

Ferguson, Moore, & Hull (2019) provide a general procedure for conducting a LPA. Step one is data inspection for standard descriptives and cleaning. Step two is evaluation of a series of models that introduce one profile at a time with the same set of variables. This step starts with a single profile (or class) and ends with somewhere between 4-6 profiles (or classes) depending on the ability of the model to converge, increase in fit, and discriminate profiles with an n greater than 5% of the total sample. For step 3, models are examined via fit indices to determine the model best fit to the data. In step 4, the model results are interpreted by examining patterns of the model profiles. The final steps involve investigating the model further with covariates if indicated and disseminating the results. This procedure was followed in the present analysis to address all three aims.

Fit Indices. There are numerous fit indices for LPA available and there is no current consensus about using any single fit test to select the best model. Fit indices are used within models across different numbers of profiles to determine which best describes the data. Per Masyn (2013), a combination of statistical and theoretical fit indices was used in the current analysis to determine the model of best fit for each aim. The following commonly used fit indices were considered in the current study to aid in model selection: Adjusted Bayesian Information Criterion (ABIC), adjusted Lo-Mendell-Rubin Likelihood Ratio Test (LMR-LRT), the parametric bootstrapped likelihood ratio test (BLRT), the approximate Bayes Factor (BF), and the correct model probability (cmP).

Information Criteria (ICs). ICs can descriptively compare models across a set of classes/ profiles, and weigh model fit against model complexity (Masyn, 2013). Therefore, ICs penalize complexity. When compared across models, the IC with the lowest value is considered to have the relative best fit. There are multiple ICs, but Akaike’s Information Criterion (AIC), Bayesian

Information Criterion (BIC) and Adjusted Bayesian Information Criterion (ABIC) are the most common. Of these, AIC is widely considered to overestimate the number of classes/profiles (Nyland, et al., 2007; Tein, Coxe, & Cham, 2013). BIC, however, has been considered to be an IC that consistently identifies the correct number of classes/profiles (Nylund, et al., 2007), while the ABIC has more recently been identified as reliable, particularly with smaller sample sizes (Tein, Coxe, & Cham, 2013; Yang, 2006). Therefore, the IC considered for these analyses was the ABIC.

Likelihood ratio tests. These statistical tests provide a likelihood ratio-based method for testing *k*-1 classes/profiles against *k* classes/profiles. The LMR-LRT provides a p-value where a significantly low value indicates that the *k* -1 class/profile model is rejected in favor of the *k* class/profile model (Masyn, 2013). The BLRT is a similar test that also compares the *k* class/profile model to the *k*-1 class/profile model and also provides a p-value that, if significant, indicates rejection of the *k*-1 class/profile model. One examination found that across model types, BLRT was the most consistent indicator of appropriate number of classes/profiles (Nylund, Asparouhov, & Muthen, 2007). Likelihood ratio tests, unlike ICs, can only compare two models at a time. The LMR-LRT and the BLRT were both considered in judging model fit in the present analyses.

Bayesian fit indices. Where ICs and likelihood ratio tests provide information about which class/profile model within a set of models has the best fit to the data, Bayesian fit indices provide a measure of how much better one model may be compared to another within a set of models or across sets of models. The Bayes Factor (BF) compares relative fit between two models within a set of models in a pairwise fashion and represents the ratio of the probability of one model being correct to another model being correct (Masyn, 2013). A BF between 1 and 3 is considered weak evidence, between 3 and 20 is considered positive evidence, between 20 and 150 is considered strong evidence, and above 150 is considered very strong evidence (Raftery, 1995). The cmP also allows comparison within a set of models. The cmP is calculated for each model within a set and if the sum equals one, the correct model is assumed to be included in the set (Masyn, 2013). A cmP greater than 0.1 is considered to be evidence for a class/profile solution. Both the BF and the cmP will be used to determine the best fitting model in the present analyses.

Entropy. Entropy refers to the level of profile, or class, specification within the model. Entropy values range from 0-1 and those that approach 1 are considered to indicate a clear delineation of classes/profiles, with a value above 0.8 being desirable (Celeux & Soromenho, 1996). Entropy values will be used to evaluate model fit in the present analysis.

Posthoc comparisons. Tukey's posthoc comparisons with correction for multiple tests were used to determine significant relationships between profiles.

Missing Data. One challenge of assessing minimally verbal children is that they may fall between assessments in terms of their developmental age being discrepant with their cognitive age. Developmentally, the items appropriate for their ability may be on an assessment such as the MSEL that does not yield standard scores for older children. Another issue is that some may be able to score on a separate, more difficult assessment (such as the Leiter) while others cannot and a MSEL must be used instead. In the present examination this second case is true for the construct of nonverbal cognition in Sample 1, where nonverbal cognition was measured by either the Leiter-R or the MSEL with overlap in about 40 participants. This challenge of analyzing multiple measures for the same construct has been faced by other groups as well and no current consensus or perfect solution exists. Although application of a prediction model based on the overlap set was explored, it ultimately did not explain more than 80% of the variability and it resulted in 79% of participants having predicted nonverbal scores. A second option is to use age equivalencies in the model (e.g. Pickles, Anderson, & Lord, 2014). Although standard or raw scores are preferable (Kasari, Brady, Lord, & Tager-Flusberg, 2013; Maloney & Larrivee, 2007), using each participant's valid age equivalency offers a comparison across the measures and was used for nonverbal cognition in the present analyses.

The rest of the missing data was due to randomly missing assessments and forms. In a few cases, missing data was due to the participant dropping out of the study post-randomization. All randomized cases are included in profile analyses on an intent-to-treat basis.

2.3 Result

Participants

Participants were included in analyses on an intent-to treat basis, and all participants who were randomized to an intervention condition met the intent-to-treat requirement for analysis inclusion. A total of 403 participants were included across analyses. Sample 1, analyzed in Aim 1, included 193 participants. Sample 2, analyzed in Aim 2, included 49 participants, and Sample 3, analyzed in Aim 3, included 161 participants. Sample 2 NDWR at entry ranged from 0-65. This was much higher than Samples 1 and 3, which had participants with less than 30 NDWR, so those participants with over 30 NDWR at entry in Sample 2 were excluded from analyses. The final total number of participants in Sample 2 was 49. One outlier was present in Sample 1, having over 40 words, and was excluded from analyses to have a final sample of 193. Intent-to treat analysis continued as planned, with all other randomized participants included in analyses.

Participants completed demographic, diagnostic, cognitive, and language assessments at baseline. Samples 1 and 3 have similar NDWR, and nonverbal age equivalent at entry. In both samples, the majority of participants were not Caucasian. Sample 2 had overall higher NDWR (11.43 v. 5.5) and higher nonverbal language age equivalent (4 years vs. 2.3) but otherwise was similar in demographic profile and in overall ADOS score versus the other minimally verbal samples. Details of participant characteristics in all three studies are described in Table 1-3 below.

Sample 1: Minimally Verbal School-Aged Sample. The 193 Sample 1 participants had a mean age 6.05 years (*SD*= 1.34), and had a mean of 5.54 (*SD*= 6.45) different words on the NLS. Nonverbal age equivalent as measured by the Leiter or the MSEL was a mean of 2.33 years (*SD*= 0.5). This sample had an approximately 3:1 ratio of male to female participants, 79.3% (n= 153), as is consistent with the literature. Mean ADOS Module 1 total scores were 19.98 (*SD*= 3.64), with a social affect domain mean of 14.56 (*SD*=2.85) and restricted and repetitive behavior domain mean of 5.42 (*SD*=1.93). Caregivers were educated, with 74.9% (n=157) of mothers having some college, college degrees, or graduate degrees. 44.6% of participants were Caucasian while the other 56.4% were from ethnically diverse backgrounds.

Sample 2: Minimally Verbal School-Aged Replication Sample. The 49 Sample 2 participants had a mean age 6.07 years (*SD*= 1.07), and mean 11.43 (*SD*= 8.09) different words on the NLS. Nonverbal age equivalent as measured by the Leiter was a mean of 4.00 years (*SD*= 1.14). An approximately 3:1 ratio of male to female participants, 79.6% (n= 39), was present as is consistent with the literature. Mean ADOS Module 1 total scores were 20.45 (*SD*= 4.29), with a social affect domain mean of 14.73 (*SD*=3.54) and restricted and repetitive behavior domain mean of 5.71 (*SD*=1.83). Caregivers were educated, with 91.8% (n=45) of mothers having some college, college degrees, or graduate degrees. 48.9% of participants were Caucasian while the other 57.1% were from ethnically diverse backgrounds.

Sample 3: Minimally Verbal Preschool-Aged Sample. The 167 Sample 3 participants had a mean age 3.80 years (*SD*= 0.46), and mean 5.36 (*SD*= 8.13) different words on the NLS. Nonverbal age equivalent as measured by an average of the Visual Reception and Fine Motor scales of the MSEL was a mean of 2.07 years (*SD*= 0.06). An approximately 3:1 ratio of male to female participants, 83.0% (n= 142), was present as is consistent with the literature. Mean ADOS Module 1 total scores were 18.69 (*SD*= 4.27), with a social affect domain mean of 14.13 (*SD*=3.48) and restricted and repetitive behavior domain mean of 4.56 (*SD*=1.87). Caregivers were educated, with 69.6% (n=119) of mothers having some college, college degrees, or graduate degrees. 35.7% of participants were Caucasian, while the other 64.3% were from ethnically diverse backgrounds.

Latent Profile Analysis

All profile analyses were processed with 40 random starts and 2 final stage optimizations to ensure that a global maxima log likelihood value was reached and replicated. If it was not reached and replicated, the number of random starts was increased to 100. Models that included a profile number less than 5% of the sample, had increasing ABIC values, or a nonsignificant BLRT value were considered to be the maximum k profile model for the set of indicator variables.

Aim 1: Profiles in minimally verbal school-age sample.

Model Selection. The indicator variables of ADOS Social Affect score, ADOS Restricted and Repetitive Behavior Score, Daily Living Raw Score, SCU, NDWR, IJA, IBR, Raw PPVT score, Play Diversity-types, and Nonverbal age equivalent were determined to be the best theoretically and statistically driven indicators of variability in Sample 1. These indicators were used to create latent profile models with one through five profiles. Details for fit statistics across all five profiles are included in Table 1-4. Results from these models indicate that a four- profile model best fits the data. The ABIC value reduces until the four profile model and then increases at the five- profile model. The entropy value of 0.882 indicates good profile separation. The LMR-RLT value of 90.30 (p= 0.017) indicates that the 3- profile model should be rejected in favor of the 4- profile model. The BPLRT was significant (p= 0.000) in the 4- profile model, versus a nonsignificant value for the 5- profile model (p= 1.00). The BF value of the 4 versus 5- profile models indicates the 4- profile model to have a superior fit, with a BF well above 150 while the BF of the 5- profile model is 0.082. Lastly, the 5- factor model includes a profile with just 2 participants and this number is far below the 5% cutoff for a sample size of 193.

Subgroup Characteristics. Table 1-5 provides indicator means for each profile in the model, with Tukey posthoc comparisons presented in Table 1-6. with a graphical description presented in Figure 1-1. Additionally, participant characteristics by profile are presented in Table 1-7. The four identified subgroups are most distinctly identified by their pattern of scores across verbal indicators (SCU, NDWR, and IJA) versus nonverbal indicators (ADOS SA, ADOS RRB, VABS DL, PPVT, Play diversity, IBR). Profiles 1, 2, and 3 had similar ADOS and Daily Living score but those of Profile 4 were higher in severity on the ADOS by about 4 points and also had lower Daily Living scores. This difference on the ADOS is enough to likely distinguish between a moderate level of autism spectrum-related symptoms and a high level of autism spectrum symptoms. Profile 4 (n=85; 44.04%), those with the highest ADOS scores, also had the fewest verbal and nonverbal communication frequencies (on SCU, NDWR, and IJA) and the lowest scores on nonverbal cognition indicators (PPVT, Play Diversity, and NVAE). IBR scores, although they are indicative of verbal and nonverbal communication, had the same pattern as the nonverbal indicators across groups. This subgroup represents those in the sample who are most impacted across both verbal and nonverbal skills. Subgroup A (n=23; 11.91%), however, represents those of the sample who are least impacted across both verbal and nonverbal indicators. This group has similar ADOS scores to groups 2 and 3 but both their verbal and nonverbal indicators have means that are the highest of all the subgroups. Groups 2 and 3 represent groups with a mixture of skills. They have the same ADOS scores, daily living scores, and very similar nonverbal indicator scores that are near those of Group 1. However, they differ on verbal scores, Group 2 (n= 48; 24.87%) has higher frequency scores for SCU, NDWR, and IJA and fall between that of Group 1 and Group 4. Group 3 (n=37; 19.17%) has verbal indicator means that are very similar to those of Group 4 and are low in frequency.

Aim 2: Profiles in minimally verbal school-age confirmation sample.

Model Selection. The indicator variables of ADOS Social Affect score, ADOS Restricted and Repetitive Behavior Score, SCU, NDWR, IJA, IBR, Raw PPVT score, Play Diversity-types, and Nonverbal age equivalent were included in the analysis with Sample 2 to provide as close a replication of Aim 1 as possible. This sample did not have VABS Daily Living scores so these were not an indicator in the model. These indicators were used to create Latent Profile models with one through four profiles. Details for fit statistics across all four profiles are included in Table 1-8. Results from these models indicate that a three- profile model best fits the data. The SABIC does reduce until the four profile model but the difference between the four profile and three profile model represents a small improvement. The entropy value of 0.915 indicates good profile separation. The LMR-RLT value of 49.06 (p= 0.239) indicates that the 3- profile model should not be rejected in favor of the 4- profile model. However, the BPLRT was significant (p= 0.000) in the 4- profile model, versus a nonsignificant value for the 5- profile model (p= 1.00). The BF value of the 4 versus 5- profile models indicates the 4- profile model to have a superior fit, with a BF well above 150 while the BF of the 5- profile model is 0.0001. Similarly, the cmP of the 3- profile model is 0.997 while that of the 4- profile models is 0.0001. As a whole, the most robust fit indicators of BF and cmP indicate that the 3- profile model is best fit to the data.

Subgroup Characteristics. Means for each indicator for each profile of the 1-4 profile models can be found in Table 1-9, with Tukey posthoc comparisons presented in Table 1-10 and a visual representation in Figure 1-2. The small sample size should be considered when interpreting the results. The three profile model provided interesting profiles. Profile 1 and Profile 2 had similar indicator means for ADOS scores and IBR scores. Profile 1 (n= 19; 38.77%) means indicate nonverbal indicators and verbal indicators at a level that is in the higher portion of the sample. Profile 2 (n= 26; 53.06%) means indicate nonverbal indicators that are generally similar to Profile 2 but verbal language indicator means that are much lower. Profile 3 is small (n=4; 8.13%) but interesting, with the lowest ADOS means (SA= 10.15; RRB= 4.04), verbal scores in the middle of Profile 1 and Profile 2, and the highest nonverbal indicator scores (PPVT= 53.47; Diversity= 39.77; NVAE= 61.99).

Aim 3: Profiles in minimally verbal preschool-age sample.

Model Selection. The indicator variables of ADOS Social Affect score, ADOS Restricted and Repetitive Behavior Score, Daily Living raw score, SCU, NDWR, IJA, IBR, Play Diversity-types, and Nonverbal age equivalent were included in the analysis with Sample 3 to provide as close a replication of Aim 1 as possible. This sample did not have PPVT scores so MSEL Receptive Language domain raw scores were used in place of PPVT raw scores. These indicators were used to create latent profile models with one through six profiles. Details for fit statistics across all six profiles are included in Table 1-11. Results from these models indicate that a five-profile model best fits the data. The SABIC does reduce until the six profile model but the difference between the six profile and five profile model represents a small improvement. The entropy value of 0.926 indicates good profile separation. The LMR-RLT value of 94.74 (*p*= 0.355) indicates that the 5- profile model should not be rejected in favor of the 4- profile model. However, the BPLRT was significant (*p*= 0.000) in the 5- profile model indicating that it is a better fit. The BF value of the 5 versus 4- profile models indicates that the 4- profile model has a superior fit, with a BF well above 150 while the BF of the 6- profile model is 2.71. The cmP of the 5- profile model is 0.268, indicating an acceptable model. The 6- profile model does have a superior cmP of 0.730, but one of the profiles has an *n* of 8, which is less than 5% of the total sample, 167. Taken as a whole, the BF fit indicator and the fact that the 6- profile model includes a subgroup with less than 5% of the sample, the 5- profile model is best fit to the data.

Subgroup Characteristics. Means for each indicator for each profile of the 1 through 6-profile models for Sample 3 can be found in Table 1-12, with Tukey posthoc comparisons in Table 1-13 and graphical representation of the profiles in Figure 1-3. The 5- profile model of sample 3 represents a variety of profiles. Profile 1 (n=14; 8.3% represents the profile with the overall highest verbal and nonverbal scores and the least severe ADOS scores. Conversely, Profile 5 (n= 91; 54.49%) represents the profile with the lowest nonverbal and verbal scores and the highest ADOS scores. Profiles 2-3 represent a more mixed skill profile. Profile 2 (n= 23; 13.7%) mirrors Profile 1 (n=14, 8.6%) with lower ADOS scores and higher nonverbal scores, but they are distinguished by their verbal frequencies (SCU= 15.10; NDWR= 12.37) which are in between the highest (Profile 1(SCU= 25.95; NDWR= 23.05)) and lowest (Profile 5 (SCU= 0.51; NDWR= 0.58)) scores. Profile 3 (n= 26; 15.56%) has ADOS severity scores comparable to Profile 2, in the more severe range, but nonverbal scores comparable to Profile 1 that are at the higher end of scores for the sample. Profile 3 has verbal language frequencies (SCU= 2.33;

NDWR= 2.36) that are almost as low as Profile 5 and overall has a profile that is similar to Profile 5 but with high nonverbal scores. Profile 4 (n= 13; 7.7%) has a very similar profile to Profile 5 with higher ADOS means and lower nonverbal means, but has verbal language that is more frequent with more words than both Profile 5 and Profile 3 (SCU= 6.49; NDWR= 6.42).

Summary of profiles across early childhood.

School-age. The school-age sample was best classified by a four-profile model. The profiles were distinguished by where they fell overall on the verbal versus nonverbal indicators relative to the rest of the sample. Profile 1 scores were at the top of the sample across both verbal and nonverbal indicator variables. Profile 2 and Profile 3 scores were equal to Profile 1 for nonverbal indicator variables: both ADOS domains, daily living scores, initiations of behavior requests, PPVT scores, play diversity, and nonverbal age equivalents. Profiles 1, 2, and 3 differed on verbal indicator scores. Profile 1 had the highest frequency of communication, number of different words, and initiations of joint attention. Profile 2 was in the middle on all of these variables and represent a group with higher nonverbal scores and verbal scores in the middle of the sample. Profile 3 had IJA scores that were equal to Profile 2 but greater than profile 4, although on frequency of spontaneous communication and number of different words, Profile 3 was equal to profile 4. Profile 4 represents the group with the highest ADOS severity, lowest nonverbal indicator scores, and lowest verbal scores. Profile 4 also had the most children, at 85.

The confirmation school-age sample was best classified by a three-profile model. The different entry criteria of 24 versus 12 months resulted in a higher-functioning sample with more language. Profile 3 of this sample was very small, with only 4 participants, but profiles 1 and 2 mirrored the higher-verbal samples of Aim 1, with one having high nonverbal and more spoken language and the other also having higher nonverbal scores but a middle amount of spoken language. There was less variability in this sample due to the higher nonverbal inclusion criteria and the fact that there were fewer participants overall (61, narrowed down to 50 when excluding those with more than 30 different words).

Preschool-age. The preschool-age sample was best classified by five subgroups, with more variability than the other samples. The patterns of variability among the preschool participants were very similar to that of the school-age participants. Participants were again classified based on where they fell on verbal versus nonverbal indicator variables across a variety of measures and cognitive constructs. Profiles 1-3 mirrored the school-age Profiles 1-3, with Profile 1 being at the top of the sample on verbal and nonverbal indicator variables, Profile 2 having equal nonverbal scores but middle verbal scores, and Profile 3 having high nonverbal scores but verbal scores at the bottom of the sample. Profile 5 is similar to the school-age Profile 4 with low scores across nonverbal and verbal measures and increased ADOS severity. The preschool sample Profile 4 represented a new profile, with low nonverbal scores but verbal scores at the middle of the sample.

3. STUDY 2: Latent profiles and short-term intervention response in school-age minimally verbal children with ASD

3.1 Aims

The secondary analysis of Study 2 builds on the profiles of Study 1 to determine whether response to intervention varies by profile. It uses the profiles established for Sample 1 in Aim 1 of Study 1 to address all research aims in the current study. The primary aims of the current analysis are:

Aim 1: For the primary outcomes of verbal language and responder rating, determine whether quick (6-week) response to intervention differs for this minimally verbal school-aged sample by profile subgroup and whether intervention effects are different by profile subgroup.

Aim 2: For the secondary outcomes of prelinguistic indicators (eye contact, gestures, and using eye contact and gestures in combination with language), determine whether quick (6-week) response to intervention for this minimally verbal school-aged sample differs by profile subgroup and whether intervention effects are different by profile subgroup.

3.2 Method

Study Procedure

Participants. Participants from a multisite randomized, controlled trial comprise the current study sample. This sample is the same as Sample 1 as described in Chapter 1. The current analysis has no additional inclusion or exclusion criteria and participants were included in analyses on an intent-to-treat basis. All participants were recruited from public schools local to the study research centers.

Original Study Design. See Figure 2-1 for a visual diagram of the original study design and the focus of this study. The original RCT is a Sequential Multiple Assignment Randomized Trial (SMART) design, with multiple phases and a mid-treatment randomization based on response to intervention after phase 1. It compares two active interventions, Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER) and discrete trial training (DTT) in the first phase and then, based on response to intervention, adds parent training, continues the same course of intervention, or moves to a blended approach. The current secondary data analysis looks at data from the baseline visit and the phase 1 response visit after 6 weeks, before any rerandomization occurs, to answer response to intervention aims.

Interventions

NDBI- Joint Attention Symbolic Play and Engagement Regulation (JASPER; Kasari, Gulsrud, Kwon, & Locke, 2010; Kasari, Paparella, Freeman, & Jahromi, 2008). JASPER is a child-led NDBI and forms the basis for the primary intervention group in all present aims. JASPER focuses on using play routines to improve engagement, social communication, and play. Skills are taught via strategies such as modeling, environmental arrangement, responding to verbal and nonverbal communication, and appropriate prompting and pacing. JASPER has been shown to be effective at improving spoken communication (Kasari, et al., 2008). Interventionists consistently target individual child goals in the areas of play, engagement, social communication, and language. Nonverbal communication is taught via repeated modeling and programming such as pausing and offering choices to allow the child to spontaneously initiate gestures or eye contact. Verbal communication is taught via repeated language that is the same length as the child's utterance length. Therapists focus on using comments in the session rather than questions and allow the child space to respond or initiate after each utterance. The original RCT used JASPER in combination with EMT (JASP-EMT). Enhanced Milieu Teaching (EMT; Kaiser & Goetz, 1993; Kaiser, Hancock, & Nietfeld, 2000) is an intervention that focuses on spoken language acquisition. EMT is a NDBI with similar strategies as compared to JASPER (responding with target language, expanding utterances, arranging the environment). The addition of EMT to JASPER added occasional systematic prompting. JASP-EMT was delivered for 5 45-minute sessions per week for 6 weeks.

EIBI- Discrete Trial Training (DTT: Smith, 2001). DTT is a highly structured, adult-led approach to teaching a wide range of skills. The adult manages the environment to reduce distractions, uses clear and consistent prompt language, and incorporates highly motivating reinforcements to reward correct responses. DTT is derived from the earliest work on intervention for individuals with autism (Lovaas, 1987). Based in operant conditioning, teaching is centered on the idea that explicit skills can be taught to the child when the adult provides a clear, consistent instruction and a clear, consistent response when the child answers either correctly or incorrectly (Skinner, 1953). DTT programs follow a preset curriculum map for play, communication, fine motor, and nonverbal skills where the starting goal is based on the child's skill level and one skill is mastered before moving on to the next. Verbal and nonverbal communication are taught through repeated tightly controlled trials, with targets along the curriculum map that are not necessarily developmentally informed but do line up with standardized cognitive testing items. A target such as matching would be taught with the adult first delivering the instruction- saying, "Match." Then, the adult would respond to an incorrect child response by correcting the child to match correctly and saying "This is match" in a flat tone. The adult would respond to a correct response by giving the child praise and a highly motivating toy to engage with for a few moments. These steps are repeated moving to the next task. DTT is the active comparison group for the study. Sessions took place for 45 minutes each, 5 times a week, for 6 weeks.

Measures

Participant Characteristics. A demographic questionnaire was used to obtain descriptive information about child and family characteristics. Demographic information pertaining to race/ ethnicity, parent education, and child age, was used to characterize the sample.

Profile measures. Assessments used to create the profiles are described in detail in Study 1 and include nonverbal and verbal indicators.

Response to intervention measures. Measures and variables for the present study are presented in Table 2-1.

*Naturalistic Language Sample (*NLS; Kasari, et al., 2014). The NLS is a standardized, naturalistic assessment where the assessor and child play with a specific set of toys for 20 minutes. The assessment is videotaped and then later transcribed for analysis. The adult is trained to only occasionally prompt the child or direct their language and to primarily respond to child initiations of verbal or nonverbal communication. Research staff blind to randomization status administered the NLS at 90% fidelity. Coded transcripts are used for the outcome variables of Aim 1 analyses.

Early Social Communication Scales (ESCS; Mundy, et al., 2003). The ESCS is a structured, videotaped play-based assessment. The assessor administers the assessment with a standard set of toys and with a standard set of opportunities for the child to exhibit social communication. The assessment lasts 15-20 minutes and is administered by a blinded staff member trained to above 80% fidelity. The videotapes are then coded for initiations of joint attention (IJA) and initiations of behavior regulation (IBR) by a blinded coder. ESCS outcomes are secondary outcomes in the present analysis and are analyzed as part of Aim 2.

Clinical Global Impression Scale- Improvement (CGI-I*;* Guy, 1976). The CGI-I is used to assess responder status in the present analysis. It consists of a likert scale with ratings from 1-7, with 1 indicating the most improvement and 7 indicating the least improvement. It was rated at 6 weeks by the participant's interventionist, with 20% of ratings coded by all study Principal Investigators for reliability. The CGI in this study is administered as a function of the intervention, not an outcome measure, which is why the interventionist is tasked with completing it.

Coding and reliability- Response to intervention outcome variables. All variables were coded by raters blind to intervention and timepoint to a reliability of at least 80%. Details are provided in Table 1-2.

Spontaneous Communicative Utterances (SCU; Kasari, et al., 2014). SCU refers to comments, requests, and protests that the child initiates spontaneously. SCU is derived from NLS transcripts. Staff transcribed the videos using the Systematic Analysis of Language Transcripts (SALT) conventions. Blinded raters coded and verified the transcripts to note whether each child utterance was spontaneous rather than scripted and whether the utterance functioned to comment, request, or serve another purpose. Raters are trained to a reliability above 80% as measured by intraclass correlation coefficients. Spontaneous utterances of all types are included in SCU. SCU is a primary outcome of Aim 1 analyses.

Number of Different Word Roots (NDWR; Kasari, et al., 2014). NDWR refers to the number of unique words used by a child in the NLS. It is coded from transcripts according to the same conventions described for SCU. NDWR is an Aim 1 primary outcome.

Responder Status. The likert scale of the CGI-I was recoded into a binary indicator of responder status. A 1 or 2 rating, originally indicating an improvement in social communication, was recoded into a 1 to indicate fast response to intervention. A 3 rating or higher, originally indicating a slower rate of improvement, was recoded into a 0 to indicate slow response to intervention. Responder status is a primary outcome measured in Aim 1 analyses.

Initiations of Joint Attention (IJA; Mundy, et al., 2003). IJA is coded from the ESCS videotapes. For the purposes of this study, IJA frequencies are a secondary outcome variable. IJA frequencies are the number of times a child uses nonverbal or verbal communication spontaneously for the purpose of sharing with a social partner. Blinded coders maintained a reliability of 80% or above as measured by intraclass correlation coefficients. To investigate patterns of response within initiations of joint attention, the outcome was divided into two discrete variables: Initiations of joint attention- eye contact and/or gestures only, and initiations of joint attention- language alone or in combination with eye contact and/or gestures.

Initiations of Behavioral Requests (IBR*;* Mundy, et al., 2003). IBR was coded according to the same conventions described in IJA. IBR refers to spontaneous requesting behavior and can be language or nonverbal such as eye contact or gestures. For the purposes of analysis, IBR was divided into two separate outcomes: IBR- nonverbal eye contact and/or gestures and IBR- language alone or in combination.

Analysis

Profile subgrouping determination. Profiles were determined using the LPA process described in Study 1. For the current models, Profiles 1 through 3 from Aim 1 were collapsed into a new Subgroup A, representing those with higher nonverbal scores as determined by the LPA in Study 1. Profile 4 was renamed Subgroup B, representing those lower nonverbal scores as determined by the LPA in Study 1. Collapsing individual profiles was necessary to power modeling the interaction of treatment group differences within profile, particularly for powering the appropriate hurdle models for language outcome.

Influence of Subgroup on treatment response. Generalized linear models (GLMs) and linear mixed models (LMMs) were used to determine the response of Subgroup A and Subgroup B to differing interventions at 6 weeks. Site was initially included as a covariate in all analyses as there were some site differences across outcomes. When nonsignificant, site was removed from the final model. Additionally, entry scores of the outcome variable were included as a covariate in all models. All models included individual treatment, profile, and interaction terms to investigate the potential moderating effect of profile on change over time and on treatment response. All models were run in R (R Core Team, 2019).

As the sample is specifically comprised of low frequency communicators and the outcome variables are primarily count or frequency outcomes, all outcomes were evaluated for normality, zero-inflation, and overdispersion. Outcome variable normality descriptive information is provided in Table 2-2. Responder status was the only binary outcome and was modeled with a binary logistic generalized linear model (GLM) using the *lme4* package in R (Bates, Maechler, Bolker, & Walker, 2015). IBR- EC/Gestures was normally distributed and did not have zero-inflation, but was overdispersed. To model IBR- EC/Gestures, a linear mixed model with participant-level random effects was fitted using the *lme4* package in R (Bates, Machler, Bolker, & Walker, 2015). The rest of the outcome variables -- SCU, NDWR, IJA-EC/Gestures, IJA- Language, and IBR- Language – were not normally distributed, had large proportions of zeroes, and were overdispersed. These outcomes were best modeled with a zero-truncated (hurdle) negative binomial GLM. A hurdle model was the most appropriate method to address the process of gaining a single word or JA skill from having zero versus having one and gaining more. The zero-truncated negative binomial models were fitted using the *pscl* package in R (Jackman, 2020). Non-zero values were modeled with a negative binomial distribution with a log link and zero scores were modeled with a binomial distribution with logit link. All variables and the corresponding model used are presented in Table 2-3.

Missing data. Multiple imputation was used to replace missing data so that all randomized participants could be included in analyses per intent to treat principles. Multiple imputation was done via a sequential regression multivariate imputation algorithm implemented with the *mice* package in R (van Buuren & Groothis-Oudshoorn, 2011). The imputation model included all outcome variable scores at baseline and at 6-week response.

3.3 Result

Participant Characteristics.

193 participants were included in present analyses with a mean chronological age of 6.05 years. Original profile information from Study 1 is reproduced in Table 2-4, with the addition of combined Subgroup A and B for the present study as described above. The new Subgroups A and B are displayed, with means converted to z-scores, in Figure 2-2. The combined Subgroup A (n=108) represents the portion of the sample with higher nonverbal indicator scores (nonverbal age equivalent mean= 3.94 years). With Profiles 1-3 from Study 1- Aim 1 combined, the verbal scores are more variable but are still at the higher end of the sample with an average of 8.71 NDWR. Subgroup B is the same as Profile 4 in Chapter 1- Aim 1, and represents nonverbal scores at the lower end of the sample (nonverbal age equivalent mean= 2.38 years) and verbal scores also at the lower end of the sample (mean NDWR= 1.34 words).

Full participant descriptives as a whole sample and by subgroup can be found in Table 2-5. Descriptive information for each subgroup by treatment group for the primary and secondary outcomes can be found in Table 2-6. As a whole, the sample was fairly diverse, with 44.6% of participants identified as White/Caucasian and the rest of the participants as minority or mixed ethnicities. The two subgroups did not significantly differ on demographic characteristics of chronological age, gender, mother's education, or ethnicity.

Aim 1: Primary language and treatment response outcomes

Table 2-7 summarizes significant effects in outcome models.

Frequency of spontaneous communicative utterances (SCU). SCU was modeled with a truncated negative binomial model: a dual model containing a binomial model with logit link to model zero values and a truncated negative binomial model with log link to model nonzero values. The likelihood ratio test was used to determine effects of predictor variables. Site was included as a covariate in model formulation but was a nonsignificant term and was removed from the final model. Final model terms included entry levels of SCU, subgroup, intervention group, and an intervention by subgroup interaction. Entry level of SCU was a significant model term for both the count and zero models (zero-model: OR= 1.83, z-value= 3.51; p -value= 0.000; count model: B= 0.03, z-value= 4.88, p= 0.000). Results for the zero model showed a significant effect for subgroup as an independent term but not as an interaction term with treatment group (OR= 0.11, z-value= -1.95, p = 0.050). Model results are presented in Table 2-8 and Figure 2-3 presents SCU from entry to exit by profile and treatment group. Specifically, for those with zero words, Subgroup A made the most gains in SCU over the 6-week period.

Number of different word roots (NDWR). NDWR was also modeled with a truncated negative binomial model. Site was a nonsignificant covariate and was excluded from the final model. Model terms included entry levels of NDWR, intervention group, subgroup, and an intervention by subgroup interaction. Both the zero and count models had significant effects of entry SCU (zero-model: OR= 2.31, z-value= 3.70; p -value= 0.000; count model: B= 0.08, z-value= 7.95, p= 0.000). Effects of subgroup and a subgroup by treatment interaction differed between the count and zero models. Subgroup was a significant independent effect, controlling for entry levels of NDWR, in the zero model (OR= 0.18, z-value= -1.97, p-value= 0.048). A subgroup by intervention group interaction was significant for the count model (B = -0.65, z-value= -2.50, p- value= 0.012). Specifically, for those with one or more words, those in

Subgroup A gained more NDWR with JASPER, while those in Profile 4 gained more NDWR with DTT over the course of six weeks. Table 2-8 presents model results and Figure 2-4 shows change scores by subgroup and intervention group.

Responder status (CGI-I). The binary outcome of responder status (either a fast or slow response to intervention) was modeled with a logistic binomial regression model, across the two subgroups, per the methods section above. The likelihood-ratio test provided a chi-square score to test significance of model terms. Model terms were treatment group, site, subgroup, and a subgroup*treatment group interaction. Site was overall a significant model term (Wald χ^2= 8.9; p=0.031), driven by a significant difference in likelihood of being rated a responder between Site 1 and Site 4 (Wald z= -2.76, p = 0.005). Subgroup was a significant model term, although the subgroup by intervention interaction was not (Wald z= 14.8, p = 0.036). Specifically, those in Subgroup A were more likely to be responders to intervention, regardless of which one they received. Table 2-9 presents model results and Figure 2-5 shows responder percentage by profile.

Aim 2: Secondary prelinguistic outcomes

Initiations of requests- eye contact and/or gesture (IBR- EC/Gesture). IBR-EC/Gesture was modeled with linear mixed models with a random effects intercept to control for overdispersion due to between-participant variance. Further details are presented in the methods section. Model fixed effects included site, time, treatment group, and subgroup with interaction effects of time*treatment group, time* subgroup, treatment* subgroup, and the three-way interaction time*treatment group* subgroup. Site had a significant effect and was therefore left in the final model. Type-II Wald Chi-Square tests were used to determine significance of model terms. Site was the only significant model term (Wald χ^2 = 9.76, p-value= 0.020). Specifically, those at sites 2 and 4 were more likely to increase IBR- EC and Gesture, regardless of subgroup or intervention (*B*= 3.98, t-value= 3.07; *B*= 2.58, t-value= 2.06). Table 2-10 presents the details for the model, with scores by subgroup and intervention group displayed graphically in Figure 2-6.

Initiations of joint attention- eye contact and/or gesture (IJA- EC/Gesture). IJA-EC/Gesture was modeled with a zero-truncated negative binomial GLM. Model terms included site, entry levels of IJA- gesture, study site, intervention group, subgroup, and a treatment group by subgroup interaction. Across both the zero and count models, IJA- EC/Gesture at entry was a significant term (OR= 1.15, z-value= 2.33, p-value= 0.019; *B*= 0.06, z-value= 4.29, *p*-value= 0.000). Additionally, site was a significant model term, determined by likelihood ratio test (χ^2 = 8.6, *p*-value= 0.03). Specifically, those in the count model were more likely to have higher IJA-EC and Gesture frequencies at 6 weeks at Site 2 versus Site 1 and those in the zero model were more likely to improve IJA- EC/Gesture frequencies at Site 1 versus Site 3. There were no significant subgroup or subgroup by intervention interaction effects. Model details are provided in Table 2-11 and raw means are graphed by subgroup and intervention group from entry to 6-week response in Figure 2-7.

Initiations of joint attention- language (IJA- Language). IJA- Language was modeled with a zero-truncated negative binomial GLM, with additional model details provided in the Analysis portion of the Method section. Entry levels of IJA-Language were included in the model with site, treatment group, subgroup, and a treatment* subgroup interaction. Site was not a significant term and was excluded from the final model. Significant effects were present in both the count model and zero model for entry levels of IJA- Language (OR= 1.22, z-value= 2.03, p-value= 0.042; *B*= 0.04, z-value= 3.27, *p*-value= 0.001) and for subgroup as an independent effect (OR= 0.17, z-value= -3.62, p-value= 0.000; *B*= -0.72, z-value= -1.97, *p*-value= 0.047). There were no other significant effects in the hurdle model. Specifically, IJA- Language frequencies differed by subgroup at 6-weeks, controlling for entry levels of IJA- Language. Those with zero or more than zero words were more likely to have more IJA- Language at 6 weeks if they were in Subgroup A, controlling for entry levels of IJA- Language. Model details are presented in Table 2-12, with a graph of IJA-Language scores in Figure 2-8.

Initiations of requests- language (IBR- Language). IBR- Language was modeled with a zero-truncated negative binomial GLM, with additional model details provided in the Analysis portion of the Method section. Entry levels of IBR-Language were included in the model with site, treatment group, subgroup, and a treatment* subgroup interaction. Site was a nonsignificant term and was therefore removed from the final model. Significant effects were present across both the zero and count models for entry levels of IBR-Language (OR= 1.25, z-value= 2.74, p-value= 0.005; B= 0.04, z-value= 3.14, p-value= 0.001). The zero hurdle model had a significant independent effect of subgroup, controlling for entry levels of IBR- Language (OR= 0.25, z-value= -2.29, p-value= 0.021) Specifically, the effect of subgroup favoring Subgroup A is present for those with zero values when entry levels of IBR- Language are controlled for. Model details are presented in Table 2-12, while the entry and exit scores by subgroup are presented in Figure 2-9.

Summary of school-age subgroup outcomes

Much work has been done investigating predictors related to intervention response. Little of this has focused on either a school-age sample, a minimally verbal sample, or comparison of active interventions. Current findings highlight the importance of comparing high-quality active interventions that are known to be efficacious to determine which intervention will most benefit an individual.

Frequency of eye contact, gesture, and language use. Short-term increases in communication frequency for the school-age participants were shown to be largely dependent upon individual child characteristics. Nonverbal eye contact and gesture use at 6 weeks had no relation to subgroup or intervention response differences by profile and only depended upon entry levels of nonverbal communication. Verbal language frequency and combinations with gestures were not different within subgroup by intervention group, but were predicted at 6 weeks by subgroup in an effect that went beyond entry levels of language use.

Responder status. Global ratings of response to intervention showed differences by subgroup that did not depend on intervention group. Subgroup A, those with the highest nonverbal and verbal scores, was more likely to be rated a responder at the 6-week timepoint versus those in Subgroup B.

Number of different words used. Short-term increases in number of words used were dependent upon subgroup and intervention. Those in the subgroup with lower nonverbal scores and one word or more gained more words over 6 weeks with high quality DTT, delivered approximately five hours per week. Those in the subgroup with higher nonverbal scores and more than one word, however, gained more words with JASPER, the naturalistic approach.

4. STUDY 3: Latent profiles and intervention response in preschool-age minimally verbal children with ASD

4.1 Aims

The present secondary analysis builds on the profiles of Study 1 to determine whether response to intervention varies by profile at the preschool age. It uses the same profiles established for Sample 3 in Aim 3 of Study 1 to create subgroups and address all research aims in the current chapter. The primary aims of the current analysis are:

Aim 1: For the primary verbal language outcomes, does 6-month response to intervention differ for this minimally verbal preschool-aged sample by subgroup? Are intervention effects (DTT v. JASPER) different by subgroup?

Aim 2: For the secondary outcomes of prelinguistic indicators (eye contact, gestures, and using eye contact and gestures in combination with language), does 6-month response to intervention differ for this minimally verbal preschool-aged sample by subgroup? Are intervention effects (DTT v. JASPER) different by subgroup?

4.2 Method

Study Procedure

Participants. Participants from a multisite randomized, controlled trial comprise the current study sample. This sample is the same as Sample 3 as described in Study 1. Sample 3 was a multisite study that recruited participants through local public schools near three different research centers. Only participants with less than 30 spontaneous words on the natural language sample at entry were included in the present analyses.

Original Intervention Study Design. Project 3 was a traditional RCT comparing an NDBI (JASPER) to an EIBI (DTT), with added parent training at the end of intervention and tapered treatment intensity after the first two-thirds of intervention. The current secondary analysis examines data from Project 3 from the baseline visit at entry and the exit visit after 6 months. Figure 3-1 displays the original study design and focus of this secondary data analysis. The original RCT compared two active interventions, JASPER and DTT. In both conditions, active treatment consisted of 5 60-minute sessions per week, delivered for a total of 4 months, then 3 times a week for the next month, and 2 times a week for the final month of the entire 6-month active treatment period. Sessions were conducted primarily in the school setting by study staff, with occasional sessions at home if school was closed or unavailable. Intervention details are provided in Study 2.

Measures

Measures and variables for the present study are presented in Table 3-1.

Participant Characteristics. A demographic questionnaire was used to obtain descriptive information about child and family characteristics. Demographic information pertaining to parent education, child age, and race/ethnicity were used to characterize the sample.

Profile measures. Assessments used to create the profiles are described in detail in Study 1 and include nonverbal and verbal indicators.

6-month outcome measures

Parent-Child Interaction (PCX; Kasari, et al., 2010). The PCX is a videotaped interaction between a caregiver and their child. The set of toys is consistent across timepoints and participants. During the PCX, caregivers are instructed to interact with their child how they typically would. Videos are then coded at a later time for language, number of spontaneous utterances (SCU) and number of different words (NDWR), used as primary aim outcome variables in child intervention response analyses.

Early Social Communication Scales (ESCS; Mundy, et al., 2003). The ESCS is a structured and videotaped play-based assessment. The assessor administers the assessment with a standard set of toys and with a standard set of opportunities for the child to exhibit social communication. The assessment lasts 15-20 minutes and is administered by a blinded staff member trained to above 80% fidelity. The videotapes are then coded for nonverbal- eye contact and gestures- and verbal initiations of joint attention (IJA) and initiations of behavior regulation

(IBR) by a blinded coder. ESCS outcomes are secondary outcomes in the present analysis and are analyzed as part of Aim 2.

Coding and reliability- Response to intervention outcome variables. All variables were coded by raters blind to intervention and timepoint to a reliability of at least 80%. Details are provided in Table 3-2.

Spontaneous Communicative Utterances (SCU; Kasari, et al., 2014). SCU refers to comments, requests, and protests that the child initiates spontaneously. SCU is derived from PCX transcripts. Staff transcribed the videos using the Systematic Analysis of Language Transcripts (SALT) conventions. Blinded raters coded and verified the transcripts to note whether each child utterance was spontaneous rather than scripted and whether the utterance functioned to comment, request, or serve another purpose. Raters are trained to a reliability above 80% as measured by intraclass correlation coefficients. Spontaneous utterances of all types are included in SCU. SCU is a primary outcome of Aim 1 analyses.

Number of Different Word Roots (NDWR; Kasari, et al., 2014). NDWR refers to the number of unique words used by a child in the PCX. It is coded from transcripts according to the same conventions described for SCU. NDWR is an Aim 1 primary outcome.

Initiations of Joint Attention (IJA; Mundy, et al., 2003). The ESCS is coded for spontaneous child communications. For the purposes of this study, IJA frequencies are a secondary outcome variable. IJA frequencies are the number of times a child uses nonverbal or verbal communication spontaneously for the purpose of sharing with a social partner. Blinded coders maintained a reliability of 80% or above as measured by intraclass correlation coefficients. To investigate patterns of response within initiations of joint attention, the outcome was divided into two variables: Initiations of joint attention- eye contact and/or gestures, and initiations of joint attention- language alone or in combination with eye contact and/or gestures.

Initiations of Behavioral Requests (IBR*;* Mundy, et al., 2003). IBR was coded according to the same conventions described in IJA. IBR refers to spontaneous requesting behavior and can be language or nonverbal such as eye contact or gestures. For the purposes of analysis, IBR was divided into two outcomes: IBR- nonverbal eye contact and/or gestures and IBR- language alone or in combination with eye contact and/or gestures.

Analysis

Profile determination. Profiles were determined using the LPA process described in Study 1. For the current models, Profiles 1-3 from Aim 3 were collapsed into a new Subgroup A representing those with higher nonverbal scores. Profiles 4 and 5 were collapsed into a new Subgroup B representing those with lower nonverbal scores. Collapsing individual profiles was necessary to power modeling the interaction of treatment group differences within profile.

Influence of profile on treatment response. Generalized linear models (GLMs) and linear mixed models (LMMs) were used to determine the response of subgroups identified in Chapter 1 to intervention at 6 months. Site was included as a covariate in all analyses and when significant was included in the final models. Additionally, entry scores on the outcome were included as a covariate in all models. All models included individual treatment, subgroup, and treatment by subgroup interaction terms to investigate the potential moderating effect of subgroup on change over time and on treatment response. All models were run in R (R Core Team, 2019).

As the sample is specifically comprised of low frequency communicators and the outcome variables are primarily count or frequency outcomes, all outcomes were evaluated for normality, zero-inflation, and overdispersion. Outcome variable normality descriptive information is provided in Table 3-2. IBR- eye contact and gestures was normally distributed and did not have zero-inflation, but was overdispersed. To model IBR-eye contact and gestures, a linear mixed model with participant-level random effects was fitted using the *lme4* package in R (Bates, Machler, Bolker, & Walker, 2015). The rest of the outcome variables -- SCU, NDWR, IJA- eye contact and gestures, IJA- language, and IBR- language – were not normally distributed, had large proportions of zeroes, and had large variances that created overdispersion. These outcomes were best modeled with a zero-truncated (hurdle) negative binomial GLM. A hurdle model was the most appropriate method to address the process of gaining a single word or JA skill from having zero versus having one and gaining more. The zero-truncated negative binomial models were fitted using the *pscl* package in R (Jackman, 2020). Non-zero values were modeled with a negative binomial distribution with log link and zero scores were modeled with a binomial distribution with logit link. Zero-truncated model fit was compared to fit of a traditional negative binomial model and was used if the fit was equal or superior. All outcome variables and the corresponding model used are presented in Table 3-3.

Missing data. Multiple imputation was used to replace missing data so that all randomized participants could be included in analyses per intent to treat principles. Multiple imputation was done via a sequential regression multivariate imputation algorithm implemented with the *mice* package in R (van Buuren & Groothis-Oudshoorn, 2011). The imputation model included all outcome variable scores at baseline and at 6-month response.

4.3 Result

A summary of significant effects of model terms by outcome is provided in Table 3-7.

Profile determination.

161 participants were included in present analyses. Profile information from Study 1 is reproduced in Table 3-4 with the addition of the new combined subgroups. Subgroup means were converted to z-scores for the visual description of Figure 3-2.

Subgroup A (n= 59) and Subgroup B (n= 102) are the groups modeled in all outcome analyses of Aim 1 and Aim 2. Subgroup A represents the higher nonverbal- higher verbal ability group. Within the overall sample, their scores fell at the higher end across nonverbal verbal indicators (e.g. NVAE mean= 30.14 months) Since all high nonverbal profiles from Aim 3 of Study 1 were collapsed, this subgroup has a range of verbal ability, but on average falls at the top of the sample on verbal indicators (e.g. mean NDWR= 10.49 words). Subgroup B represents the lower nonverbal- lower verbal ability group. The lower nonverbal profiles from Aim 3 of Study 1 were collapsed for this subgroup, so while there is some range in verbal ability, it is on average at the low end of the sample (e.g. NDWR mean= 1.46 words). The original Profiles 4 and 5 were at the low end for nonverbal indicators, so Group B is also lower on nonverbal indicators (e.g. NVAE mean= 21.66 months). Within the collapsed subgroup, Subgroup A has 31 (51.2%) participants who were randomized to receive DTT and 28 (47.4%) who received the JASPER intervention. Subgroup B has 48 (47.0%) participants who were randomized to receive DTT and 54 (52.9%) who received JASPER.

Participant Characteristics.

Full participant descriptive information as a whole sample and by subgroup can be found in Table 3-5. Full descriptive information for each subgroup by treatment group for the primary and secondary outcomes can be found in Table 3-6. Additionally, the sample has been described in Study 1. Between the two subgroups, there are no significant differences on the demographic characteristics of gender, mother's highest education, racial/ethnic background, and child's chronological age. There are significant differences in nonverbal and verbal scores as described above.

Aim 1: Primary language and treatment response outcomes

Frequency of spontaneous communicative utterances (SCU). SCU was modeled using a truncated negative binomial (hurdle) GLM. This type of model is equivalent to running two models simultaneously- one for zero values and one for non-zero values. A binomial model with logit link modeled zero values and a truncated negative binomial model with log link modeled nonzero values. The likelihood ratio test was used to determine effects of predictor variables. Site was not a significant model term and was therefore removed from the final model. Entry level of SCU was included as a covariate in the model and was the only significant model term (zero-model: OR= 1.25, z-value= 2.69; p -value= 0.006; count model: B= 0.03, z-value= 2.93, p= 0.003). Nonsignificant model terms were intervention, subgroup, and an intervention by subgroup interaction. Full model results are presented in Table 3-8 and Figure 3-3 presents SCU from entry to 6-month exit by subgroup and intervention group.

Number of different word roots (NDWR). NDWR was also modeled with a truncated negative binomial hurdle GLM. NDWR also did not show a significant site effect, so site was not included as a covariate in the final model. Model terms were entry NDWR scores, intervention group, subgroup, and an intervention by subgroup interaction. Both the zero model and count models had significant effects of entry levels of NDWR (zero-model: OR= 1.32, z-value= 2.98 ; p -value= 0.002; count model B= 0.04, z-value= 2.93, p= 0.003) Count model results showed a significant subgroup by treatment interaction that was not present in the zero model (count model: B= -0.48, z-value= -1.96, p= 0.049). Specifically, these results show that compared to Subgroup A, those with one or more words in Subgroup B - less nonverbal ability- gained more

NDWR in 6 months with the DTT intervention versus JASPER. Table 3-8 presents model results and Figure 3-4 shows entry and exit scores by subgroup and treatment group

NDWR was also modeled across time with a negative binomial GLM with log link to determine whether short-term NDWR results from Study 2 held with the preschool sample. Results indicated no differences by profile at the 2-month or 4 month midpoints of the intervention. A significant effect of treatment by subgroup interaction occurred in this series of models for the time between 6-month exit and 12-month exit. In the course of this time period, those in Subgroup A benefited more, by gaining more words in the follow-up period, from their previous JASPER intervention, while those in Subgroup B benefitted more from their previous DTT intervention (B= -1.16, z-value= -3.03, p= 0.002). Full results for models of NDWR across the course of the study are presented in Table 3-9, with a graph of NDWR across time by treatment and subgroup in Figure 3-5.

Aim 2: Secondary prelinguistic outcomes

Initiations of requests- eye contact and/or gesture (IBR- EC/Gesture). IBR-EC/Gesture was modeled with a linear mixed model with a random effects intercept to control for between-participant variance and overdispersion in the data. Further details are presented in the methods section. Model fixed effects included site, time, treatment group, and subgroup with interaction terms of time*treatment group, time* subgroup, treatment* subgroup, and the three-way interaction time*treatment group* subgroup. Site was a nonsignificant model term and was removed from the final model. Type-II Wald Chi-Square tests were used to determine significance of model terms. The independent subgroup term was significant (B= -4.59, $\chi^2(1)$= 7.28, p= 0.009), as well as the time* subgroup interaction ($\chi^2(1)$= 9.89, p= 0.001). Specifically, changes over six months in nonverbal communication were variable by subgroup. Subgroup A decreased overall in IBR- EC/Gesture while Subgroup B increased in IBR- EC/Gesture. Table 3-10 presents the details for the model, with scores displayed graphically in Figure 3-6.

Initiations of joint attention- eye contact and/or gesture (IJA- EC/Gesture). IJA-EC was modeled with a zero-truncated negative binomial GLM, consisting of both a binomial model with logit link for zero values and a truncated negative binomial with log link for nonzero values. Entry levels of IJA-EC were included in the model with additional terms for treatment group, subgroup, and a treatment* subgroup interaction. Site was a nonsignificant effect and was therefore removed from the final model. IJA-EC at entry was a significant term for both the count and zero hurdle models (zero model: OR= 1.27, z-value= 2.89, p= 0.003; count model B= 0.07 z-value= 3.21, p= 0.001). Additionally, the zero model had a significant effect of subgroup as an independent term, controlling for entry levels of IJA-EC and Gestures (OR= 0.23, z-value= -2.07, p= 0.038). For IJA- EC and Gesture, those participants with zero words were more likely to gain words, regardless of intervention, if they were in Subgroup A. Table 3-11 presents model details, with entry and exit scores by subgroup and treatment group displayed graphically in Figure 3-7.

Initiations of joint attention- language (IJA- Language). IJA- Language was modeled with a zero-truncated negative binomial GLM, with a binomial model with logit link for zero values and a truncated negative binomial with log link for nonzero values. Entry levels of IJA-Language were included in the model with treatment group, subgroup, and a treatment*profile interaction. Site was a nonsignificant model term and was therefore removed from the final model. Significant effects differed for the zero and count model. A significant effect of subgroup was present in the zero model as an independent term (*OR*= 0.07*,* z-value= -0.19, p= 0.011). There was a significant interaction effect of intervention by subgroup, but only in the count model (B = -0.72, z-value= -2.08, p= 0.036) Specifically, IJA- Language frequencies for the zero values differed by profile at 6 months, controlling for entry levels of IJA-language. Subgroup A was more likely to have improvement in zero-values at six months versus Subgroup B. Additionally, those who had at least one word and were in Subgroup B had a better IJA-Language outcome with DTT versus JASPER while those in Subgroup A with at least a word improved at the same rate regardless of intervention. Model details are presented in Table 3-12, with a graph of IJA-Language scores in Figure 3-8.

Initiations of requests- language (IBR- Language). IBR- Language was modeled with a zero-truncated negative binomial GLM. Entry levels of IBR-Language were included in the model with treatment group, subgroup, and a treatment* subgroup interaction. Site was not a significant term and was removed from the final model. Significant effects were present for entry levels of IBR-Language across models (zero model: OR=1.29, z-value= 2.53, p= 0.011; count model: B = 0.05, z-value= 2.85, p= 0.000). The zero model had a significant effect of Profile as an independent term (OR= 0.26, z-value= -2.09, p= 0.036). The count model had a significant interaction for intervention*profile (B = -0.72, z-value= -2.08, p=0.036). Specifically, the effect of subgroup in the zero model is present when entry levels of IBR- Language are controlled for and indicates that those with a zero value are more likely to improve in IBR-Language if they are in Subgroup A. The interaction in the count model indicates that for those with a word or more in Subgroup B, participants gain more IBR-Language in six months with the DTT intervention. Model details are presented in Table 3-12, while the entry and exit scores by subgroup are presented in Figure 3-9.

Summary of preschool-age subgroup outcomes

The majority of ASD intervention research has arguably focused on early interventions for preschool-age children. As a result, we have some information about efficacious interventions for this population. However, as is the case with school-age children, little of this work has looked at interventions for minimally verbal children, and in particular multi-measure predictors of intervention response in preschool-age minimally verbal children (Bal, et al., 2016).

Frequency of eye contact and gesture use. Participants made gains irrespective of intervention approach or profile for the outcome of nonverbal joint attention initiations. Nonverbal requesting initiations, however, differed by subgroup across time. When participants already had a word or more, those in the higher nonverbal subgroup decreased nonverbal requesting behaviors over time while those in the lower nonverbal subgroup increased over time.

Frequency of language use. Although frequency of SCU did not differ by intervention approach or profile, IJA language/language combinations and IBR language/language combinations both had different effects of participants dependent upon subgroup and intervention approach. For both initiations of requesting language and initiations of sharing language, those with a word or more and in the lower nonverbal/lower verbal subgroup made more gains in initiation frequency with DTT over the course of the six-month intervention period.

Number of different words used. Although the school-age sample showed differences in response to intervention by profile at just 6-weeks, those in the preschool-age sample showed a difference in response to intervention by subgroup at the 6- and 12-month follow-up timepoint. Model results show that JASPER was more beneficial in gaining words for those in the higher nonverbal/ higher verbal subgroup. Conversely, DTT was more beneficial for those in the lower subgroup, those with lower nonverbal scores and lower verbal scores.

5. DISCUSSION

The present work is important to the understanding of minimally verbal children with ASD. Both characterizing heterogeneity within the minimally verbal spectrum and analyzing its impact on intervention response are essential steps to optimizing interventions for all individuals with ASD. The present trio of studies results in three primary findings. First, minimally verbal children with ASD are heterogeneous and their differences can be classified into distinct profiles. Second, minimally verbal children with autism can make progress even in short periods of time, given just one high quality hour per day of evidence-based intervention in addition to a typical school program. Third, child characteristics at the start of intervention influence response to treatment, and findings indicate that the lower ability subgroup may respond better to a more structured intervention approach while children with higher receptive language respond faster to a more naturalistic approach. Together, all three studies provide a comprehensive picture of heterogeneity and treatment response within the minimally verbal end of the autism spectrum.

5.1 Comprehensive classification of heterogeneity across early childhood

Combining individual differences across multiple domains into a comprehensive profile. In Study 1, subgroups of minimally verbal children with autism were characterized throughout early childhood-- from preschool-age to school-age. Unlike previous studies which have typically identified individual markers of heterogeneity, the current study provided a comprehensive classification of minimally verbal subgroups.

Cognitive ability within the minimally verbal label in previous reports varies from impaired to average (Bal, et al., 2018), and the current study also demonstrates variability with nonverbal age equivalents ranging from 1.26 years behind chronological age to 3.6 years behind chronological age. Expressive language in the current study ranged from 0 to 30 words, echoing previous reports of expressive language diversity within the minimally verbal label (Kasari,et al., 2014; Bal, Katz, Bishop, & Krasileva, 2016). ADOS Module 1 severity scores in the current study also ranged from 3-10 for the preschool sample and 4-10 for the school age sample. This represents a wide range of ASD-related symptoms from a low level to a high level, a diversity not previously acknowledged (Bal, et al., 2016; Chenausky, Norton, Tager-Flusberg, & Schlaug, 2018). Receptive language ability of this population has been described in some cases as ranging from equal to expressive language ability to better than expressive language (Skwerer, Jordan, Tager-Flusberg, 2016; Rapin, Dunn, Allen, Stevens, & Fein, 2019). In the current study, expressive and receptive language, nonverbal cognition, daily living skills, autism severity, and play behavior were used together to define subgroups, thus providing a more comprehensive profile than previous studies of single domain predictors or classifications.

The current study findings reflect increased heterogeneity at the earlier preschool age versus at the school age, resulting in an additional identified profile despite a smaller sample. Before age 5, 50-70% of children with ASD have no phrase speech (Ellis & Kover, 2015; Thurm, Manwaring, Swineford, & Farmer, 2014). These children have been referred to as preverbal. The expectation is that they will talk, but by age 5 there are still about 30% who are not, and at that point re-classified as minimally verbal (Distefano & Kasari, 2016). Therefore, the preschool sample profiles are capturing the additional heterogeneity of those who have less than 30 words before the age of 5 but will no longer be minimally verbal after age 5- and would therefore not have been included in the school-age sample.

Holistic classification of heterogeneity. While the majority of previous work has looked at individual predictors of outcomes, some groups have used a multimeasure classification approach to categorize heterogeneity across the whole spectrum of ASD. For example, there are some multimeasure investigations that have classified individual differences within a particular domain, such as personality or sensory behavior (Schwartzman, Wood, 2015; Uljarevic & Lane, 2016). Others have examined a particular age across several domains, and tested predictions to later development (Landa, Gross, Stuart, & Bauman, 2012. Pickles, McCauley, Pepa, Huerta, & Lord, 2020). Understanding particular patterns within a single trait and how those patterns may affect response to targeted interventions can be informative but a limitation is that this approach may ignore other features of an individual's phenotype that can inform treatment response. While other investigations have looked across different domains in children, for example early in development, to characterize individual differences and the impact of those groupings on development across time, this work may overlook the heterogeneity within minimally verbal children. In contrast to the previous work, the present study examines samples who have limited language abilities before and after age 5 across early childhood to identify subgroups based on a range of domains and instruments. This study therefore offers the unique contribution of holistic profile classifications for minimally verbal children with ASD across early childhood., 3 to 8 years.

Patterns of verbal and nonverbal cognition across early childhood. In this study, all participants were sorted into profiles based on where they scored relative to the sample across a total of ten indicator variables. Seven of the variables describing nonverbal or receptive language cognition (autism social affect scores, autism RRB scores, daily living scores, nonverbal age equivalents, initiations of requests, receptive language scores, and play diversity) dichotomously identified participants as falling either in the higher end of the sample or in the lower end of the sample. The other three indicator variables (number of different words, frequency of spontaneous verbal communication, and frequency of joint attention initiations) measured verbal language use and further stratified participants into three verbal profiles: those with higher skills relative to the sample, those in the middle of the sample, and those at the lowest end of the sample. Between the dichotomous stratification of the nonverbal indicators and the trichotomous stratification of the verbal indicators, four profiles emerged across both samples: higher nonverbal/higher verbal, higher nonverbal/middle verbal, higher nonverbal/lower verbal, and lower nonverbal/lower verbal.

Previous studies of general samples of ASD have also identified separate subgroups based verbal versus nonverbal patterns of scores (Munson, et al., 2008; Tager-Flusberg & Joseph, 2003). An examination of preschool children across the spectrum identified four clusters nearly identical to the present patterns of minimally verbal preschool profiles, though the current study found an additional group that was high nonverbal- low verbal (Kim, Macari, Koller, & Chawarska, 2016). It may be an artifact of parsing diversity within a sample, but the persistent verbal versus nonverbal cognition patterns likely points to a useful way to classify heterogeneity within ASD.

A discrepant verbal versus nonverbal phenotype. Both the preschool and school-age samples had a profile representing those with higher nonverbal skill relative to verbal ability. This discrepant phenotype has been previously identified as a potential subtype of the ASD spectrum (Joseph, Tager-Flusberg, Lord, 2002). It been noted in investigations of heterogeneity both across the spectrum and within an exclusively minimally verbal sample (e.g. Joseph, et al., 2002; Munson, et al., 2008; Kim, et al., 2016; Bal, et al. 2016). This phenotype, confirmed in the present study, may offer insight to developmental trajectory and courses of intervention.

5.2 Existing interventions are effective for minimally verbal children with ASD

Short-term intervention leads to improvements, even in a school age sample that as a whole may be slower to respond to intervention. Small gains are seen in number of words, frequency of language use, and in global ratings of response to intervention. These gains occur in language, which after age 5 is thought to be more static and potentially outside of the "critical period" of language development (Newport, Bavelier, & Neville, 2001; Klintwall, Eldevik, Eikeseth, 2015). Although less is known about language development past the age of 5, it is clear that effective interventions can encourage increased language use in minimally verbal school-age children. Additionally, responders in the school-age sample were across both subgroups, even those with low language and lower nonverbal scores. The current study shows that short-term increases in language use past the age of 5 are largely dependent upon a child's cognitive profile and whether the child uses at least a word in a natural language sample. This contribution makes it possible to further tailor interventions to a child's individual needs.

An impactful hour per day. The present work also shows that effective interventions for minimally verbal school-age and preschool-age children can be delivered for an 45 minutes to an hour per day, about 5 hours per week, versus the accepted standard of "high intensity" 40 hours per week (e.g. Eikeseth, Smith, Jahr, & Eldevik, 2007; Lovaas, 1987), or "low-intensity" 20 hours per week (Sallows & Graupner, 2005). It is important to note that the low dose of intervention was provided in the course of a typical school day, as all participants were enrolled in local public school programs. Additionally, the interventions are both evidence-based and rigorously tested, with research study staff trained to high levels of fidelity with regular review and clinical oversight. Therefore, the hour per day was a high-quality hour, provided during the school day to children who were in public school programs for 20-30 hours per week.

Nevertheless, this dose is much less than both previous reports of interventions and the current recommendations. Although the treatment dose of 30 to 40 hours per week is commonly the goal for community intervention, a recent report points out that research on ASD intervention does not note any optimal frequency or duration and that excessive hours of intervention may be unnecessary or even counterproductive (Pellechia, Iadarola, & Stahmer, 2019). A few investigations have suggested that a higher dose of early intervention offers more improvements, while others have noted that intervention delivered at 20 hours per week offers no benefit over community-delivered interventions (Smith, Groen, & Wynn, 2000; Rogers, et al., 2019). Previous work with JASPER in both minimally verbal samples with ASD and samples across the spectrum has noted that a lower intensity dose of intervention provides clear benefits to core ASD domains (Kasari, et al., 2014; Kasari, et al., 2008). It may be that improvements depend more on the quality of intervention or the active ingredients of an intervention within the dose, versus the actual dose itself (Kasari & Smith, 2013). Fully understanding the impact of dose of interventions for ASD requires continued rigorous and systematic investigations.

5.3 Entry characteristics are essential in determining intervention response

Subgroup characteristics are highly predictive of intervention outcome. Subgroup characteristics matter for response to the present interventions- those with highest nonverbal scores and entry expressive language are making the largest gains in response to intervention. Treatment response is typically analyzed without regard for individual differences, as most RCTs compare an intervention to a waitlist or community intervention group, and control for any and all individual predictors in evaluating effectiveness. Moving towards treatment personalization requires a shift in this perspective. It is important, now that effective interventions have been developed, to determine which interventions work best for whom. Current evidence suggests that minimally verbal children with higher cognition are benefitting the most from intervention while those in the with lower cognitive scores and zero words are making slower progress.

Almost all work on predictors of outcome or intervention response has been done in preschool-age children with samples across the ASD spectrum (e.g. Kasari, 2012; Yoder & Watson, 2015; Schreibman, 2009). Though some examinations have found that individual entry characteristics such as joint attention, object interest, imitation, socialization, and play matter most in outcome and treatment response (Kasari, 2012; Schreibman, 2009, Sallows & Graupner, 2005, Sigman, 2005), the current study results suggest that a cognitive profile based on verbal and nonverbal measures may offer increased value in predicting outcome. Those with more verbal ability have, in general, been shown to have better treatment response and increased language development (Kasari, 2012; Sallows & Graupner, 2005; Stevens & Rapin, 2000). Those with higher nonverbal indicator scores (lower ADOS severity, daily living, receptive language, requesting, toy play, NVAE) have been found to also have better treatment response (Anderson, 2007; Stevens & Rapin, 2000; Pickles, Cauley, 2020; Yoder & Watson, 2015; Sallows & Graupner, 2005).

In examining an exclusively minimally verbal sample, Gordon, et al. (2011) found that those who had more expressive language and less severe ADOS scores had a better response to intervention, a finding that is mirrored in the present results. Additionally, Bal, et al. (2019) found that initiating joint attention played an important predictive role in one minimally verbal sample. It seems as though within a sample, those with higher verbal and nonverbal cognition will respond more strongly to intervention. Those with the lowest cognition and language scores generally have a slower response to intervention regardless of approach.

Importance of a word for intervention response. In particular, having one word or more versus none in addition to cognitive subgroup made a difference for response to intervention approach in minimally verbal children with ASD in this study. The importance of having just one word prior to intervention as predictor of treatment response has been found previously but persists in the present results as a key factor in intervention outcome (Schreibman, 2010).

It is unclear exactly why having a word is so important, but there are a few potential explanations to consider. One aspect of having one versus zero expressed words is that if zero words are expressed on an assessment, it is unclear how far away from having a word a child may be. If the assessment is accurately reflecting zero functional words, there may be other factors involved, such as a secondary diagnosis reflecting a motoric issue or specific speech/language impairment. Rather, if the assessment is failing to capture words that a child is speaking infrequently, it may be a matter of decreasing anxiety or increasing the rate of a child's communication. Therefore, using one versus zero words may represent separate learning processes. Those with zero words did not respond any differently to the two intervention approaches, so it may be necessary to enhance current interventions or to look to new approaches to best meet their intervention needs. Additional supports such as an augmentative system (e.g., a speech generating device) have been found to be useful in increasing spoken language for minimally verbal school-age children and may be needed to increase response to intervention for those with zero words (Kasari, et al., 2014).

A more structured intervention approach may be beneficial for those with lower verbal and nonverbal cognition. High-quality DTT may offer more structure versus the naturalistic play-based approach of JASPER for increasing frequency and number of words for those who have at least a word and are the most impacted with lower scores across nonverbal indicators. The few other comparisons of active interventions have found similar patterns. Those with less receptive skill were found to respond better with DTT versus a naturalistic approach (Paul, 2013). In other active intervention comparisons, findings suggest that those with less object interest and less joint attention may make fewer gains with a play-based approach. (Yoder & Stone, 2008; Panganiban, 2019; Vivanti, et al., 2013). These findings are slightly different than some previous EIBI work which has concluded that those with more language, higher cognition, and lower ASD severity respond better to a DTT-style approach (Smith, Grown, & Wynn, 2000; Sallows & Graupner, 2005).

It is not clear exactly why those in the lower subgroup-- those with lower object interest, nonverbal cognition, and receptive language --are doing better with the more structured approach. DTT offers more structure via increased repetition, clearer reward contingencies, and increased direct instruction over an NDBI approach. These factors likely all contribute to the improvements those with lower nonverbal cognition make in the more structured intervention. For example, DTT consists of short trials with a high-value reward such as a preferred toy, overexaggerated praise, or a snack presented for correct responses. These are likely more motivating for those with less object interest versus the lower-value, more subtle social rewards present in a play-based approach. Another potential explanation is the role of repetitive direct instructions. For those with lower nonverbal cognition and receptive language, repeated short and clear directions may create an environment that encourages learning both the instruction or expectation and the correct response. The current studies build on previous work to offer comprehensive classification of the lower subgroup in a wholly minimally verbal sample, a rigorous intervention design, and a larger number of participants versus previous active intervention comparisons.

A less structured intervention approach may be beneficial for those with higher verbal and nonverbal cognition. JASPER was more beneficial for the higher-ability Subgroup A in using more words in short-term 6-week response in school-age children and in longer term 12-month outcomes in preschool-age children. Similar findings have been reported. Paul (2013) found that those with better receptive skill did better with a NDBI approach. Yoder & Stone (2006) found that those with more JA had better outcomes with a play-based approach. Panganiban (2019) and Vivanti, et al. (2013) found that those with increased object interest have better response to play-based interventions. Subgroup A represents those with more initiations of joint attention, higher receptive language cognition, and increased play diversity.

Again, it is not clear exactly why the higher ability subgroup may have increased number of words with an NDBI approach versus an EIBI, either short-term or long-term. Compared to DTT, JASPER focuses more directly on developmentally informed play and joint attention routines via subtle reinforcements and less intrusive, more indirect prompting. It is likely that this more natural way of interacting provides enough support for those with some words and higher nonverbal cognition to learn from more subtle opportunities. For example, those in Subgroup A have higher play diversity. Since JASPER is play-based, these participants may find play to be more inherently rewarding or motivating, so they are able to learn more from the social interaction. Alternately, since JASPER directly targets play, it may be that this focus is a more developmentally appropriate way to learn relevant language and those with higher ability are able to do so with a lower level of direct instruction and repetition.

5.4 Final Considerations

A one-size-fits-all approach is not necessarily appropriate for minimally verbal children- it becomes apparent that some, especially those with lower scores across domains, have a unique need for more structured and direct instruction. In general, the present results show that minimally verbal children can be classified into subgroups and, dependent upon outcome and treatment duration, profile by treatment effects suggest that DTT may be more beneficial for those with a low nonverbal/low verbal profile and a naturalistic approach such as JASPER may be better for those with higher nonverbal scores. There is no simple answer to the complicated question of which interventions are best for which individuals with ASD, but with the present findings, it is possible to illuminate a clearer picture of what might work best for minimally verbal children with ASD.

6. LIMITATIONS AND FUTURE DIRECTIONS

6.1 Limitations

Although this study represents an important first step in determining what intervention is most effective for which minimally verbal children, no study is perfect and the present one is not without limitations. One limitation results from the present secondary data analyses. As such, all available data has already been collected, in some cases over 6 years ago. Therefore, any missing data at this point is truly missing. The original studies were designed with their own aims in mind and appropriate assessments were selected to accomplish their individual goals. As there is no consensus within the autism intervention literature about which assessments to use (Kasari, Brady, Lord, & Tager-Flusberg, 2013; Fletcher-Watson & McConachie, 2017), this resulted in having different assessments to measure the same constructs across and within studies.

Another limitation is the measures themselves. Most of the included standardized measures are normed in a typically developing sample that does not include minimally verbal children or those with intellectual delays (Kasari, et al., 2013). Most of the standardized measures also primarily measure receptive language in this population in the way they are designed to be administered. As a result, it can be unclear which construct is truly under measurement (Havdahl, et al., 2013; Tager-Flusberg & Kasari, 2013). Minimally verbal children frequently have scores at the floor of the measure or scores that cannot be converted to standard scores or age equivalents. Their chronological age may be too old for the norms while their developmental age is too young to complete the assessments that would have norms for the correct chronological age (e.g. Pickles, Anderson, & Lord, 2014). Improved measurement on standardized assessments for this population is desperately needed.

A third limitation of the present analysis is the combination of identified latent profiles into two subgroups for interaction analyses. The samples under study are particularly large for ASD intervention work, let alone minimally verbal ASD intervention data research. However, the size is small for the goal of investigating interactions within and across more than two profiles, especially when the data warrants use of a hurdle model. Hopefully continued research on this population will allow for a more detailed look at response to intervention across middle discrepant profiles that were collapsed into one for the purposes of the present investigation.

6.2 Future Directions

Future studies should continue to include this population in research investigations, as there is still much to be understood. The present study examined distinct samples, but a longitudinal minimally verbal sample would be a valuable resource. Longitudinal data could provide information about which preschool-age profiles remain minimally verbal at the school-age stage or which profiles gain language to no longer have the minimally verbal designation. For example, Latent Profile Transition Analysis has been used to investigate sensory subtypes and shifts among sensory profiles over the course of 12 months (Ausderau, et al., 2014). Future studies should also aim to look at differences in trajectory and intervention response in the high nonverbal profiles with varying levels of language as previous work suggests that a higher discrepancy between nonverbal and verbal scores may be important to development (Joseph, Tager-Flusberg, & Lord, 2002). A final future direction would be to further investigate differences in response to intervention across domains over the course of an intervention and follow-up period. This information can help to maximize intervention gains and determine courses of interventions.

7. CONCLUSION

Traditionally, studies examining interventions for children with ASD exclude participants with low nonverbal scores or IQ and treat all participants as equal when examining intervention effects. The present studies clearly show that moving the intervention field forward requires a shift in this perspective toward inclusion of participants with low nonverbal cognition and consideration of entry characteristics in intervention evaluation.

The present studies show not only that heterogeneity within ASD can be characterized by phenotype, but that a participant's cognitive profile upon entering a study plays a large role in their response to an intervention. Furthermore, present findings underscore the fact that with high-quality, evidence-based intervention, an hour per day in addition to public school, is sufficient to produce change in language outcomes over the course of 6 weeks, 6 months, and 12 months—even with a minimally verbal sample. Although most ASD intervention research thus far has been something of a horse race, the current analyses underscore the need to optimally pair interventions to an individual's profile. This preliminary investigation suggests that more structured intervention approaches may be more appropriate for the subgroup of low-frequency communicators with lower scores on a range on nonverbal cognition measures while less structured approaches may encourage use of additional words in the subgroup with higher nonverbal cognition. It is still unclear whether that additional structure for the lower subgroup is needed at the start of a course of intervention, or throughout. Also, the mechanism of change and timing of learning for the two profiles remains unclear. It is, however, apparent that the effectiveness of an intervention approach for minimally verbal children with ASD depends on the child's individual phenotype and profile of cognition and behavior. It is also clear that the field has effective interventions, and the next step is determining optimal personalized courses of treatment. As a whole, these studies provide a much-needed deeper look into heterogeneity within minimally verbal children with ASD and how this heterogeneity impacts intervention response. Developing interventions to encourage each child to reach their optimal outcome requires that heterogeneity be characterized to determine which interventions work best for which individuals.

The present studies take a small step toward answering calls for a focus on personalizing intervention by diving into a sample of minimally verbal children ranging in age from 2.5-8 years old to classify their heterogenous needs. Through improving understanding of heterogeneity within minimally verbal children with ASD and their response to intervention, we can begin to move forward into the next phase of intervention research.

8. APPENDIX

8.1 Study 1 Tables and Figures

Table 1-1
Indicator Variables and Assessments

	Aim	Assessment	Variable of Analysis	Coded or Standardized
Clustering Variables				
Autism Severity		ADOS- Module 1		
Social Domain	1, 2, 3		Raw Score	Standardized
RRB Domain	1, 2, 3		Raw Score	Standardized
Adaptive Behavior		VABS		
Daily Living	1, 3		Raw Score	Standardized
Nonverbal Ability	1, 2	Leiter	Age Equivalent	Standardized
	1, 3	MSEL	Age Equivalent	Standardized
Receptive Language	1, 2	PPVT	Raw Score	Standardized
	3	MSEL	Raw Score	Standardized
Verbal Language				
SCU	1, 2	NLS	Frequency	Coded
	3	PCX	Frequency	Coded
NDWR	1, 2	NLS	Frequency	Coded
	3	PCX	Frequency	Coded
Social Communication		ESCS		
Joint Attention	1, 2, 3		Frequency	Coded
Requests	1, 2, 3		Frequency	Coded
Play Diversity- Types	1, 2, 3	SPA	Frequency	Coded

Table 1-2
Mean Inter-Observer Agreement for coded measures

Measure	Variable	Reliability Analysis	Sample 1	Sample 2	Sample 3
SPA	Play Diversity	ICC	0.87	0.89	0.87
ESCS	IJA & IBR	ICC	0.83	0.88	0.83
Language Sample	SCU & NDWR	exact agreement formula	0.98	0.88	not used
PCX-Language	SCU & NDWR	ICC	not used	not used	0.98

Table 1-3
Child Characteristics

values in mean (SD) or % (n)	Sample 1 n = 193	Sample 2 n = 49	Sample 3 n = 171
Age at entry (years)	6.05 (1.34)	6.07 (1.67)	3.80 (0.46)
Male	79.3% (153)	79.6% (39)	83% (142)
ADOS total score	19.98 (3.64)	20.45 (4.29)	18.69 (4.27)
Social Affect	14.56 (2.85)	14.73 (3.54)	14.13 (3.48)
RRB	5.42 (1.93)	5.71 (1.83)	4.56 (1.87)
Nonverbal age equivalent (years)	2.33 (0.50)	4.00 (1.14)	2.07 (0.6)
NDWR at entry	5.54 (6.45)	11.43 (8.09)	5.36 (8.13)
< 10	79.3% (153)	53.0% (26)	73.7% (126)
10-20	17.6% (34)	28.5% (14)	11.7% (20)
20-30	2.6% (5)	18.3% (9)	5.8% (10)
Mother highest education			
Less than high school	7.2% (14)	2.0% (1)	1.8% (3)
High school	9.2% (18)	0	22.3% (38)
Specialized training	6.1% (12)	2.0% (1)	4.1% (7)
College	53.0% (104)	65.3% (32)	56.1% (96)
Graduate/Professional	21.9% (43)	26.5% (13)	13.5% (23)
Race/Ethnicity			
White	44.6% (86)	48.9% (24)	35.7% (61)
African-American	7.8% (15)	16.3% (8)	17.0% (29)
Latinx	23.3% (45)	6.1% (3)	7.6 (13)
Asian	6.7% (13)	20.4% (10)	17.5% (30)
Other/Mixed	17.1% (33)	6.1% (3)	22.2% (38)
Unknown	0.06% (1)	2.0% (1)	0

Table 1-4

1 through 5 profile solutions for Aim 1 minimally verbal school-age model: Fit Indices

	1 Profile	*2 Profiles*	*3 Profiles*	*4 Profiles*	*5 Profiles*
SABIC	12768	12438	12315	12247	12252
Entropy	*na*	0.933	0.920	0.882	0.914
LMR-LRT	*na*	2 *v* 1 Value = 347.11 *p* = 0.0006	3 *v* 2 Value = 142.91 *p* = 0.220	4 *v* 3 Value = 90.30 *p* = 0.0175	4 *v* 3 Value = 17.64 *p*=0.827
BPLRT	*na*	*p*= 0.0000	*p*= 0.000	*p*=0.000	*p*=1.000
Bayes Factor	*na*	$2.18*10^{85}$	$5.11*10^{26}$	$5.83*10^{14}$	0.082
cmP	*na*	0.000	0.000	1.00	0.082
N for each profile	N=193	P1= 45 P2= 145	P1=23 P2= 54 P3= 116	P1= 23 P2= 48 P3= 37 P4= 85	P1= 30 P2= 110 P3= 31 P4= 20 P5= 2

Note: SABIC = Sample-Adjusted Bayes Information Criteria; *LMR-LRT* = Lo-Mendell-Rubin Likelihood Ratio Test; *BPLRT*= Bootstrapped Parametric Likelihood Ratio Test; *cmP*= Correct Model Probability

Table 1-5

1 through 4 profile solutions for Aim 1 minimally verbal school-age model: Variable means

Model	*n*	ADOS SA	ADOS RRB	DL Raw	SCU	NDWR	IJA	IBR	PPVT RAW	DIV TYP	NV AE
1 Profile	193	14.55	5.43	27.03	9.75	5.50	6.64	18.56	22.75	24.88	39.25
SD		2.85	1.92	6.54	12.42	6.43	7.36	9.58	19.01	15.59	14.17
2 Profiles											
Profile 1	45	13.26	4.73	31.39	27.19	15.27	12.47	24.63	28.09	34.34	49.06
Profile 2	148	14.93	5.64	25.81	4.56	2.59	4.98	16.95	21.13	21.99	36.26
3 Profiles											
Profile 1	23	13.32	4.90	29.89	35.02	18.83	14.24	25.99	32.55	34.86	48.39
Profile 2	54	13.57	4.64	30.60	14.89	8.55	8.38	20.84	26.73	31.68	45.09
Profile 3	116	15.23	5.89	24.91	2.34	1.44	4.40	16.26	19.05	19.65	34.68
4 Profiles											
Profile 1	23	13.29	4.87	29.78	35.20	18.94	14.43	26.04	32.58	34.89	48.31
Profile 2	48	14.05	4.77	30.44	16.18	9.30	8.11	19.28	25.56	30.39	44.44
Profile 3	37	12.90	5.03	30.09	3.45	1.91	5.51	22.00	29.75	32.07	49.13
Profile 4	85	15.97	6.15	23.19	2.16	1.39	4.31	14.69	15.15	15.26	28.77

Note: ADOS SA= ADOS Social Affect domain score; ADOS RRB= ADOS Restricted and Repetitive Behavior domain Score, DL Raw- VABS Daily Living domain raw score; SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; JA= Frequency of Joint Attention initiations; BR= Frequency of Behavior Request initiations; PPVT= total raw score of the PPVT; DIV TYP= total number of play levels indicated; NV AE= Nonverbal Age Equivalent, from either the Leiter-R or the MSEL.

Table 1-6

Tukey posthoc comparisons for 4-profile model

Variable	profile relationship
ADOS SA	4 > 1 = 2 = 3
ADOS RRB	4 > 1 = 2 = 3
DL	1 = 2 = 3 > 4
IBR	1 = 2 = 3 > 4
PPVT Raw	1 = 2 = 3 > 4
Diversity- Types	1 = 2 = 3 > 4
NVAE	1 = 2 = 3 > 4
SCU	1 > 2 > 3 = 4
NDWR	1 > 2 > 3 = 4
IJA	1 > 2 = 3 = 2 > 4

Note: < or > denotes significance after correction for multiple tests

Table 1-7

Participant Characteristics for 4-profile model

values in mean (SD) or % (n)	Whole Sample n = 193	Profile 1 n= 23	Profile 2 n= 48	Profile 3 n= 37	Profile 4 n= 85
Age at entry (years)	6.05 (1.34)	6.46 (1.28)	5.89 (1.22)	6.44 (1.36)	5.95 (1.22)
Male	79.3% (153)	65.2% (15)	77.1% (37)	78.4% (29)	83.5% (71)
ADOS total score mean	19.98	18.18	18.98	17.81	22.03
Social Affect	14.56 (2.85)	13.22 (3.55)	14.17 (2.52)	12.84 (2.88)	15.92 (2.12)
RRB	5.42 (1.93)	4.96 (1.96)	4.81 (1.92)	4.97 (2.03)	6.11 (1.67)
Nonverbal age equivalent (years)	3.25 (1.18)	4.25 (0.98)	3.68 (1.10)	4.23 (0.85)	2.38 (0.71)
NDWR at entry	5.54 (6.45)				
0	(10)	0	0	27% (10)	40% (34)
1-10	79.3% (153)	0	68.8% (33)	73% (27)	60% (51)
11-20	17.6% (34)	78.3% (18)	32.2% (15)	0	0
21-30	2.6% (5)	21.7% (5)	0	0	0
Mother highest education					
Less than high school	7.2% (14)	0	4.2% (2)	13.9% (5)	11.9% (10)
High school	9.2% (18)	13.0% (3)	4.2% (2)	5.4% (2)	9.4% (8)
Specialized training	6.1% (12)	8.7% (2)	6.3% (3)	10.8% (4)	3.5% (3)
College	53.0% (104)	43.5% (10)	58.3%(28)	56.7% (21)	48.3% (41)
Graduate/Professional	21.9% (43)	21.7% (5)	25.0% (12)	10.8% (4)	25% (22)
Race/Ethnicity					
White	44.6% (86)	52.2% (12)	47.9% (23)	35.1% (13)	44.7% (38)
African-American	7.8% (15)	4.3% (1)	4.2% (2)	16.2% (6)	7.1% (6)
Latinx	23.3% (45)	21.7% (5)	20.8% (10)	29.7% (11)	21.2% (18)
Asian	6.7% (13)	0	8.3% (4)	5.4% (2)	7 (8.2%)
Other/Mixed	17.1% (33)	21.7% (5)	18.8% (9)	10.8% (4)	11.8% (10)
Unknown	0.06% (1)	0	0	0	1.2% (1)

Figure 1-1

Z-score converted indicator variable means in the 4-profile latent model in the minimally verbal school-age sample

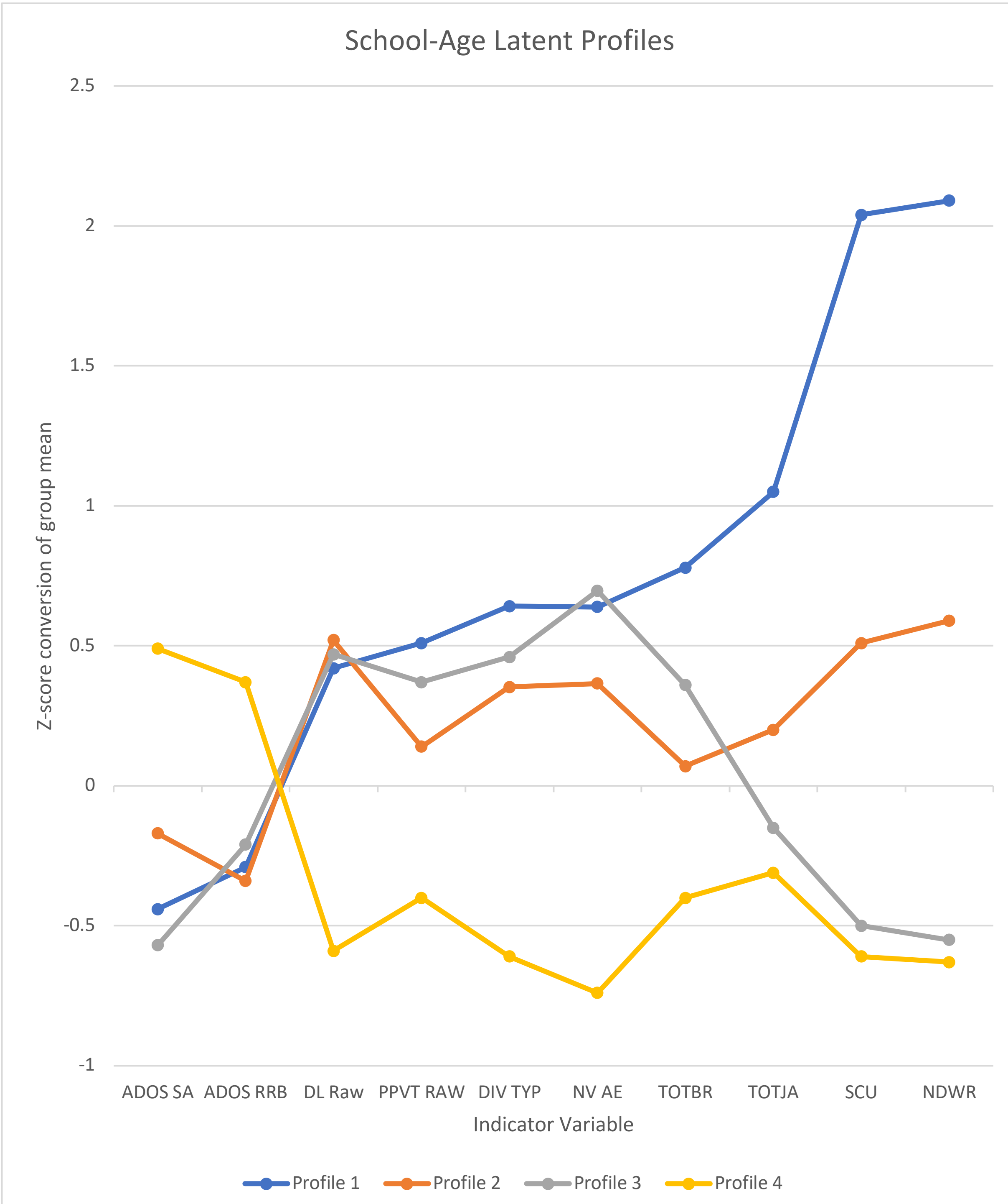


Table 1-8
1 through 4 profile solutions for minimally verbal school-age confirmation model: Fit Indices

	1 Profile	*2 Profiles*	*3 Profiles*	*4 Profiles*
Sample Adjusted BIC	2907	2863	2820	2806
Entropy	*na*	0.978	0.915	0.909
Lo- Mendell- Rubin	*na*	2 *v* 1 Value = 50.17 *p* = 0.240	3 *v* 2 Value = 49.06 *p* = 0.239	4 *v* 3 Value = 20.92 *p* = 0.852
BPLRT	*na*	*p*= 0.0000	*p*= 0.000	*p*=0.66
Bayes Factor	*na*	403.42	403.42	0.0001
cmP	*na*	0.002	0.997	0.0001
N for each profile	P1=49	P1= 45 P2= 4	P1= 19 P2= 26 P3= 4	P1=17 P2= 16 P3= 4 P4= 12

Note: SABIC = Sample-Adjusted Bayes Information Criteria; *LMR-LRT* = Lo-Mendell-Rubin Likelihood Ratio Test; *BPLRT*= Bootstrapped Parametric Likelihood Ratio Test; *cmP*= Correct Model Probability

Table 1-9
1 through profile solutions for minimally verbal school-age confirmation model: Variable means

Model	*n*	ADOS SA	ADOS RRB	SCU	NDWR	IJA	IBR	PPVT	DIV TYP	NV AE
1 Profile	49	14.73	5.71	22.00	11.42	4.95	13.58	31.59	18.93	48.60
SD		3.50	1.81	15.42	8.00	4.96	8.38	16.44	10.26	12.59
2 Profiles										
Profile 1	45	15.14	5.86	22.68	11.63	3.87	12.83	29.62	16.99	47.36
Profile 2	4	10.11	4.01	14.35	9.09	15.15	20.74	53.65	39.71	62.14
3 Profiles										
Profile 1	19	15.63	5.95	35.59	20.01	4.71	12.70	37.07	18.84	52.50
Profile 2	26	14.83	5.80	13.99	5.99	3.06	12.91	24.55	15.67	43.75
Profile 3	4	10.15	4.04	15.02	9.14	14.53	20.75	53.47	39.77	61.99
4 Profiles										
Profile 1	17	14.96	6.09	8.90	3.66	1.80	10.07	25.08	15.37	44.46
Profile 2	16	14.48	5.72	27.01	11.22	4.61	16.40	27.67	16.84	46.17
Profile 3	4	10.04	4.06	15.13	20.74	14.23	9.01	61.69	53.37	39.38
Profile 4	12	16.39	5.74	36.18	23.44	4.48	10.11	38.54	19.22	52.86

Note: ADOS SA= ADOS Social Affect domain score; ADOS RRB= ADOS Restricted and Repetitive Behavior domain Score; SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; JA= Frequency of Joint Attention initiations; BR= Frequency of Behavior Request initiations; PPVT= total raw score of the PPVT; DIV TYP= total number of play levels indicated; NV AE= Nonverbal Age Equivalent, from either the Leiter-R or the MSEL.

Table 1-10

Tukey posthoc comparisons for 3-profile model; < or > denotes significance with correction for multiple tests

Variable	3-profile relationship
ADOS SA	3 > 1 = 2
ADOS RRB	1 = 2 = 3
IBR	1 = 2 = 3
PPVT Raw	3 > 1 = 2
Diversity- Types	3 > 1 = 2
NVAE	2 = 3 > 1 = 2
SCU	2 > 3 = 1
NDWR	2 > 3 = 1
IJA	3 > 2 = 1

Figure 1-2

Z-score indicator variable means of the 3- profile latent model in the minimally verbal school-age confirmation sample

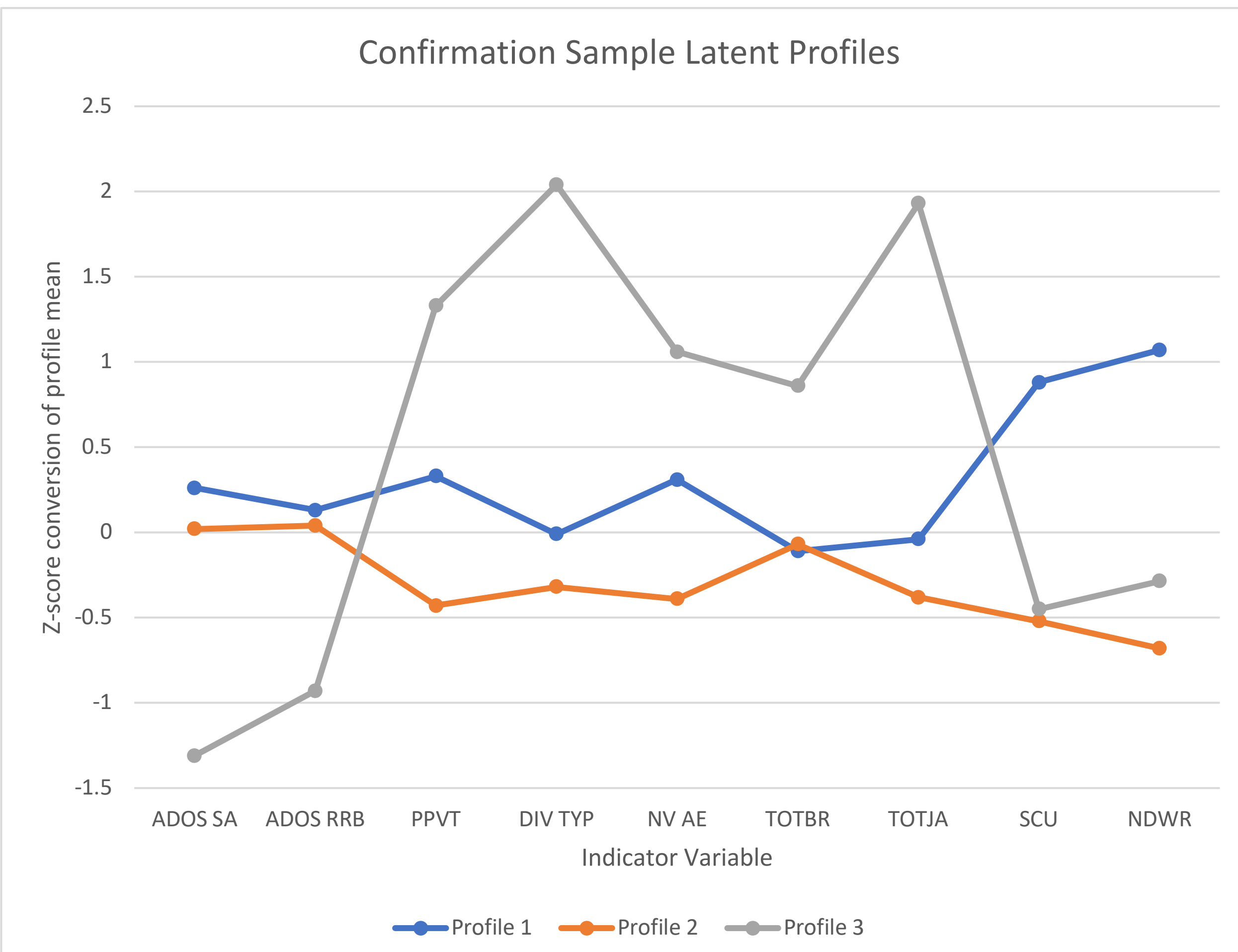


Table 1-11

1 through 6 profile solutions for preschool-age model: Fit Indices

	1 Profile	*2 Profiles*	*3 Profiles*	*4 Profiles*	*5 Profiles*	*6 Profiles*
SABIC	10147	9648	9493	9418	9372	9335
Entropy	*na*	0.969	0.929	0.922	0.926	0.938
LMR-LRT	*na*	2 *v* 1 Value = 511.01 *p* = 0.0006	3 *v* 2 Value = 173.48 *p* = 0.047	4 *v* 3 Value = 94.74 *p* = 0.515	5 *v* 4 Value = 115.74 *p*=0.355	6 *v* 5 Value= 57.38 *p*=0.384
BPLRT	*na*	*p*= 0.000	p= 0.000	*p*=0.000	*p*=0.000	*p*=0.000
Bayes Factor	*na*	$5.07 * 10^{100}$	$1.142 * 10^{26}$	$4.85 * 10^{8}$	244.69	2.71
cmP	*na*	0.000	0.000	0.001	0.268	0.730
N for each profile	P1= 167	P1= 127 P2= 40	P1= 106 P2= 34 P3= 27	P1= 102 P2= 22 P3= 28 P4= 15	P1= 13 P2= 91 P3= 23 P4= 26 P5=14	P1= 8 P2= 13 P3= 90 P4= 23 P5=21 P6= 12

Note: SABIC = Sample-Adjusted Bayes Information Criteria; *LMR-LRT* = Lo-Mendell-Rubin Likelihood Ratio Test; *BPLRT*= Bootstrapped Parametric Likelihood Ratio Test; *cmP*= Correct Model Probability

Table 1-12

1 through 6 profile solutions for the preschool-age model: Variable means

Model	*n*	ADOS SA	ADOS RRB	DL Raw	SCU	NDWR	TOTJA	TOTBR	RL RAW	DIV TYP	NV AE
1 Profile	167	14.17	4.52	30.14	5.44	4.86	5.07	14.65	17.09	19.98	24.85
SD		3.39	1.84	5.51	8.37	6.97	5.71	9.78	6.91	10.52	6.16
2 Profiles											
Profile 1	45	10.21	3.79	34.23	18.14	15.57	8.29	22.53	23.76	27.35	29.75
Profile 2	148	15.48	4.77	29.05	1.45	1.47	4.03	12.15	14.99	17.61	23.31
3 Profiles											
Profile 1	34	12.35	4.29	32.80	5.14	5.07	6.85	19.27	24.67	26.29	32.20
Profile 2	27	10.56	3.80	34.35	21.93	18.25	8.59	22.79	23.57	26.19	27.69
Profile 3	106	15.78	4.97	28.50	1.25	1.30	3.56	11.06	12.96	15.72	21.77
4 Profiles											
Profile 1	22	11.52	3.67	32.55	14.03	12.41	7.49	21.94	23.89	24.96	29.94
Profile 2	28	13.47	4.41	32.99	2.38	2.40	6.77	19.15	23.47	28.54	30.51
Profile 3	15	8.86	4.05	35.83	26.25	21.68	9.27	22.16	23.62	29.46	28.51
Profile 4	102	15.84	4.84	28.35	1.25	1.30	3.43	10.71	12.78	15.34	21.63
5 Profiles											
Profile 1	14	9.87	4.04	35.19	25.95	23.05	8.67	20.78	23.03	29.13	27.00
Profile 2	23	10.72	3.26	33.26	15.10	12.37	8.13	22.77	24.36	25.56	30.78
Profile 3	26	13.51	4.55	33.17	2.33	2.36	6.59	19.07	24.41	28.25	30.99
Profile 4	13	14.93	6.09	26.13	6.49	6.42	4.63	12.60	16.33	12.79	24.33
Profile 5	91	15.89	4.59	28.78	0.51	0.58	3.34	10.68	12.31	16.14	21.30
6 Profiles											
Profile 1	8	10.08	3.71	41.70	1.62	1.44	5.59	34.07	18.68	37.92	19.95
Profile 2	13	15.01	6.15	25.97	6.49	4.73	4.73	12.70	15.93	12.29	24.23
Profile 3	90	15.93	4.60	28.62	0.51	0.57	3.34	10.52	12.22	15.93	21.21
Profile 4	23	10.72	3.63	33.18	14.96	12.30	8.11	22.65	24.43	25.45	30.92
Profile 5	21	14.45	4.73	31.27	2.55	2.59	6.48	13.90	25.42	24.59	31.22
Profile 6	12	10.01	4.10	34.92	25.94	23.04	8.90	19.59	23.45	28.60	27.24

Note: ADOS SA= ADOS Social Affect domain score; ADOS RRB= ADOS Restricted and Repetitive Behavior domain Score, DL Raw- VABS Daily Living domain raw score; SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; JA= Frequency of Joint Attention initiations; BR= Frequency of Behavior Request initiations; PPVT= total raw score of the PPVT; DIV TYP= total number of play levels indicated; NV AE= Nonverbal Age Equivalent, from either the Leiter-R or the MSEL.

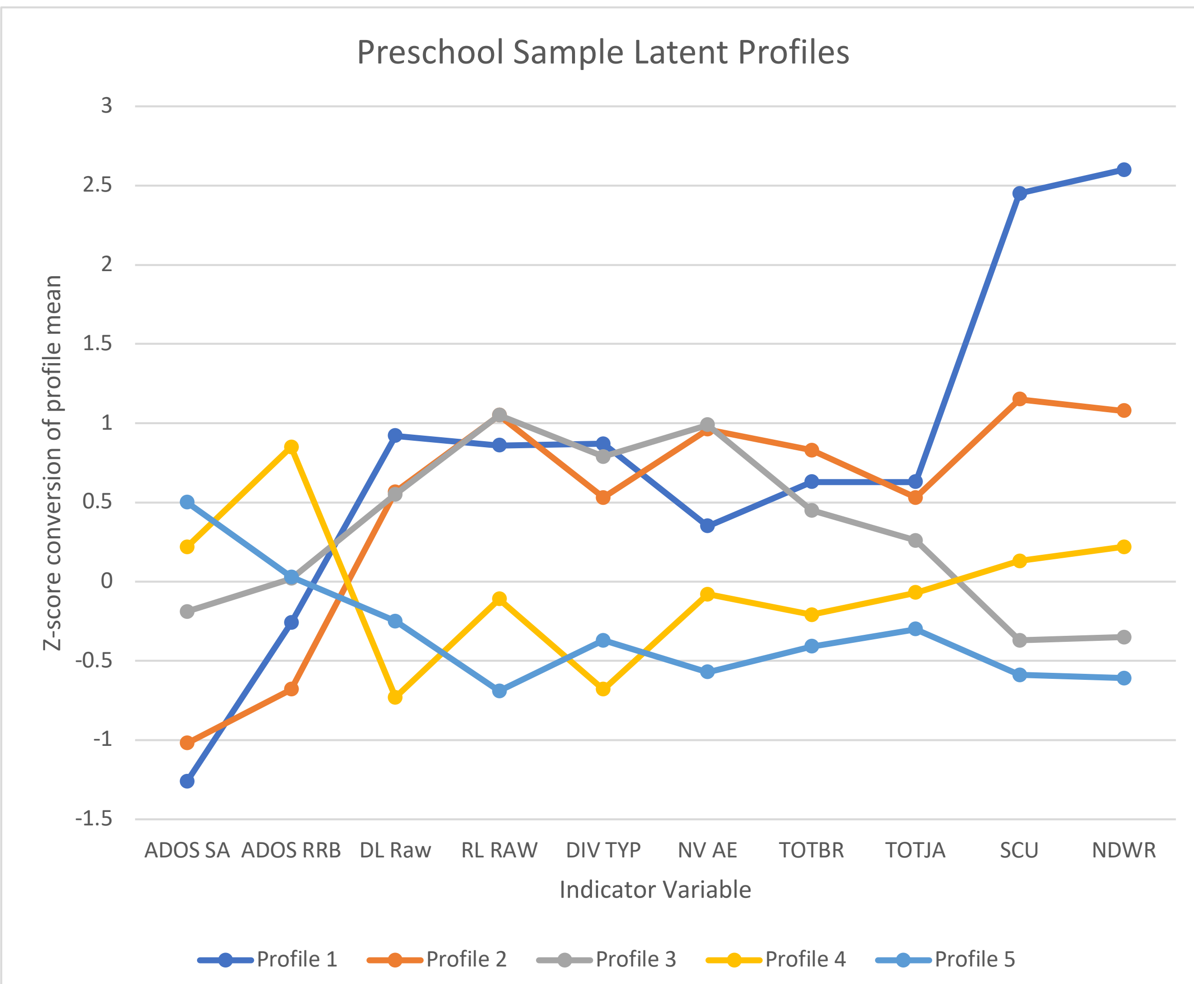
Table 1-13

Tukey posthoc comparisons for 5-profile model; < or > denotes significance with correction for multiple tests

Variable	5-profile relationship
ADOS SA	5 > 3 = 4 = 3 > 2 = 1
ADOS RRB	4 > 5 = 3 = 2 = 1
DL	1 = 2 = 3 > 4 = 5
IBR	1 = 2 = 3 > 4 = 5
RL	1 = 2 = 3 > 4 = 5
Diversity- Types	1 = 2 = 3 > 4 = 5
NVAE	1 = 4 = 3 = 2 > 4 = 5
SCU	1 > 2 > 4 > 3 = 5
NDWR	1 > 2 > 3 > 4 > 5
IJA	2 > 5 = 4 = 3 = 1

Figure 1-3

Z-score indicator variable means of latent profiles in the 5-profile preschool sample model



8.2 Study 2 Tables and Figures

Figure 2-1

Original RCT study design, with focus of analysis highlighted in yellow

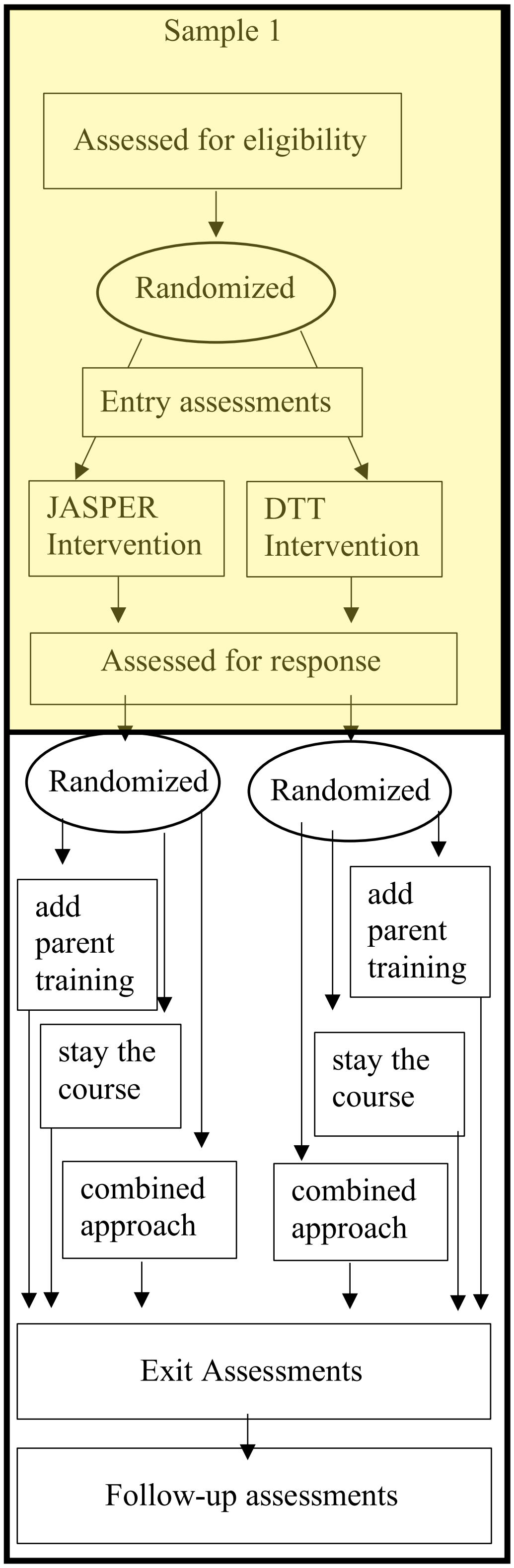


Table 2-1
Measures and Variables

Outcome variable	Aim	Assessment	Variable of Analysis	Coded or Standardized
Verbal Language		NLS		
SCU	1		Frequency	Coded
NDWR	1		Frequency	Coded
Response to Intervention				
Global Improvement Rating	1	CGI-I	Likert Scale	Rating
Prelinguistic Indicator				
Social Communication Initiations		ESCS	Frequency	Coded
Joint Attention- Eye Contact and Gestures	2		Frequency	Coded
Joint Attention- Language	2		Frequency	Coded
Requesting- Eye Contact and Gestures	2		Frequency	Coded
Requesting- Language	2		Frequency	Coded

Table 2-2
Outcome variables- normality descriptives

Outcome	Skew	Kurt	Percent zeroes: n (%)	Mean	Variance
Entry					
SCU	1.80	3.29	41 (20.9%)	9.69	154.9
NDWR	1.41	1.50	44 (22.4%)	5.47	41.50
JA- EC & Gesture	1.42	1.92	38 (19.7%)	4.51	25.21
JA-Language	4.94	29.57	140 (71.4%)	1.80	27.658
BR- Language	1.74	2.64	60 (30.6%)	5.27	50.97
BR- EC& Gesture	0.61	0.72	6 (3.1%)	13.25	57.05
6 week					
SCU	2.21	5.72	31 (15.8%)	16.02	408.99
NDWR	1.81	3.21	34 (17.3%)	9.33	126.04
JA- EC & Gesture	1.65	2.52	39 (20.2%)	4.79	25.78
JA-Language	3.13	12.16	88 (44.9%)	3.10	27.76
BR- Language	1.61	2.34	42 (21.4%)	7.82	89.81
BR- EC & Gesture	0.75	0.87	8 (4.1%)	13.49	62.04

Table 2-3
Model used for each outcome

Outcome variable	Non-parametric?	Zero-inflated?	Over-dispersed?	Model Used
SCU	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
NDWR	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
Responder Status	yes	no	no	Binary Logistic GLM
IJA- EC & Gestures	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
IJA- Language	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
IBR- EC & Gestures	no	no	yes	Linear Mixed Model with Participant-level Random Effects
IBR- Language	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM

Table 2-4
Original 4- profile subgroups and combined profile subgroups: Variable means

Model	*n*	ADOS SA	ADOS RRB	DL Raw	SCU	NDWR	IJA	IBR	PPVT RAW	DIV TYP	NV AE
Original 4- Profile LPA solution											
Profile 1	23	13.29	4.87	29.78	35.20	18.94	14.43	26.04	32.58	34.89	48.31
Profile 2	48	14.05	4.77	30.44	16.18	9.30	8.11	19.28	25.56	30.39	44.44
Profile 3	37	12.90	5.03	30.09	3.45	1.91	5.51	22.00	29.75	32.07	49.13
Profile 4	85	15.97	6.15	23.19	2.16	1.39	4.31	14.69	15.15	15.26	28.77
Combined profiles for interaction analyses											
Subgroup A	108	13.51	4.90	29.98	15.70	8.71	8.73	22.22	28.18	32.33	47.33
Subgroup B	85	15.97	6.15	23.19	2.16	1.39	4.31	14.69	15.15	15.26	28.77

Note: ADOS SA= ADOS Social Affect domain score; ADOS RRB= ADOS Restricted and Repetitive Behavior domain score, DL Raw- VABS Daily Living domain raw score; SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; IJA= Frequency of Joint Attention initiations; IBR= Frequency of Behavior Request initiations; PPVT= total raw score of PPVT; DIV TYP= total number of play levels indicated; NV AE= Nonverbal age equivalent, from either the Leiter-R or the MSEL.

Figure 2-2

Subgroup means- converted to z-scores for display

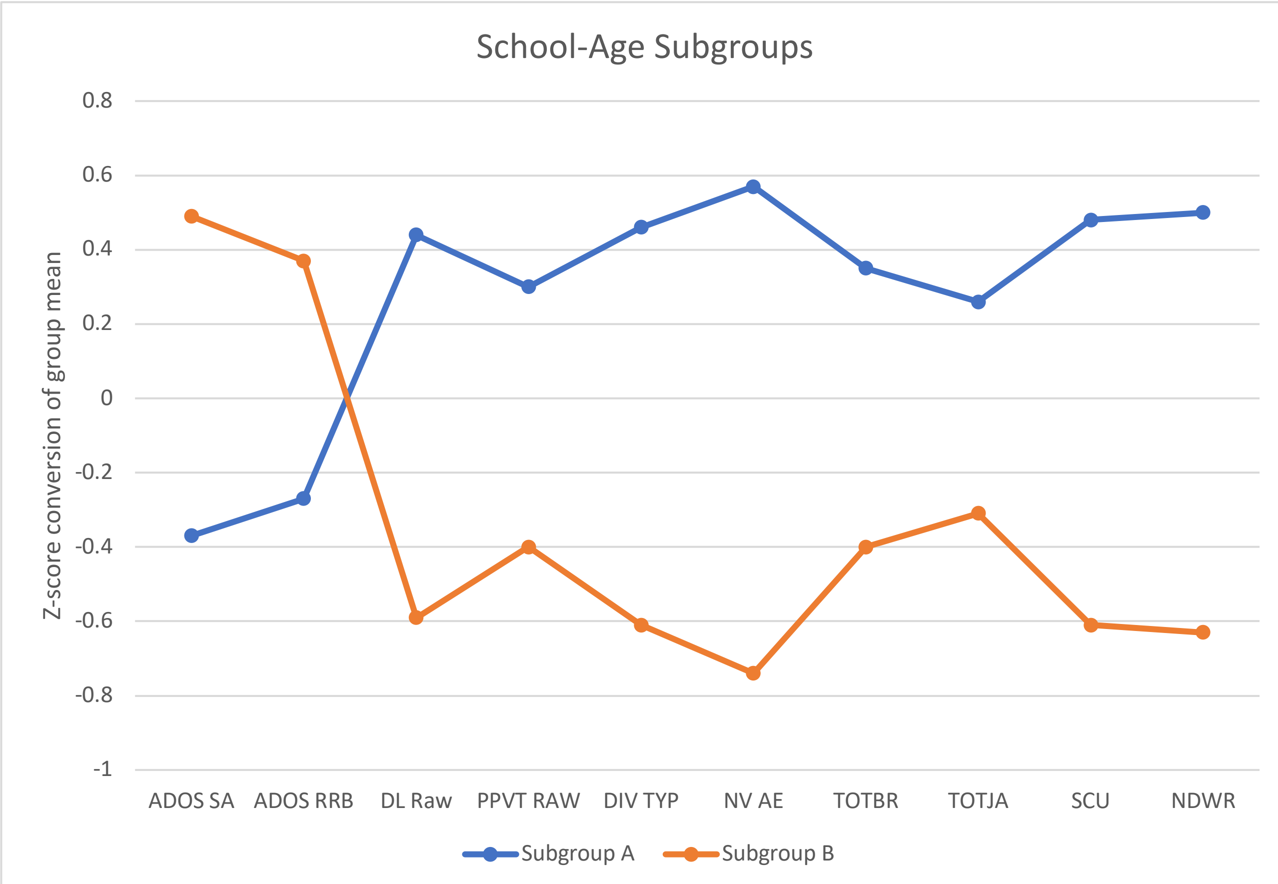


Table 2-5
Participant Characteristics

Variable: mean (SD) or % (n)	Whole Sample n = 193	Subgroup A n= 108	Subgroup B n= 85	p-value (t-test or ANOVA)
Age at entry (years)	6.05 (1.34)	6.19 (1.30)	5.95 (1.22)	0.081
Male	79.3% (153)	75.0% (81)	83.5% (71)	0.061
ADOS total score mean	19.98	18.41	22.03	
Social Affect	14.56 (2.85)	13.51 (2.92)	15.92 (2.12)	0.000**
RRB	5.42 (1.93)	4.90 (1.95)	6.11 (1.67)	0.000**
Nonverbal age equivalent (years)	3.25 (1.18)	3.94 (1.02)	2.38 (0.71)	0.000**
NDWR at entry	5.54 (6.45)			0.000**
0	22.7% (44)	9.3% (10)	40% (34)	
1-10	57.5% (111)	55.5% (60)	60% (51)	
11-20	17.6% (33)	30.3% (33)	0	
21-30	2.6% (5)	4.6% (5)	0	
Mother highest education				0.623
Less than high school	7.2% (14)	6.5% (7)	11.9% (10)	
High school	9.2% (18)	6.5% (7)	9.4% (8)	
Specialized training	6.1% (12)	8.3% (9)	3.5% (3)	
College	53.0% (104)	57.4% (62)	48.3% (41)	
Graduate/Professional	21.9% (43)	19.4% (21)	25% (22)	
Race/Ethnicity				0.836
White	44.6% (86)	44.4% (48)	44.7% (38)	
African-American	7.8% (15)	8.3% (9)	7.1% (6)	
Latinx	23.3% (45)	24.1% (26)	21.2% (18)	
Asian	6.7% (13)	5.6% (6)	7 (8.2%)	
Other/Mixed	17.1% (33)	16.7% (18)	11.8% (10)	
Unknown	0.06% (1)	0.9% (1)	1.2% (1)	

Table 2-6
6- week outcome means by subgroup and intervention

Variable	Subgroup A		Subgroup B	
	DTT	JASPER	DTT	JASPER
	n= 56	n=51	n=40	n= 45
Baseline Outcomes				
SCU	15.63	15.98	1.92	2.18
NDWR	8.34	9.24	1.36	1.33
n at 0	6	4	16	18
IJA EC & Gesture	3.59	4.73	4.50	3.89
IJA Language	3.39	3.45	0.09	0.25
IBR EC & Gesture	13.52	14.48	13.98	11.71
IBR Language	8.57	7.78	1.17	2.16
N at site				
1	18	13	6	11
2	11	11	12	14
3	15	11	6	8
4	12	16	16	12
Outcomes at 6 weeks				
SCU	21.50	23.35	8.79	6.67
NDWR	12.21	15.61	4.56	2.98
n at 0	2	3	14	14
IJA EC & Gesture	4.41	6.18	5.00	4.91
IJA Language	4.98	4.76	0.85	0.62
IBR EC & Gesture	13.64	12.76	14.08	13.60
IBR Language	10.41	11.18	3.08	3.91
Responder % (n)	64.3% (36)	54.9% (28)	40% (16)	39.02% (16)

Table 2-7
School-age model summaries

Outcome	Effect of Subgroup?	Subgroup* Intervention interaction?
Primary outcomes		
SCU	yes	no
NDWR	yes	yes
Responder	yes	no
Secondary Outcomes		
IJA- Nonverbal	no	no
IBR- Nonverbal	no	no
IJA- Language Combinations	yes	no
IBR- Language Combinations	yes	no

Table 2-8

Language outcomes- from the NLS

Truncated Negative Binomial (hurdle) models

Outcome	Fixed Effects	Zero Hurdle Model Binomial with logit link			Count Model Truncated Negative Binomial with log link		
		OR	z-value	p-value	Estimate	z-value	p-value
SCU	Intercept	7.79	1.94	0.052	2.37	13.57	0.000**
	SCU at Entry	1.83	3.51	0.000**	0.03	4.88	0.000**
	Intervention	0.13	-1.54	0.122	0.12	0.69	0.487
	Subgroup	0.11	-1.95	0.050*	0.03	0.15	0.875
	Intervention*Subgroup	8.68	1.56	0.117	-0.52	-1.67	0.093
NDWR	Intercept	4.19	1.84	0.065	1.64	11.63	0.000**
	NDWR at Entry	2.31	3.70	0.000**	0.08	7.95	0.000**
	Intervention	0.34	-1.02	0.303	0.12	0.82	0.512
	Group	0.18	-1.97	0.048*	0.04	0.25	0.801
	Intervention *Group	3.51	1.09	0.273	-0.65	-2.50	0.012*

Note: SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; site was not a significant model term and was removed from the final model; OR= Odds Ratio

**p* =/< 0.05, ** *p*<0.01

Figure 2-3

6-week SCU scores by subgroup and intervention

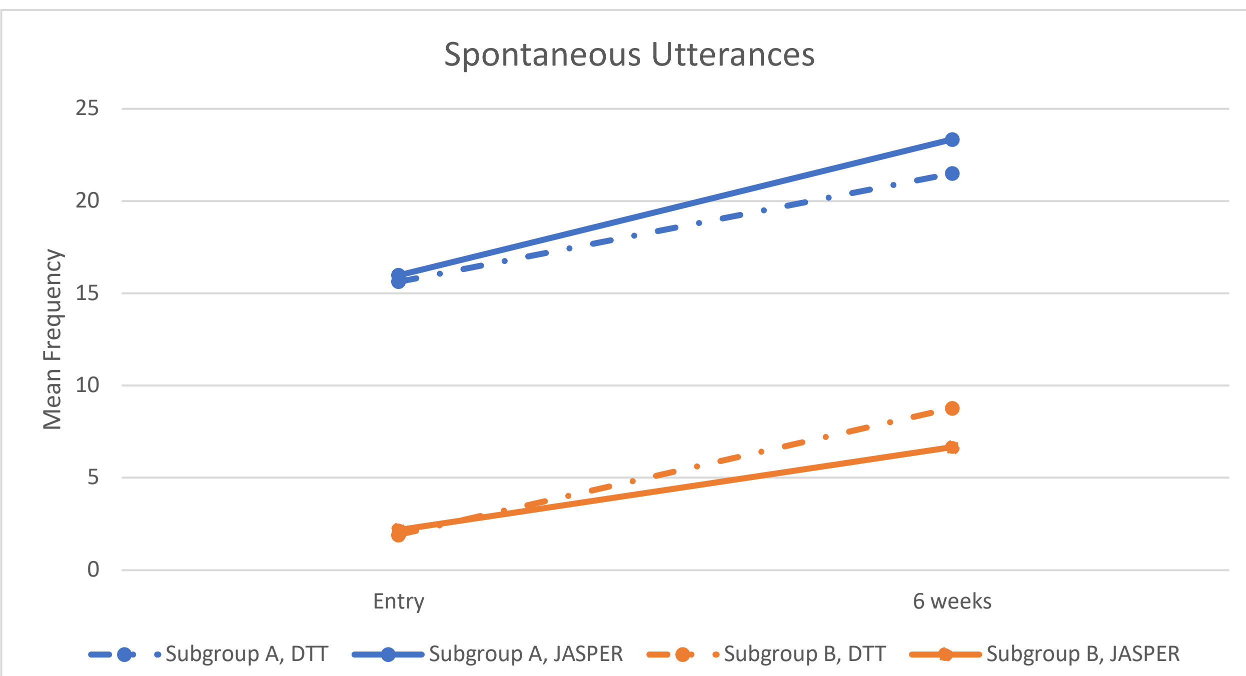


Figure 2-4

6-week NDWR scores by subgroup and intervention

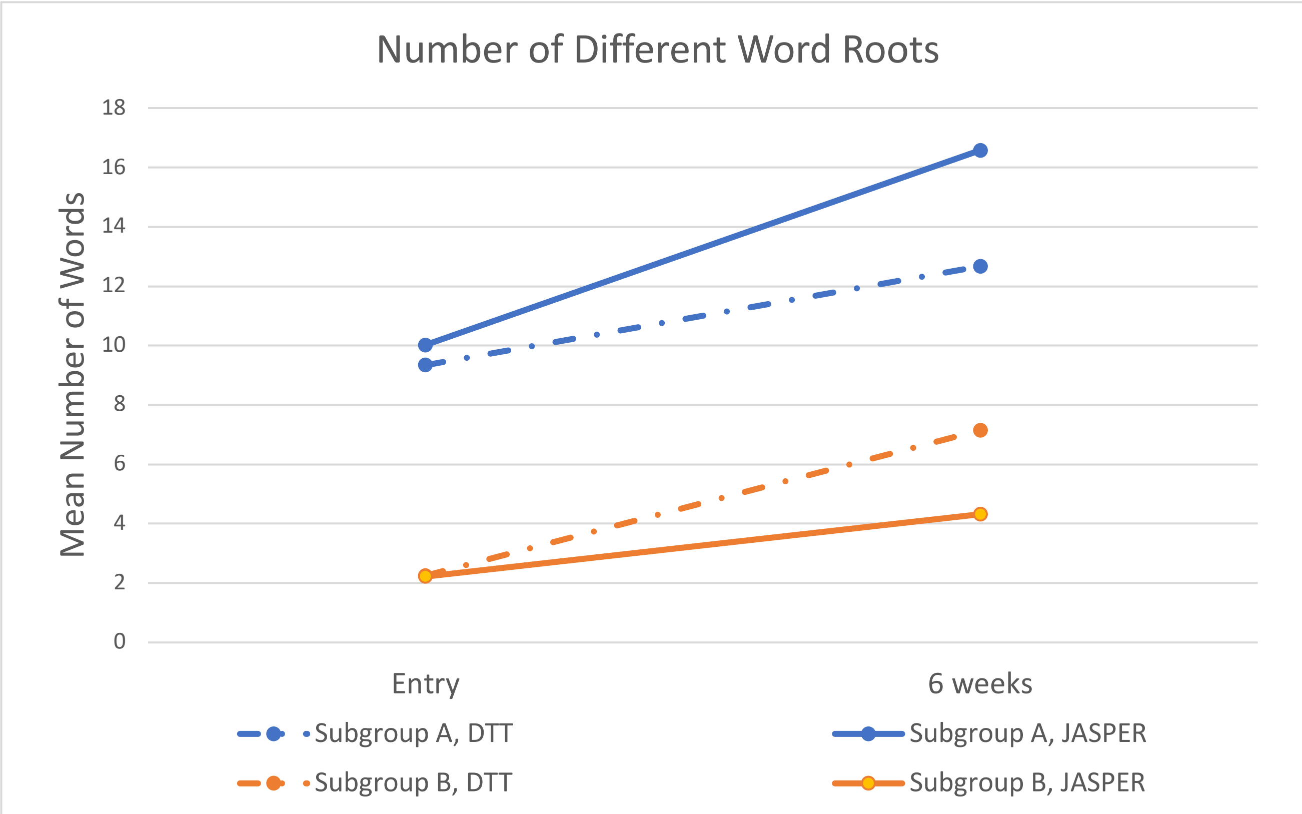


Table 2-9

Logistic binomial regression model for responder status across subgroups

Model	Model Term	Odds Ratio	SE	Wald z statistic	p-value
Responder Status	Intercept	3.36	0.39	3.80	0.002
	Site 1 as reference group			Wald χ^2= 8.9	0.031*
	Site 2	0.69	0.43	-0.84	0.396
	Site 3	0.42	0.45	-1.88	0.060
	Site 4	0.30	0.42	-2.76	0.005**
	Intervention	0.75	0.40	-0.70	0.482
	Subgroup	0.39	0.44	-2.09	0.036*
	Intervention * Subgroup	0.95	0.61	-0.07	0.943

*$p < 0.05$, ** $p< 0.01$

Figure 2-5

Responders by subgroup and intervention

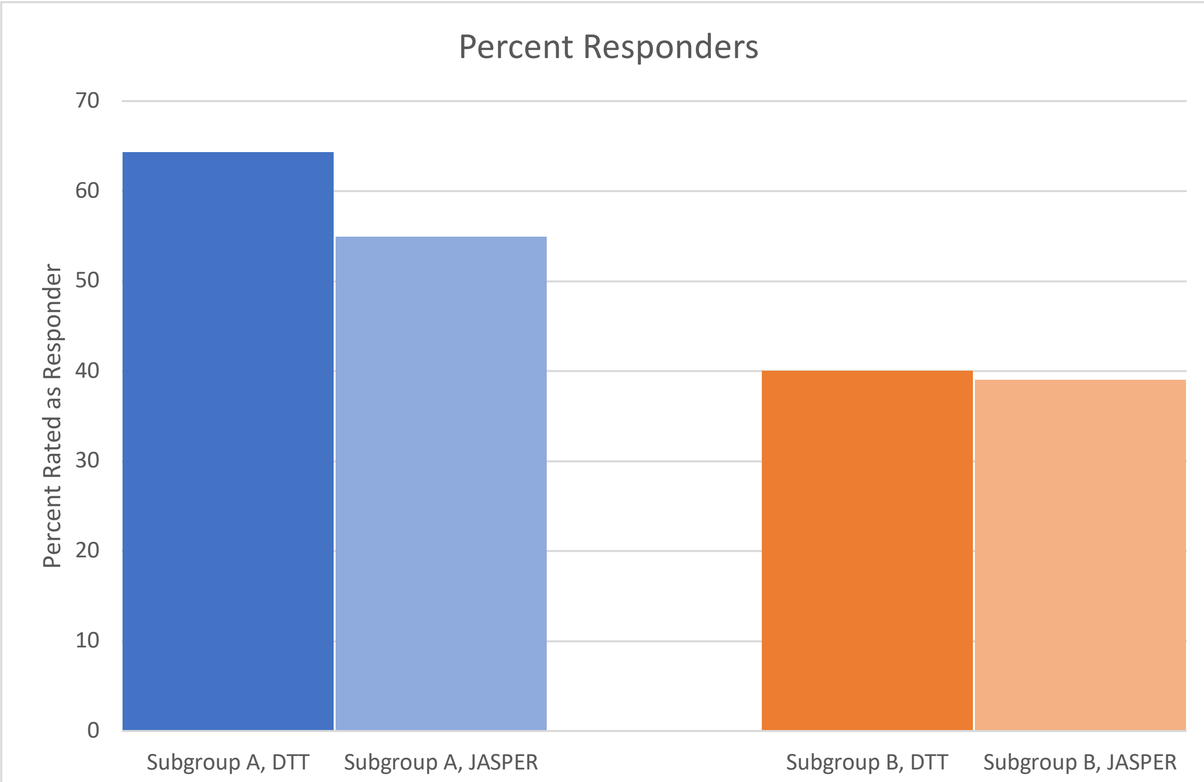


Table 2-10

Prelinguistic outcomes – IBR- Eye Contact and Gesture

Linear mixed model, including control for site and participant-level random effects

Model	Fixed Effects	Estimate	SE	Wald χ^2 / t-value	p-value
IBR- Eye Contact & Gesture	Intercept	11.56	1.24		
	Site: Site 1 as reference			9.76	0.020*
	Site 2	3.98	1.29	3.07*	
	Site 3	2.30	1.34	1.71	
	Site 4	2.58	1.25	2.06*	
	Time	0.12	1.14	0.00	0.946
	Intervention	0.75	1.47	0.42	0.512
	Subgroup	-0.16	1.59	0.53	0.466
	Intervention*Subgroup	-2.78	2.22	0.27	0.599
	Time*Subgroup	-0.02	1.78	2.10	0.146
	Time*Intervention	-1.85	1.66	0.03	0.846
	Time*Intervention*Subgroup	3.63	2.50	2.11	0.145

*$p < 0.05$, ** $p < 0.01$

Figure 2-6

Scores by subgroup and intervention - IBR Eye Contact & Gesture

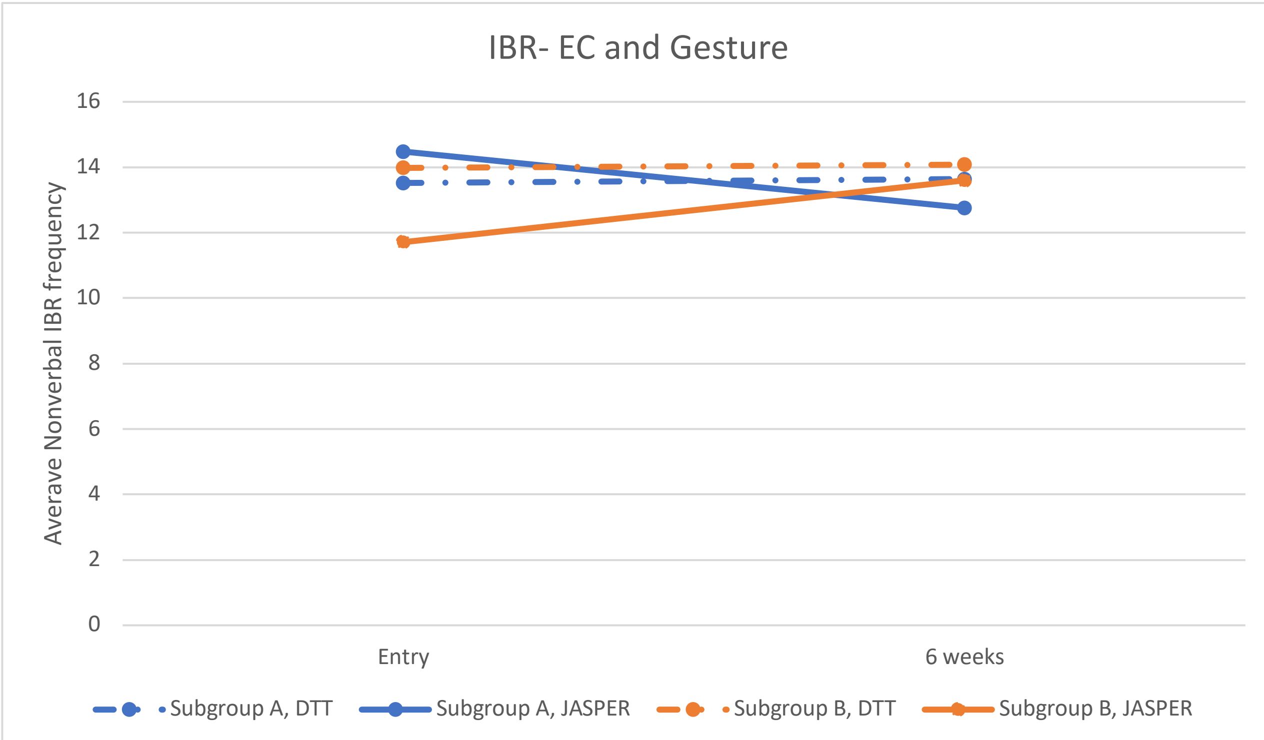


Table 2-11

Prelinguistic outcomes from the ESCS: IJA Eye Contact & Gesture
Zero-Inflated Truncated Negative Binomial Model

Model	Fixed Effects	Zero Hurdle Model Binomial with logit link			Count Model Negative Binomial with log link		
		Odds Ratio	z value	p-value	Estimate	z value	p-value
IJA- EC & Gesture	Intercept	3.90	2.31	0.020*	0.68	3.02	0.002**
	Entry IJA-EC & Gesture	1.15	2.33	0.019*	0.06	4.29	0.000**
	Intervention	0.98	-0.02	0.981	0.08	0.39	0.649
	Site 1 as reference group			likelihood ratio test $\chi^2(3)$= 8.6	p= 0.03*		
	Site 2	1.89	0.82	0.408	0.59	2.86	0.004**
	Site 3	0.12	-3.52	0.000**	0.47	1.71	0.086
	Site 4	0.75	-0.44	0.656	0.39	1.89	0.057
	Subgroup	1.18	0.28	0.773	0.21	0.96	0.335
	Intervention*Subgroup	1.40	0.39	0.694	-0.07	-0.02	0.981

*$p < 0.05$, ** $p<0.01$

Figure 2-7
Scores by subgroup and intervention - IJA Eye Contact & Gesture

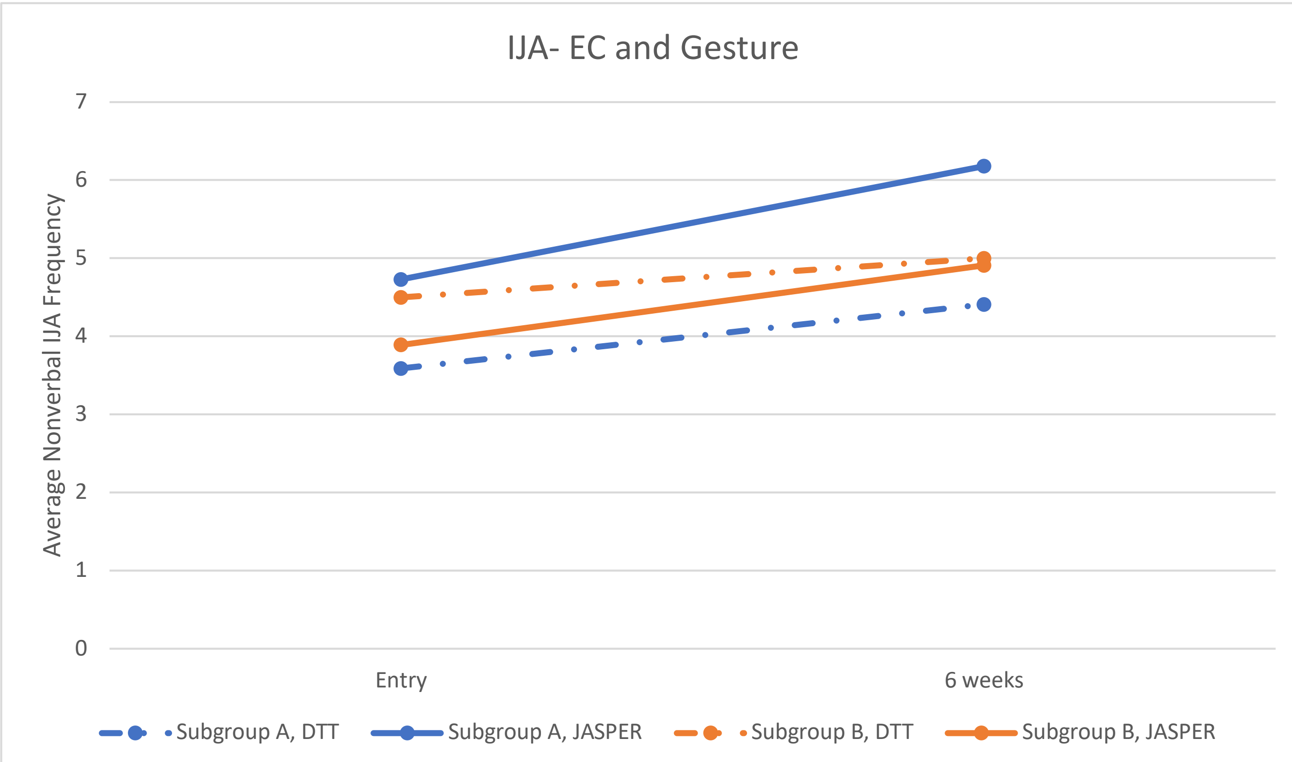


Table 2-12
Language combination outcomes from the ESCS
Negative Binomial GLM

Model	Fixed Effects	Zero Hurdle Model			Count Model		
		Binomial with logit link			Truncated Negative Binomial with log link		
		OR	z value	p-value	Estimate	z value	p-value
IJA-LANG	Intercept	2.03	2.23	0.025*	1.56	9.40	0.000**
	IJA-Lang at entry	1.22	2.03	0.042*	0.04	3.27	0.001**
	Intervention	1.31	0.57	0.568	-0.13	-0.63	0.527
	Subgroup	0.17	-3.62	0.000**	-0.72	-1.97	0.047*
	Intervention*Subgroup	0.71	-0.48	0.629	-0.34	-0.64	0.517
IBR-LANG	Intercept	3.79	2.55	0.010*	1.88	9.25	0.000**
	IBR-Lang at entry	1.25	2.74	0.005**	0.04	3.14	0.001**
	Intervention	0.55	-0.90	0.364	0.20	0.94	0.347
	Subgroup	0.25	-2.29	0.021*	-0.44	-1.51	0.130
	Intervention*Subgroup	3.83	1.66	0.095	-0.27	-0.72	0.466

Note: site was not a significant model term and was removed from the final model
**p* < 0.05, ** *p*<0.01

Figure 2-8

Scores by subgroup and intervention - IJA Language and Language Combinations

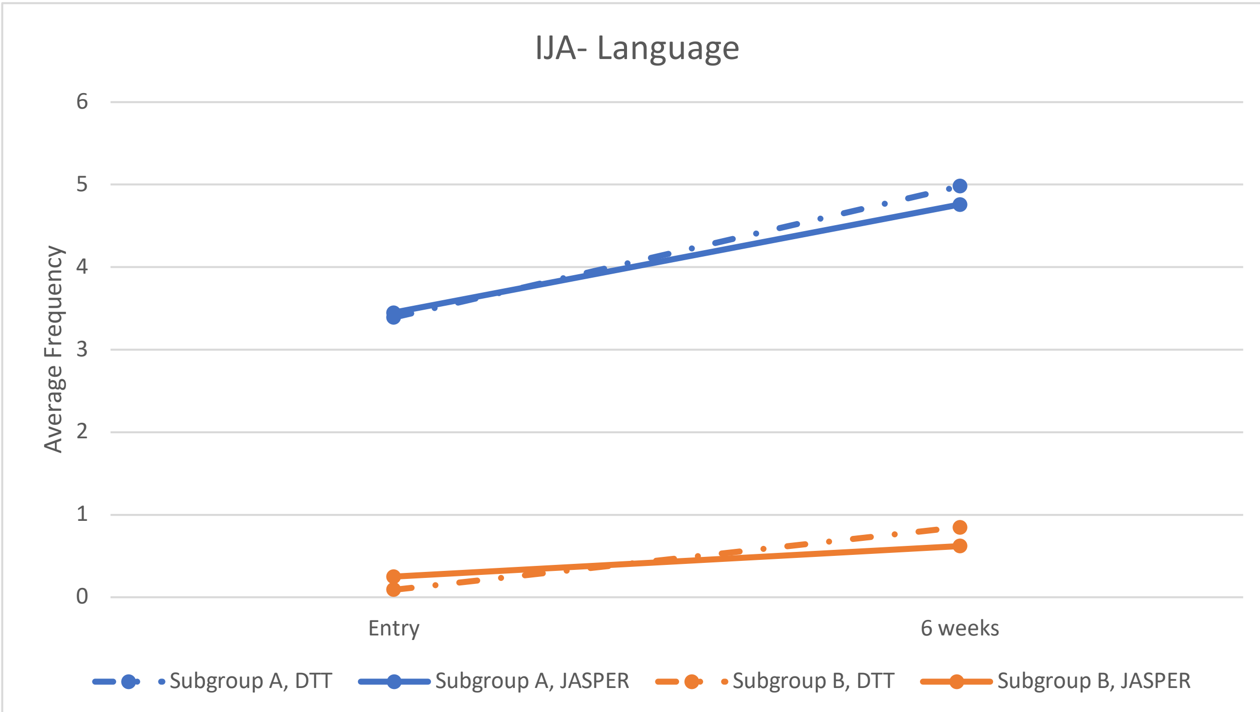
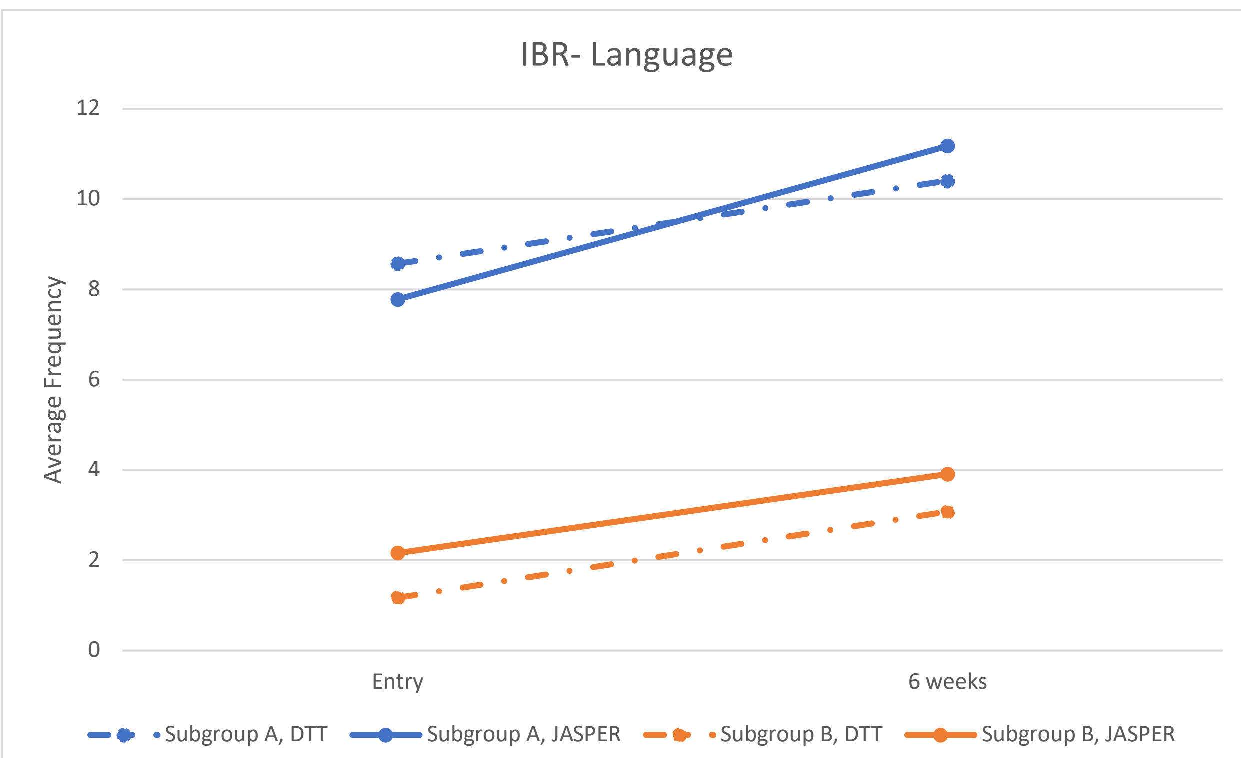


Figure 2-9

Scores by subgroup and intervention - IBR Language and Language Combinations



8.3 Study 3 Tables and Figures

Figure 3-1

Preschool-age study design: Focus of analysis highlighted in yellow

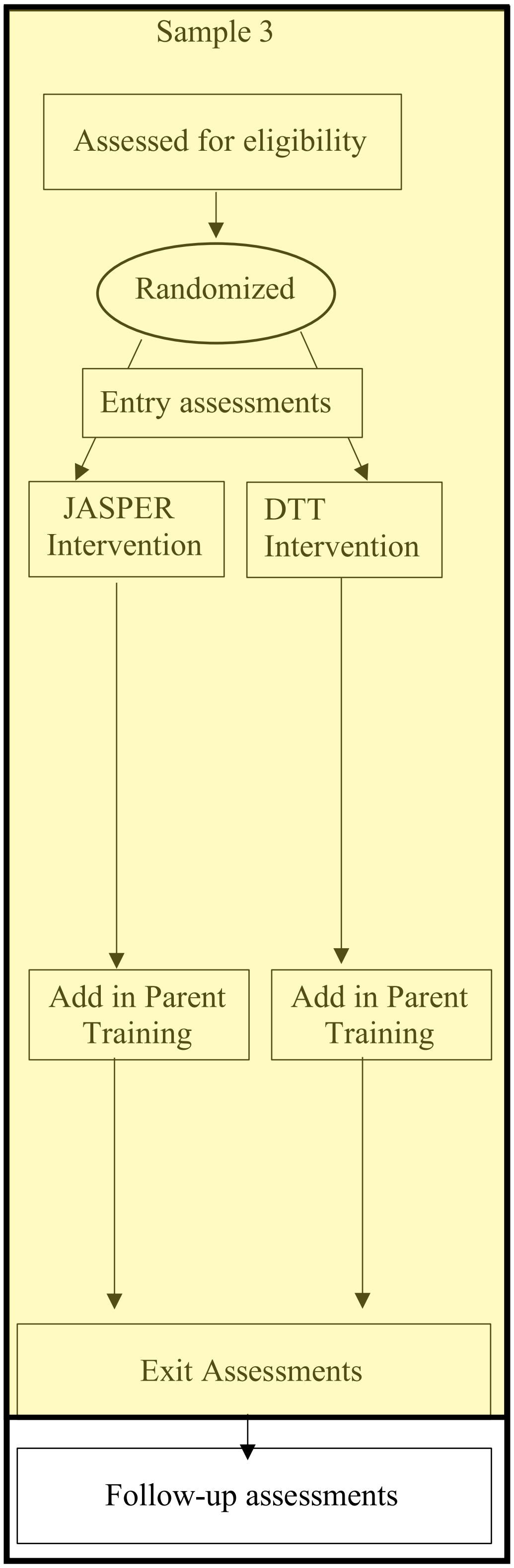


Table 3-1
Preschool- age model measures and variables

Outcome variable	Aim	Assessment	Variable of Analysis	Coded or Standardized
Verbal Language		PCX		
SCU	1		Frequency	Coded
NDWR	1		Frequency	Coded
Prelinguistic Indicator: Communication Initiations		ESCS		
Joint Attention- Eye Contact and Gestures	2		Frequency	Coded
Joint Attention- Language	2		Frequency	Coded
Requesting- Eye Contact and Gestures	2		Frequency	Coded
Requesting- Language	2		Frequency	Coded

Table 3-2
Outcome variables- normality descriptives

Outcome	Skew	Kurt	Percent zeroes: n (%)	Mean	Variance
Entry					
SCU	1.949	3.505	65 (40.4%)	5.37	68.96
NDWR	1.66	2.049	67 (41.6%)	4.77	48.26
JA- Eye Contact & Gestures	2.585	8.56	44 (27.3%)	3.22	19.3
JA-Language	2.50	6.32	104 (64.6%)	1.65	10.85
BR- Language	2.16	4.43	86 (53.4%)	2.84	24.24
BR- EC/Gest	1.43	2.72	9 (5.6%)	11.28	72.45
6 week					
SCU	2.45	8.50	45 (28.0%)	9.68	179.42
NDWR	2.08	5.14	45 (28.0%)	10.01	173.06
JA- Eye Contact & Gestures	2.33	6.53	48 (29.8%)	4.07	31.31
JA-Language	1.74	2.52	67 (41.6%)	5.35	61.90
BR- Language	1.32	0.72	58 (36.0%)	7.02	81.31
BR- EC/Gest	1.18	1.96	9 (5.6%)	10.54	62.60

Table 3-3
Model used for each outcome

Outcome variable	Non-parametric?	Zero-inflated?	Over-dispersed?	Model Used
SCU	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
NDWR	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
IJA- Eye Contact and Gesture	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
IJA- Language	yes	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM
IBR- Eye Contact and Gestures	no	no	yes	Linear Mixed Model with Participant-level Random Effects
IBR- Language	no	yes	yes	Zero-Truncated (Hurdle) Negative Binomial GLM

Table 3-4
Preschool-age model: Variable means

Model	*n*	ADOS SA	ADOS RRB	DL Raw	SCU	NDWR	IJA	IBR	RL Raw	DIV TYP	NV AE
5 Original Profiles											
Profile 1	13	9.87	4.04	35.19	25.95	23.05	8.67	20.78	23.03	29.13	27.00
Profile 2	23	10.72	3.26	33.26	15.10	12.37	8.13	22.77	24.36	25.56	30.78
Profile 3	23	13.51	4.55	33.17	2.33	2.36	6.59	19.07	24.41	28.25	30.99
Profile 4	13	14.93	6.09	26.13	6.49	6.42	4.63	12.60	16.33	12.79	24.33
Profile 5	89	15.89	4.59	28.78	0.51	0.58	3.34	10.68	12.31	16.14	21.30
2 Profile regrouping											
Subgroup A	59	11.75	4.05	33.10	12.37	10.49	7.41	20.69	24.17	27.42	30.14
Subgroup B	102	15.75	4.79	28.48	1.32	1.46	3.41	10.38	12.74	15.75	21.66

Figure 3-2
Z-score indicator variable means of latent profiles in the 2- subgroup preschool sample model

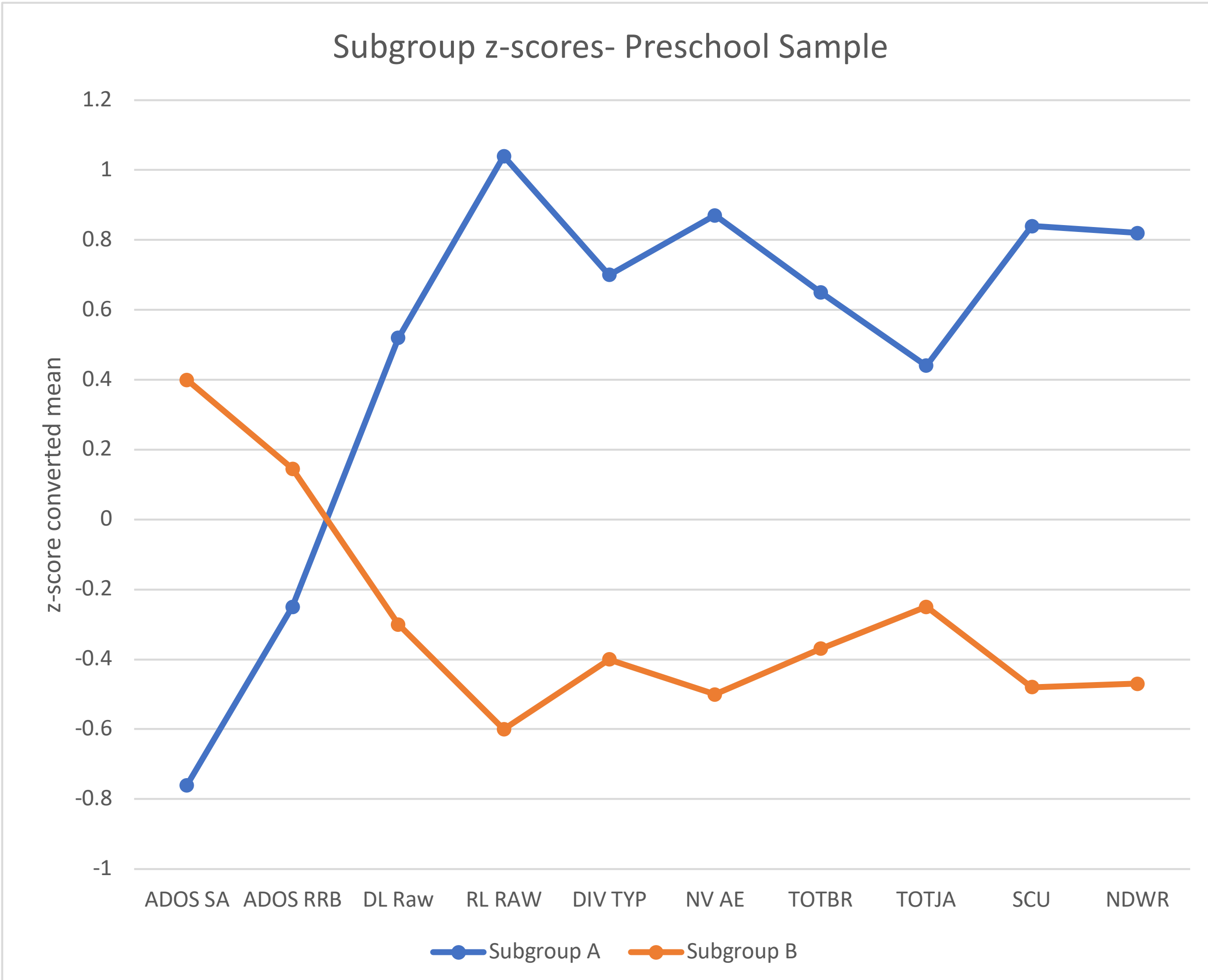


Table 3-5
Participant characteristics at entry

Variable: mean (SD) or % (n)	Whole Sample n = 161	Subgroup A n= 59	Subgroup B n= 102	p-value (ANOVA or t-test)
Age at entry (years)	3.80 (0.45)	3.90 (0.43)	3.74 (0.46)	0.619
Male	83.8% (135)	81.4% (48)	84.3% (75)	0.516
ADOS scores				
Social Affect	14.29 (3.33)	11.75 (3.62)	15.75 (2.03)	0.000**
RRB	4.52 (6.17)	4.05 (1.59)	4.79 (1.96)	0.016*
Nonverbal age equivalent (years)	2.06 (0.51)	2.51 (0.52)	1.80 (0.27)	0.000**
NDWR at entry				0.000**
0	41.6% (67)	8.5% (5)	60.8% (62)	
1-10	39.1% (63)	40.6% (24)	39.2% (39)	
11-20	13.04% (21)	33.9% (20)	1.0% (1)	
21-30	6.2% (10)	17.0% (10)	0	
Mother highest education				0.487
< high school	6.2% (10)	6.8% (3)	6.9% (7)	
High school	18.0% (29)	20.3% (12)	16.7% (17)	
Specialized training	4.3% (7)	5.1% (3)	3.9% (4)	
College	53.4% (86)	57.6% (34)	56.9% (58)	
Graduate/Professional	14.3% (23)	11.9% (7)	15.7% (16)	
Ethnicity				0.648
White	35.4% (57)	28.8% (17)	39.2% (40)	
African-American	16.7% (27)	11.9% (7)	19.6% (20)	
Latinx	6.8% (11)	11.9% (7)	3.9% (4)	
Asian	18.0% (29)	20.3% (12)	16.7% (17)	
Other/Mixed	19.8% (32)	27.2% (16)	19.6% (20)	
Unknown	0	0	0	

Table 3-6
6- month outcome means by subgroup and intervention

Outcome Variable	Subgroup A		Subgroup B	
	DTT	JASPER	DTT	JASPER
	n= 31	n= 28	n= 48	n= 54
Baseline				
SCU	10.94	13.96	1.15	1.48
NDWR	8.42	12.79	1.21	1.69
n at 0	3	2	28	34
IJA EC and Gesture	4.81	3.36	3.44	1.88
IJA Language	2.23	4.46	0.79	0.63
IBR EC and Gesture	13.97	15.36	9.38	9.31
IBR Language	4.19	8.11	0.71	1.22
N at site				
Site 1	18	16	14	16
Site 2	9	6	14	19
Site 3	4	6	20	19
6-month exit				
SCU	15.29	19.54	5.33	5.20
NDWR	17.45	20.64	5.63	4.13
n at 0	3	2	17	23
IJA EC and Gesture	5.52	4.00	3.67	3.63
IJA Language	8.45	11.89	3.40	1.93
IBR EC and Gesture	11.94	9.32	10.19	10.69
IBR Language	11.26	12.18	5.98	2.85

Table 3-7
Model Summaries

Outcome	Effect of Subgroup?	Subgroup* Intervention interaction?
Primary outcomes		
SCU	no	no
NDWR	yes	yes
Secondary Outcomes		
IJA- Nonverbal	no	no
IBR- Nonverbal	yes	no
IJA- Language Combinations	yes	yes
IBR- Language Combinations	yes	yes

Table 3-8
Language outcomes- from the PCX
Truncated Negative Binomial (hurdle) models

Model	Fixed Effects	Zero Hurdle Model Binomial with logit link			Count Model Truncated Negative Binomial with log link		
		OR	z value	p-value	Estimate	z value	p-value
SCU	Intercept	2.60	1.39	0.164	2.19	8.64	0.000**
	SCU at Entry	1.25	2.69	0.006**	0.03	2.93	0.003**
	Intervention	0.86	-0.14	0.888	0.25	0.98	0.325
	Subgroup	0.55	-0.79	0.427	-0.27	-0.93	0.35
	Intervention*Subgroup	0.79	-0.20	0.839	-0.14	-0.41	0.68
NDWR	Intercept	2.59	1.39	0.161	2.49	11.94	0.000**
	NDWR at Entry	1.32	2.98	0.002**	0.04	2.93	0.003**
	Intervention	0.78	-0.23	0.818	0.03	-0.23	0.846
	Subgroup	0.52	-0.87	0.383	-0.48	-1.96	0.049*
	Intervention*Subgroup	0.86	-0.13	0.894	-0.25	-0.80	0.418

Note: SCU= Spontaneous Communicative Utterances; NDWR= Number of Different Word Roots; Site was not a significant term and was removed from the final models
$^*p < 0.05$, $^{**} p<0.01$

Figure 3-3
SCU across time by subgroup and intervention

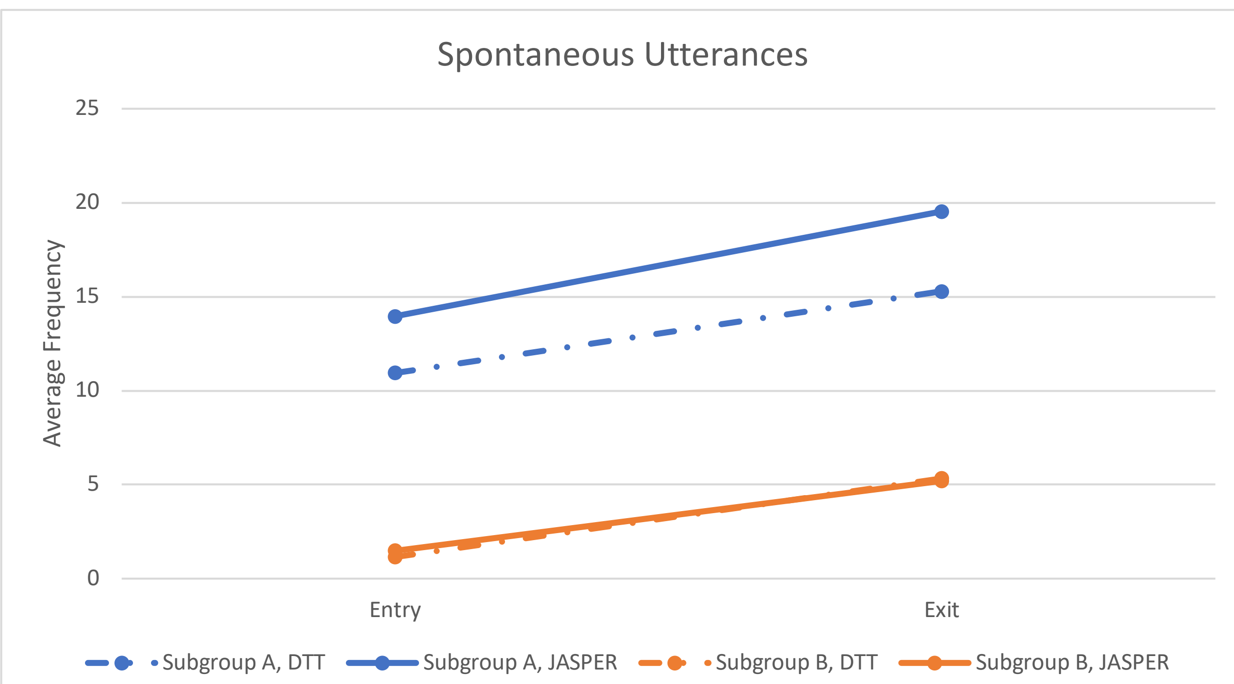


Figure 3-4

NDWR across time by subgroup and intervention

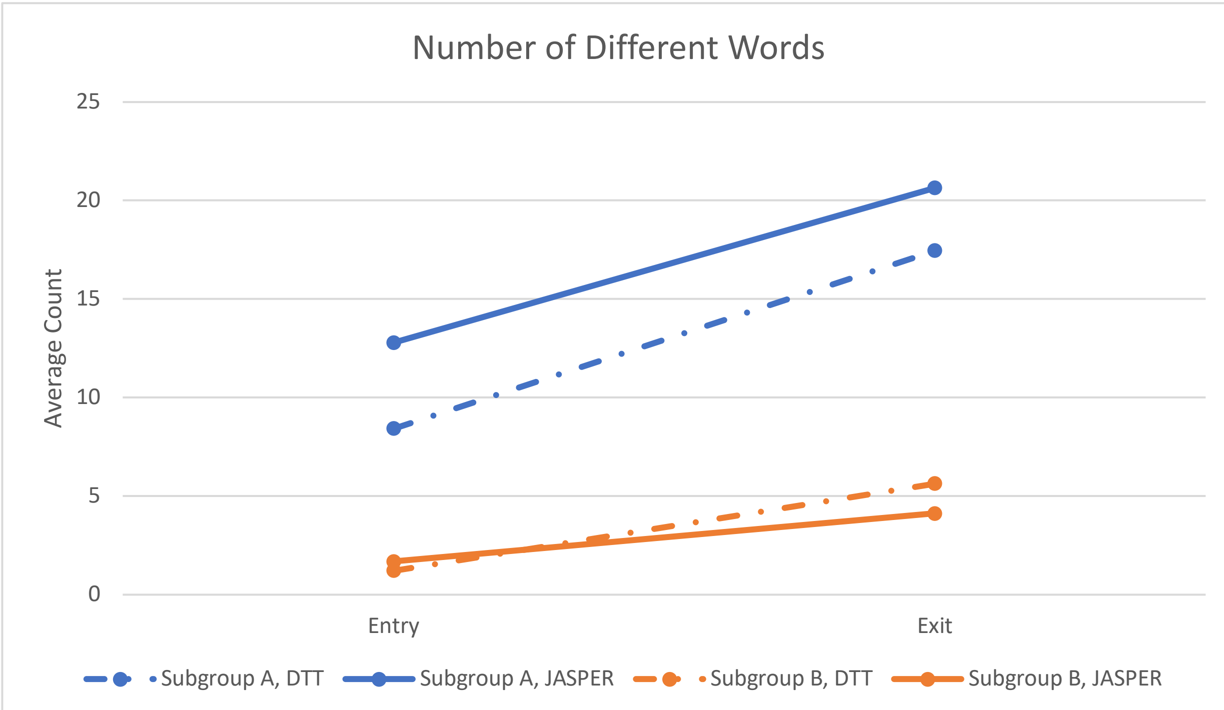


Table 3-9
NDWR across the course of intervention and follow-up incremental models

Model	Fixed Effects	Negative Binomial with log link			
		Estimate	SE	z value	p-value
2 month midpoint	Intercept	1.21	0.27	4.41	0.000**
	NDWR at entry	0.12	0.01	6.71	0.000**
	Intervention	0.01	0.32	0.04	0.965
	Subgroup	-0.16	0.32	-0.50	0.614
	Intervention*Subgroup	-0.16	0.41	-0.40	0.687
4 month midpoint	Intercept	1.94	0.24	7.81	0.000**
	NDWR at 2mo	0.05	0.01	5.73	0.000**
	Intervention	-0.22	0.32	-0.68	0.494
	Subgroup	-0.45	0.29	-1.53	0.126
	Intervention*Subgroup	-0.23	0.41	-0.55	0.581
Exit	Intercept	1.66	0.24	6.74	0.000**
	NDWR at 4mo	0.06	0.00	7,62	0.000**
	Intervention	-0.16	0.30	-0.05	0.577
	Subgroup	-0.59	0.28	-2.11	0.034*
	Intervention*Subgroup	0.01	0.39	0.04	0.965
Follow-up	Intercept	2.04	0.25	8.14	0.000**
	NDWR at exit	0.05	0.01	6.54	0.000**
	Intervention	0.40	0.29	1.35	0.175
	Subgroup	-0.26	0.28	-0.94	0.343
	Intervention*Subgroup	-1.16	0.38	-3.03	0.002**

Note: When site was not a significant term it was removed from the final model; models are incremental
**p* < 0.05, ** *p*<0.01

Figure 3-5

NDWR across the course of intervention by subgroup and intervention

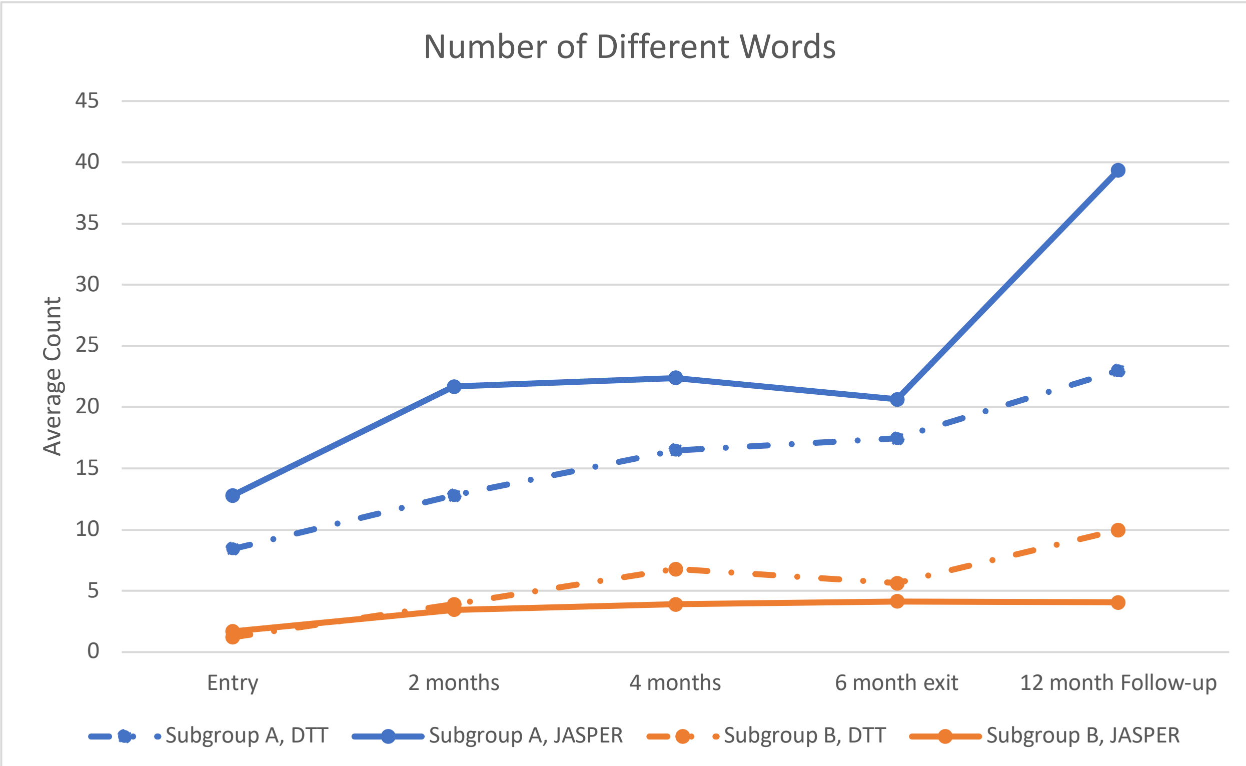


Table 3-10

Prelinguistic outcome - from the ESCS

Linear mixed models, including control for site and participant-level random effects

Model	Fixed Effects	Estimate	SE	Wald χ^2 (1)	p-value
IBR- EC/Gesture	Intercept	13.96	1.43		
	Time	-2.03	1.77	0.89	0.343
	Treatment	1.38	2.07	0.01	0.930
	Subgroup	-4.59	1.83	7.28	0.006**
	Tx*Time	-4.00	2.58	0.50	0.475
	Time*Subgroup	2.84	2.28	9.89	0.001**
	Tx*Subgroup	-1.45	2.60	0.16	0.684
	Tx*Time*Subgroup	4.56	1.40	1.97	0.159

Note: When site was not a significant term it was removed from the final model

$^*p < 0.05$, $^{**}\ p < 0.01$

Figure 3-6

IBR- Eye Contact & Gesture

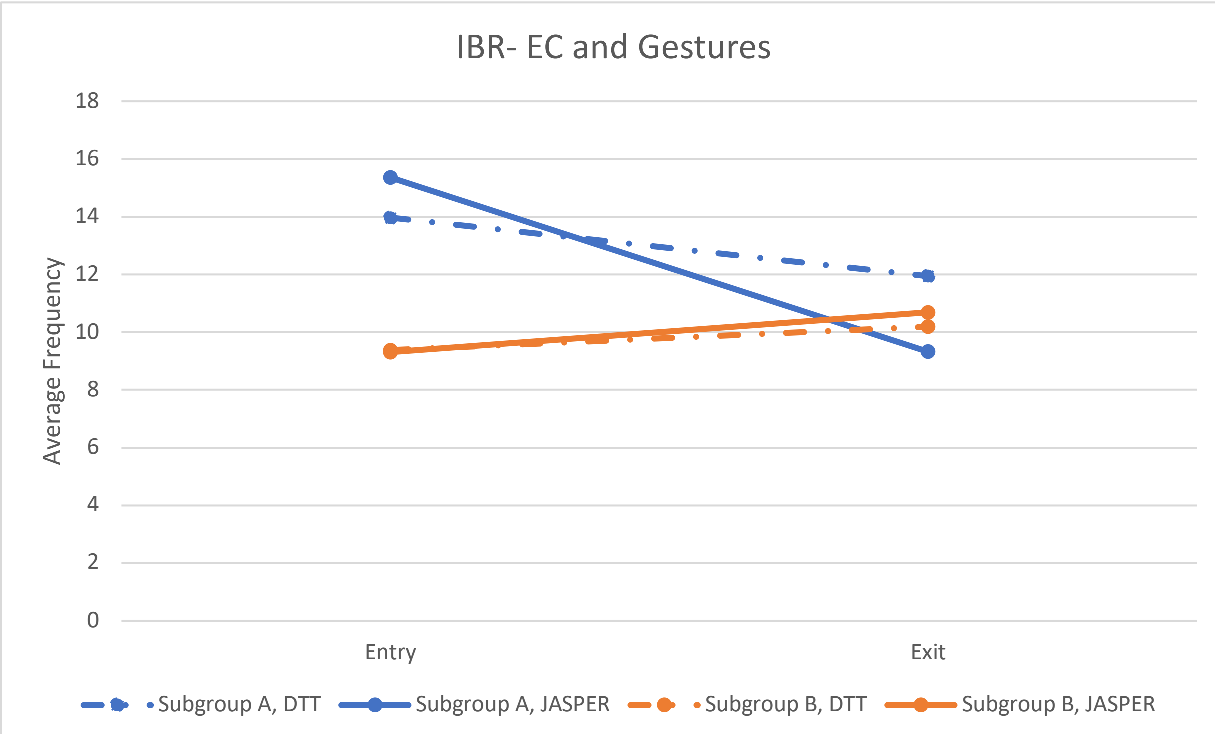


Table 3-11

Prelinguistic outcomes from the ESCS

Truncated Negative Binomial (Hurdle) Models

Model	Fixed Effects	Zero Hurdle Model Binomial with logit link			Count Model Truncated Negative Binomial with log link		
		Odds Ratio	z value	p-value	Estimate	z value	p-value
IJA- EC and Gesture	Intercept	4.51	2.35	0.018*	1.03	3.65	0.000*
	IJA-EC at entry	1.27	2.89	0.003**	0.07	3.21	0.001*
	Intervention	0.25	-1.79	0.072	0.08	0.24	0.809
	Subgroup	0.23	-2.07	0.038*	0.05	0.16	0.866
	Intervention*Subgroup	3.91	1.57	0.115	0.19	0.43	0.663

Note: When site was not a significant term it was removed from the final model

$^*p < 0.05$, $^{**}p < 0.01$

Figure 3-7

IJA- Eye Contact & Gesture

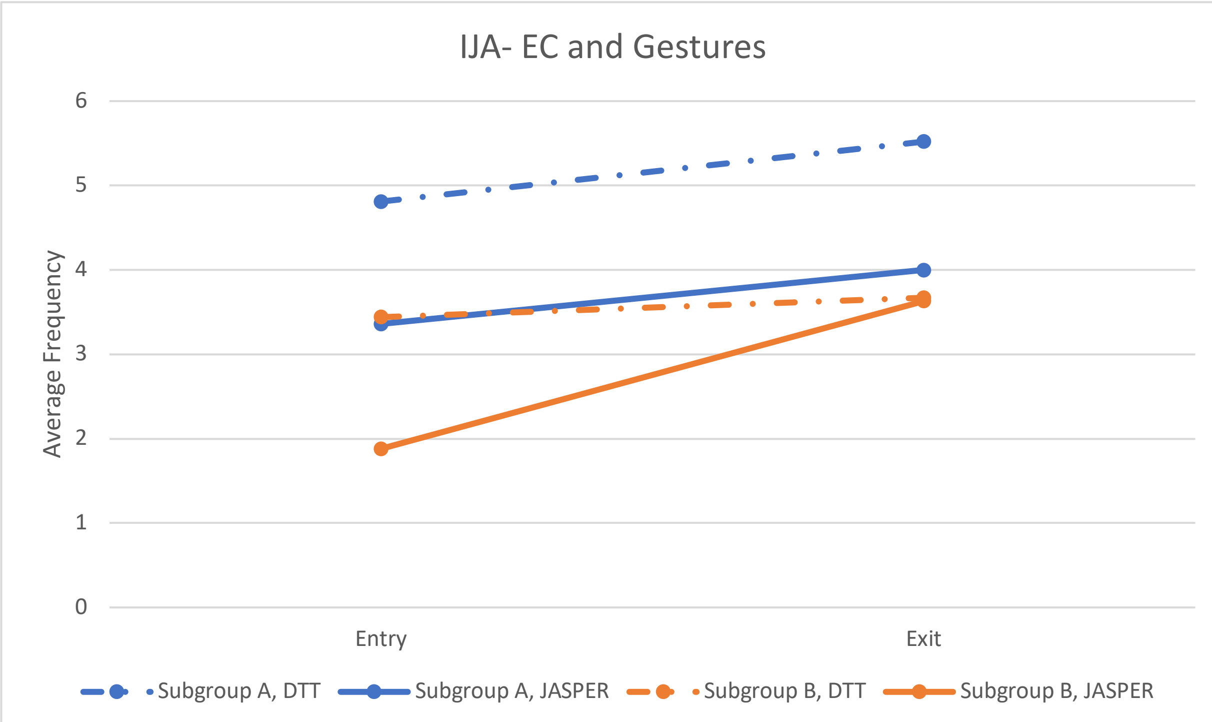


Table 3-12

Language combination outcomes from the ESCS

Truncated Negative Binomial (Hurdle) Models

Model	Fixed Effects	Zero Hurdle Model			Count Model		
		Binomial with logit link			Truncated Negative Binomial with log link		
		OR	z value	p-value	Estimate	z value	p-value
IJA-LANG	Intercept	7.39	3.22	0.001**	1.98	9.13	0.000***
	IJA-Lang at entry	1.14	1.54	0.121	0.05	1.54	0.122
	Intervention	0.71	-0.38	0.701	0.30	1.06	0.288
	Subgroup	0.07	-0.19	0.000**	-0.05	-0.19	0.849
	Intervention*Subgroup	1.50	-2.11	0.672	-0.94	-2.11	0.034*
IBR-LANG	Intercept	3.45	2.15	0.030*	2.25	12.16	0.000**
	IBR-Lang at entry	1.29	2.53	0.011*	0.05	2.85	0.000**
	Intervention	0.69	-0.42	0.674	-0.11	-0.45	0.650
	Subgroup	0.26	-2.09	0.036*	0.06	0.27	0.785
	Intervention*Subgroup	1.15	-0.15	0.879	-0.72	-2.08	0.036*

Note: When site was not a significant term it was removed from the final model

**p* < 0.05, ** *p*<0.01

Figure 3-8
IJA- Language & Language Combinations

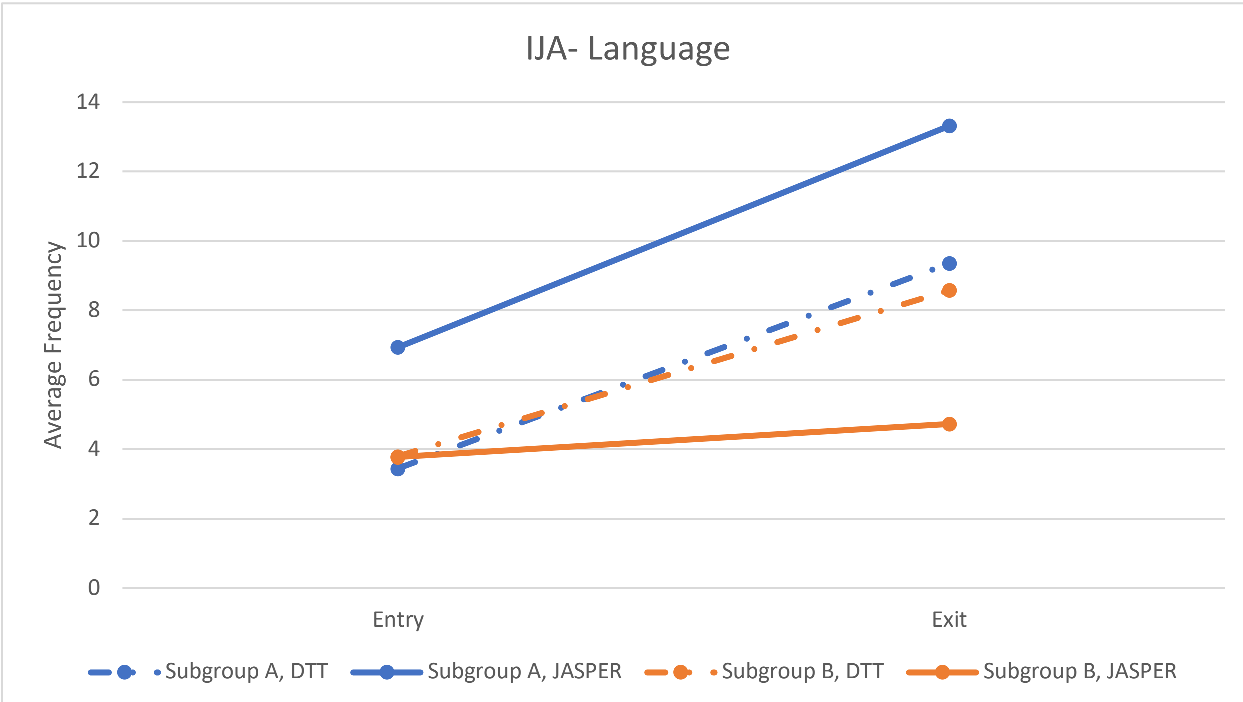
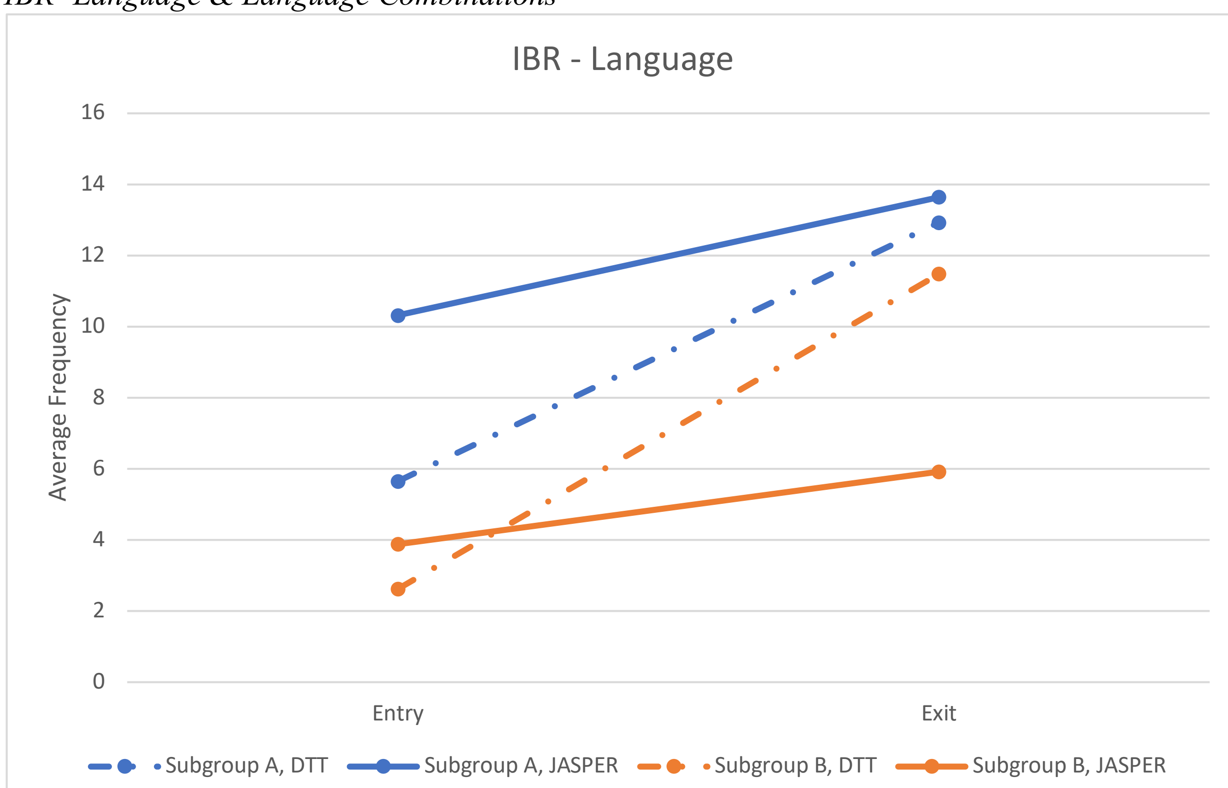


Figure 3-9
IBR- Language & Language Combinations



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