Title: Changing Developmental Trajectories through Early Treatment

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1. Full title: **Changing Developmental Trajectories through Early Treatment**
Short title: Early Treatment Interaction

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2. Abstract:

The overarching goal of this research protocol is to identify the health and developmental implications for age of screening and age of entry into early intervention for children at risk of Autism Spectrum Disorder (ASD). With increased number of young children identified with ASD, there is a pressing need for evidence-based, manualized, cost-efficient treatments that are accessible to and feasibly implemented by parents within their natural environments in community-based settings. Additionally, significant disparities in diagnosis and treatment of ASD have been found in racial and ethnic minority populations thereby increasing the need for families from diverse cultural and socioeconomic backgrounds. The major objective of this research protocol is to directly compare two parent intervention conditions of Early Social Interaction (ESI) for 9 months on developmental trajectories of infants showing early risk for ASD. The control treatment is an information, education and support group (Group) offered weekly; the experimental treatment is a parent-implemented intervention (Individual) offered in 2 weekly individualized sessions to teach parents how to embed strategies that support social communication skills, emotional regulation, and transactional supports skills within everyday routines, activities, and places, in combination with Group. This protocol will recruit 92 parent-infant dyads at 12 months of age from both the high and low risk siblings being studied in the Emory Autism Center of Excellence Projects 1 and 2. High risk infants will screen positive on 2 of 4 screening measures indicating the presence of diagnostic features of ASD by 12 months of age. Low risk infants who screen positive on 2 of 3 screening measures at the 12 month visit will receive a subsequent home observation measure. Any children who screen positive on this measure will qualify for treatment. Families will be randomly assigned through the process of minimization to either Group or Group and Individual for 9 months. The specific aims of this investigation are: Aim 1) Effectiveness of Treatment – to compare the effectiveness of Group +Individual on developmental trajectories of social communication, autism symptoms, social visual engagement, developmental skills, and adaptive behavior, compared to Group alone; Aim 2) Mediators of Treatment – to determine whether growth trajectories of child active engagement and parent transactional support are mediators of response to intervention; and Aim 3) Moderators of Treatment – to identify individual child and family characteristics which predict response to intervention.

3. Introduction and Background

Mounting evidence exists of the effectiveness of intensive early intervention for a substantial proportion of children with autism spectrum disorders (ASD; Dawson & Osterling, 1997; National Research Council (NRC), 2001). Furthermore, age of entry into intervention may be predictive of outcome. Children with ASD in intensive interventions beginning by 3.5 years of age had significantly better outcomes than those after age 5 (Fenske, Zalenski, Krantz, & McClannahan, 1985; Harris & Handleman, 2000). These findings support the importance of early identification and intervention for improving outcomes. These findings also support the importance of addressing the significant disparities in diagnosis and treatment of ASD that have been found in some populations. Families of racial/ethnic minority, lower levels of education, and those who live in non-metropolitan areas have been found to experience greater limitations in accessing services for ASD (Thomas, Ellis, McLaurin, Daniels, & Morrissey, 2007). Black and Hispanic children have been found to have lower odds of having a documented ASD classification than white children (Mandell, Wiggins, Arnstein Carpenter, Daniels, Durkin et al., 2009) and of those children who do receive an ASD diagnosis, many of them are not diagnosed in early childhood. The age of first ASD diagnosis received has been found to be significantly older for African American and Latino children compared to white children (Mandell, Listerud, Levy, & Pinto-Martin, 2002). For these reasons, it is important that the effectiveness of intensive early intervention for children with ASD is examined across varying cultural and socioeconomic backgrounds.

Importance of Evidence-Based Early Intervention for Children with ASD

The NRC (2001) conducted a systematic research review on educational interventions for children with ASD and concluded that a large body of research has indicated significant progress in response to intervention with a substantial proportion of children. The committee concluded that there is a convergence of evidence that the following characteristics are essential active ingredients of effective interventions for children with ASD:

1) entry into intervention programs as soon as ASD is suspected;
2) active engagement in intensive instruction for a minimum of five hours per day, five days a week;
3) use of repeated planned teaching opportunities structured over brief periods of time;
4) sufficient individualized adult attention on a daily basis;
5) inclusion of a family component, including parent training;
6) mechanisms for ongoing assessment with corresponding adjustments in programming; and 7) priority for instruction on a) functional, spontaneous communication; b) social instruction across settings; c) play skills with a focus on peer interaction; d) new skill maintenance and generalization in natural contexts; and e) functional assessment and positive behavior support to address problem behaviors.
Building on the efforts of the NRC committee, a NIMH working group developed guidelines for designing research studies of psychosocial interventions for children with ASD (Smith et al., 2007). They delineated steps for

developing, validating, and disseminating interventions and made two recommendations to guide investigators and help funding agencies identify important needs and standardize criteria: 1) resources should be dedicated to support manual development and effectiveness studies of manualized interventions; and 2) new interventions should be developed and tested to address core features of ASD. Furthermore, the Interagency Autism Coordinating Committee Strategic Plan for ASD stresses that to further the development of such interventions, research should include 1) the application of methods from an established treatment paradigm to a diverse community setting; 2) the collection of information about the model of delivery, intensity, and duration for interventions targeting families with limited resources; and 3) the collection of first-hand insights and perspectives of family members and caregivers of children with ASD that will inform intervention research addressing the needs of diverse populations.

Meaningful Intervention Outcome Measures for Very Young Children with ASD

Research conducted over the past two decades has identified core deficits in joint attention, shared affect, and conventional and symbolic aspects of communication and play in young children with ASD. It has also shown that these deficits are significant predictors of developmental outcomes (Mundy, Sigman, & Kasari, 1990; Sigman & Ruskin, 1999; Stone, Ousley, Yoder, Hogan, & Hepburn, 1997; Wetherby, Prizant, & Hutchinson, 1998; Wetherby, Watt, Morgan, & Shumway, 2007; Wetherby et al., 2004). Several very recent publications reporting on studies of infant siblings have documented that delays in social communication are evident by 12 to 14 months of age in younger siblings who later receive a diagnosis of ASD (Landa, & Garrett-Mayer, 2006; Mitchell et al., 2006; Zwaigenbaum et al., 2005). These findings provide further support that children with ASD can be identified and distinguished from children with developmental disorders and typical development before 18 months of age.

Thus, social communication skills are important intervention outcome measures for children with ASD. Although a large number of studies have delineated core deficits associated with ASD, very few have documented the effects of interventions on these deficits (NRC, 2001). In a multiple-baseline-design study involving four children with ASD, Whalen and Schreibman (2003) demonstrated that changes in initiating and responding to joint attention can be systematically taught using pivotal response training. In a randomized-group-design study, Aldred, Green, and Adams (2004) implemented a monthly parent-training program for 14 preschool children compared to 14 children in a community-treatment control group. They found significantly lower Autism Diagnostic Observation Schedule (ADOS) scores, indicating fewer autism symptoms in the treatment group, and significantly better outcomes regarding parental positive synchronous communication and rate of child communicative acts; however, they found no significant difference between the two groups in number of episodes in which the parent and child shared attentional focus. Aldred et al.’s results suggest that significant gains in some aspects of social communication can be achieved by teaching parents how to enhance their children’s communication in a cost-effective treatment, but gains in joint attention may require a more intensive or different approach to intervention.

Meaningful changes that reflect core social communication deficits in children with ASD still need to be documented. Current research has indicated that multiple aspects of social communication need to be measured to better characterize this population. Even studies of the most effective treatments for children with ASD have shown variable outcomes (NRC, 2001), and a child’s social communication skills before treatment may influence the response to treatment. Little is known about the potential impact of interventions that target the social communication skills of children with ASD younger than 3 years of age.

Most studies reviewed by the NRC included children 3 to 5 years of age. There is very limited research on children with ASD under 3 years of age primarily because the median age for diagnosis in the US based on record review is 5.5 years (Shattuck et al., 2009). Two studies support the application of the NRC recommendations for younger children. McGee, Morrier and Daly (1999) reported good verbal outcomes of 28 toddlers with ASD in a center-based incidental teaching program. Since they did not have a control group, it is not possible to sort out treatment effects from maturation and other confounding variables or determine whether this sample of children with ASD is representative. Stone and Yoder (2001) found a strong positive association between the number of hours of speech therapy received between the ages of 2 and 3 and language skills at age 4 in 35 toddlers with ASD. These findings suggest that beginning intervention before age 3 may have a greater impact than later intervention. With advances in earlier screening and diagnosis, there is a pressing need to develop early intervention programs that are appropriate and effective with very young children with ASD.

The Early Social Interaction Project

Providing intervention of adequate intensity for young children with ASD is challenging for the healthcare and education systems. Services delivered by professionals within Part C of the Individuals with Disabilities Education Improvement Act of 2004 (IDEA; PL 108-446; USDOE, 2004) average 2-3 hours per week (NEILS). Only a few states have designated intensive services for children with ASD; services in these states may be as high as 20+ hours per week. Providing intervention in the natural environment is a way to maximize learning throughout the day and enhance generalization using routines, materials, and people common to the family and child (Dunst, Hamby, Trivette, Raab, & Bruder, 2000; Woods Cripe & Venn, 1997). Training parents to implement intervention strategies during everyday activities is a logical method for achieving the intensity of active engagement recommended by the NRC (2001). The effectiveness of parent-implemented interventions for children with developmental disabilities has been well-established. However, only a small number of studies have included children with ASD, and those studies are on children 3 years of age or older.

The Early Social Interaction (ESI) Project is an intervention program developed for toddlers at risk for ASD and their families as a model demonstration project funded by the U.S. Department of Education. ESI was designed to incorporate the NRC recommendations within the context of a family-centered, natural-environments approach, which is considered recommended practice for delivery of IDEA Part C services. Following are the major components of ESI (Woods & Wetherby, 2003):

1. Routines-Based Intervention in Natural Environments: The provision of support and intervention in natural environments to enhance the child’s participation in everyday routines and the family’s participation in community activities. Routines and activities important to each family become the context for the intervention.
2. Individualized Curriculum: The curriculum is individualized for the child’s unique profile. A developmental framework that targets social interaction, joint attention, communication, imitation, play, and emotional regulation guides the curriculum-based assessment process (Prizant, Wetherby, & Rydell, 2000) to establish goals for the child.
3. Parent-Implemented Intervention: Interventionists teach families to create

learning opportunities and use specific intervention strategies to practice the child's goals within daily routines. Collaborative problem-solving allows the family members to take advantage of teaching opportunities throughout the day, to feel confident about their abilities to engage the child in meaningful activities, and to facilitate social communication skills.

Based on the steps delineated by Smith et al. (2007), we have: 1) developed an intervention manual to standardize the critical treatment components of ESI with protocols for implementing and evaluating the manualized intervention, 2) conducted single-subject design studies on the intervention strategies, and 3) conducted feasibility testing of ESI with a group of 17 families (Wetherby & Woods, 2006). Our findings are presented in the Preliminary Studies section of this proposal. The next step recommended by Smith et al. is a multi-site randomized clinical trial to test the efficacy of the intervention, which is the aim of the proposed research study.

Interaction of Core Deficits of ASD, Brain Development, and the Learning Environment

Neuroplasticity, a developmental mechanism that reflects the brain's capacity to be molded by the environment (Pascual-Leone, Amdei, Fregni, & Merabet, 2005), is heightened in the first few years of life, and diminishes with age. The 2nd year of life is a time period associated with developmental regression in children with ASD (Rogers, 2004). Regression in children with ASD has been documented in language and communication and other developmental domains for 21% to 48% of children with ASD (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Goldberg et al., 2003; Lord, Shulman, DiLavore, 2004) and occurs most often between 18 and 21 months of age (Goldberg et al., 2003; Shinnar et al., 2001). The findings on developmental regression are compelling in relation to recent brain research which has suggested that there is an overgrowth of the brain of children with ASD over the first few years of life. Studies of head circumference and brain volume have indicated enlargement in individuals with autism that may be restricted to early childhood (Courchesne et al., 2001; 2003; Lainhart et al., 1997; Piven et al., 1996; Sparks et al., 2002; Stevenson et al., 1997). Significant brain volume enlargement has been found in a study of children with autism from 2-4 years that was not present in participants in the 5-16 year age range (Courchesne et al., 2001; Piven et al., 1996). Although the processes leading to increased brain volume are not yet known, these studies suggest that the timing of brain enlargement in children with ASD is consistent with an underlying mechanism that diminishes the normal process of dendritic pruning (Huttenlocher, 1990). Synaptogenesis in the cortex is characterized by overproduction of synapses in the first months of life followed by pruning that extends into the preschool period (Huttenlocher & Dabholkar, 1997). Studies of experience-dependent synaptogenesis conducted on rats reared in complex environments showed more mature synaptic structure and more synapses per neuron (Black & Greenough, 1998; Greenough & Black, 1992). An important implication of these findings is that early intervention could have enduring effects on human brain development and the impact of those effects may be time-limited. The research of Landry et al. (Landry, Smith, Swank, & Loncar, 2000; Landry, Smith, Miller-Loncar, & Swank, 1998) suggests a critical or sensitive period early in children's development.

While it is known that ASD is a neurobiological disorder, current theories emphasize the interaction of abnormal brain development, the child's social communication profile, and the learning environment. Mundy and Burnette (2005) suggested that an initial neurological deficit in infants with autism leads to an early impairment in social orienting and joint attention, which contributes to subsequent neurodevelopmental pathology by an attenuation of social input.

This transactional process can lead to a cumulative spiraling that may compromise subsequent neurological and behavioral development or possibly be ameliorated through early intervention. Core deficits that have been identified in the 2nd year of life may attenuate the quality of social input of children with ASD very early in life and through a transactional process have a cascading effect on later developmental outcome and autism symptoms (Wetherby et al., 2007). In other words, the symptoms of ASD may further disrupt brain development and this disruption may be cumulative. Developmental regression may reflect this process. Because of the transactional and cumulative detrimental impact on brain development, these core social deficits may be critical targets for early intervention in order to enhance social communication skills likely to impact the social environment, and thus, lead to better outcomes for children with ASD. This leads to the question of whether very early intervention can prevent or attenuate the subsequent cascading effect on neurodevelopment and behavioral outcomes that potentially arise from early impoverished social interactions in the 2nd year of life. Very early intervention may be viewed as a mechanism to prevent the full unfolding of symptoms of ASD by minimizing the associated secondary abnormalities in brain development.

National Significance of the Need for Improving Early Detection of ASD

Although there have been significant advances in genetic and biomedical research on ASD, there is currently no biological marker for autism or ASD. Consequently screening and diagnosis of ASD must be based on behavioral features (Filipek et al., 1999). The Centers for Disease Control (CDC) has initiated the “Learn the Signs. Act Early.” campaign to alert health care professionals and parents to the early signs of ASD. Several screening tools for ASD are currently being studied and offer promise (Robins, Fein, Barton, & Green, 2001; Stone, Coonrod, Turner, & Pozdol, 2004; Wetherby et al., 2004). Despite such campaigns, rates of early diagnosis remain low, particularly in racial and ethnic minority populations and in families of lower socioeconomic status (Mandell et al., 2009; Mandell & Novak, 2005). When parents or caregivers do voice concerns early, many primary care providers take a “wait and see” stance because interventions for intervention protocols for young children are still relatively new and not all physicians are yet aware of the positive impact . There is a critical need to document whether early intervention beginning in the 2nd year of life leads to better outcomes than beginning in the 3rd year of life. Such findings may be able to define a critical window in the 2nd year to screen for ASD and to provide the impetus to urge primary care providers to refer very young children for a diagnosis of ASD and early intervention.

National Significance of the Need for Improved Early Intervention for Children with ASD

Most children with ASD require special education at school age. The average annual cost for educating a child with ASD, based on 2005 figures from the US Government Accountability Office, is $18,800, compared to $12,500 for the average special education student and $6,556 for a regular education student. Additionally, a recent study by the Harvard School of Public Health shows that the annual cost of caring for a child with autism is upwards of $67,000 (Ganz, 2007). With effective early intervention services, the future is more promising. We know that providing intervention early has a greater impact; between 60 and 90% of children in intensive early intervention programs beginning by age 3 can learn to talk, and about half can make it into regular kindergarten, compared to 10% without early intervention (NRC, 2001). Documenting that early intervention provided in the 2nd year of life can lead to better outcomes would have very important ramifications for substantially reducing the cost of education.

4. Objectives

There is a pressing need to improve early detection of autism spectrum disorders (ASD) because research indicates that earlier intervention maximizes children's outcomes (National Research Council, 2001). In spite of the severity of the behavioral characteristics of ASD, the median age for diagnosis in the US based on record review is 5.5 years (Shattuck et al., 2009) far past the window of opportunity for early intervention. The average delay between initial evaluation and diagnosis of ASD was 13 months in a study of surveillance records (Wiggens, Baio, & Rice, 2006). Closing the gap in time between initial parent concern, initial evaluation, and age of diagnosis would greatly reduce the age of entry into intervention. The American Academy of Pediatrics (AAP) recommends that all children be screened for autism at the 18- and 24-month visits (Johnson & Myers, 2007). Ongoing research on early markers of ASD will lower the window for the possibility of early detection to infancy, heightening the need for interventions that are effective and appropriate for infants and very young toddlers. The AAP practice guidelines and the new Interagency Autism Coordinating Committee Strategic Plan for ASD Research make the need for early intervention that is feasible to implement in community-based settings a high priority.

In response to RFA-HD-12-195, this treatment project is designed to address two significant public health challenges- the need for validated, manualized treatments for young children with ASD that are cost-efficient and feasible for community-based implementation, and the need to reduce the age of entry into early intervention. The major objective is to directly compare two parent intervention conditions for 9 months: 1) an information, education and support group (Group) offered weekly, and 2) an individualized parent-implemented intervention (Individual) offered in 2 weekly sessions to teach parents how to embed strategies to support social communication skills within everyday routines, activities, and places. The Emory ACE Center will recruit 92 parent-infant dyads at 12 months of age from theboth high and low risk siblings being studied. Inclusion criteria for high risk infants will be a positive screen on 2 of 4screening measures indicating the presence of diagnostic features of ASD by 12 months of age. Inclusion criteria for low risk infants will be a positive screen on 2 of 4 screening measures indicating the presence of diagnostic features of ASD by 12 months of age. Families will be randomly assigned to either Group or Group +Individual for 9 months. Outcome measures of social communication, autism symptoms, developmental level, and adaptive behavior will be gathered every 6 months from 12 to 36 months of age to measure treatment and follow-up effects. Measures of parent transactional support and child active engagement will be collected monthly beginning at 12 months until 36 months of age to examine change in developmental trajectories.

This project is conceptualized as a series of research questions (RQ) for each specific aim to examine the effects of intervention on outcomes of toddlers with ASD. The specific aims and research questions are:

Aim 1. Effectiveness of Treatment: To compare the effects of Group alone to Group plus Individual implemented from 12 to 21 months of age on outcome measures of social communication skills, autism symptoms, developmental levels, and adaptive behavior from 12 to 36 months. Research will address specific questions with regard to whether there are: RQ1a) differences in growth trajectories from 12 to 36 months on social communication skills and autism symptoms, and RQ1b) differences in trajectories of developmental level and adaptive behavior from 12 to 36 months for children receiving

Group alone versus Group plus Individual for 9 months from 12 to 21 months of age. Although the treatment group may qualify at 12 months of age, treatment bay begin up to age 15 months.

Aim 2. Mediators of Treatment: To determine whether parent transactional support and child active engagement are mediators of response to intervention. Specific research questions will address whether: RQ2a) there are differences in trajectories of parent's use of transactional supports and child's level of active engagement during everyday activities with their child during intervention and follow-up booster sessions until 36 months of age for parents participating in Group alone and Group +Individual, and RQ2b) the degree of parent transactional support and child active engagement predict change in children's social communication skills and severity of autism symptoms between at 18, 24 and 36 months of age.

Aim 3. Moderators of Treatment: To identify individual child and family characteristics which predict response to intervention. Specific research questions will address: RQ3a) what moderator variables predict response Group, and RQ3b) what moderator variables predict response to Group +Individual?

The expected outcomes of this study will have the following important implications: 1) documentation of improved outcomes for very young toddlers with ASD receiving a manualized, community-based, cost efficient, appropriate, and effective intervention; 2) evidence that parent individualized intervention beginning by 12 months of age leads to better outcomes than group education and support; and 3) substantiation of the critical need for screening and identification of ASD in the 2nd year of life, rather than waiting until the 3rd year or later, because this may be a crucial developmental period for effective early intervention.

5. Study Design, Methods and Participant Selection

Sample Recruitment. 92 parent-child dyads will participate in this study. The Emory ACE Center will recruit 92 parent-infant dyads at 12 months of age from the pool of 230 "High-Risk for Developing ASD" younger siblings and from the pool of 100 low risk infants being studied. Inclusion criteria for high-risk infants will be a positive screen on 2 of 4 screening measures indicating the presence of diagnostic features of ASD by 12 months of age. In addition, one of these positive screens must be a SORF measure. Inclusion criteria for low-risk infants will be a positive screen on 3 of 4 screening measures, including positive screens on both SORF measures. It is important to note that a diagnosis of ASD cannot be made reliably at 12 months of age but early signs will be evident in children who will end up with ASD, the broader autism phenotype (BAP), or developmental delay (DD). The Clinical Assessment Core will follow children and clinical diagnosis will be confirmed at 36 months of age.

The following screening protocol will be used with infants at 9 and 12 months of age. The procedures and records for the screening protocol are part of the Clinical Assessment Core and are covered in a separate IRB application. All 230 infants will be given the ***Infant-Toddler Checklist*** (ITC) a broadband parent report screen for communication that has norms and cut scores at each month from 6 to 24 months of age and has been documented to detect children with ASD down to 9 months of age. Infants who have a positive screen on the ITC will be given the following three autism-specific screening tools: 1) Early Screening for Autism and Communication Disorders (**ESAC)**, an autism-specific parent report screen with 35 recognition format or closed-choice items and 6 open-ended items; 2) Systematic Observation of Red Flags (***SORF) Clinic***, the SORF rating from the CSBS (see Clinical Assessment Core), Behavior Sample from a video recording of a structured observation in a clinical setting; and 3) **SORF-Home,** the

SORF rating from the home observation of the parent engaged in interaction with the child in everyday activities (meals and snacks, caregiving, play with toys or objects, play with people, book sharing, and family chores. The ESAC and SORF were chosen because these are the only empirically-supported screening tools for ASD at this age. FSU has extensive experience conducting screening and diagnostic evaluations of infants and toddlers using these tools and will oversee selection of referrals for this study. For high-risk infants, the selection criterion for participation in this treatment study is a positive screen on 2 of the 4 autism-specific screening tools with one of those positive screens being a SORF. For low-risk infants, selection criteria for participation includes a positive screen on both SORF measures and one additional measure (e.g., 3 out of 4 measures). The purpose of this early treatment study is to contribute to the overarching aims of the Emory ACE Center to study risk and resilience in ASD. Therefore, we are targeting infants who are genetically at risk and who show early signs of autism and communication delay. Thus, we are casting a broader net than only children who will end up with a diagnosis of ASD but are selecting siblings who are at the highest risk for having ASD or a developmental delay.

Random Assignment of Participants to Experimental Groups. Children who meet the selection criteria and whose parents give consent to participate in the study will be given a computer-generated random assignment to one of two groups- Group plus Individual or Group alone. As a complement to random assignment, we will covary pretest variables that end up being correlated with the outcome variables, in our statistical analysis, if the groups are not equivalent on these variables. The diagnosticians for all measures and raters for intervention fidelity and treatment mediators will be kept blind to group assignment.

Sample Retention and Attrition. Our strategies to promote retention are particularly geared for families with environmental risks and include: 1) assisting families in filling out questionnaires and maintaining frequent contact to remind them about returning forms and upcoming appointments; 2) coordination of appointments with other agencies; 3) offering small financial incentives to compensate for their time for assessment visits; 4) offering families an hour a month of consultation to provide information needed about ASD and to coordinate referrals to other agencies; and 5) to provide the 2 weekly Individual sessions in the home and incorporate the families' everyday activities. Because the Group only group is at a greater risk for attrition, we have made an effort to design that treatment to be appealing to families by offering it weekly and have limited the length to 9 months. In Georgia, the public Part C early intervention programs for children under 36 months do not offer specialized or intensive services for children with autism or ASD. Like the majority of states, non-categorical eligibility based on developmental delay is customary and the usual services provided in these states are 1 to 3 hours of clinician-implemented therapy per week. Thus, it is anticipated that both groups will utilize the community services comparably and that because of the low intensity of community services, they are not anticipated to diffuse Individual treatment effects, and may actually contribute to retention in this study. That is, families will be motivated to participate in Group or Individual as a supplement to community services. Because the parents of children in this study have an older sibling with ASD, they will be more motivated to participate in early intervention for the high-risk sibling showing early diagnostic features of ASD. We anticipate a possible attrition rate between 10 and 12%. With this attrition rate, we will complete intervention for at least 80 children.

Timeline for Assessment Measures and Intervention Activities.

Infants will be recruited during Years 2 and 3 of the Emory ACE, 46 children in each year totaling 92 children. Children will be followed until 36 months of age and follow up assessments will be completed during years 3-5. The timeline for assessment measures and intervention activities is included in Appendix 1.

Dependent Variables [CAC= Emory ACE Clinical Assessment Core (IRB#65732)]

The following dependent variables will be collected by the CAC and coded by raters blind to treatment condition before treatment at 12 months and again at 24 months and 36 months of age. Additionally, the Social Communication Measures will be completed at 15 months and 21 months of age for all children enrolled into the Early Social Interaction project.

Social Communication Measures. The Communication and Symbolic Behavior Scales (CSBS) Behavior Sample will be video recorded to measure social communication. Reliability and validity of the CSBS has been reported (see CAC). The raw scores will be summed to form a social, speech, and symbolic composite.

Autism Symptoms. The *Autism Diagnostic Observation Schedule (ADOS)* (see CAC) is the gold standard diagnostic measure of ASD. The revised algorithms forming Social-Affect and Restricted Repetitive Behavior ratings of autism symptoms will be used.

Developmental Levels. The Mullen Scales of Early Learning MSEL (see CAC) measures developmental level with separate scores for four cognitive scales that form an early learning composite. A nonverbal DQ based on age equivalent divided by chronological age multiplied by 100 will be calculated from the average of the Fine Motor and Visual Reception scales and a verbal DQ will be calculated from the Receptive and Expressive Language scales.

Adaptive Behavior. The Vineland Adaptive Behavior Scales *VABS-II* (Survey Interview Form; see CAC) yields a standard score in four domains— Communication, Daily Living, Social, and Motor, and an Adaptive Behavior Composite.

Expressive Language Phase. The child's expressive language phase will be determined at each assessment based on the benchmarks delineated by Tager-Flusberg and colleagues and recommended for evaluating the efficacy and comparing outcomes across NIH-funded intervention studies. Based on multiple sources of information about language benchmarks, the language will be categorized as: *Preverbal Communication, First Words, Word Combinations, or Sentences, to* provide a clinically meaningful measure of language outcome.

Mediator Variables

The home observation measure will be collected monthly as the context to chart developmental trajectories of mediator variables. This context provides an hour of parent-child interaction during a variety of everyday activities in the natural environment without the clinician present and is an index of generalization of parent and child learning over the course of the treatment study. It is hypothesized that parent implementation of transactional supports is a mediator of child active engagement, which is a mediator of treatment outcome. These mediators will be evaluated from the monthly home observations with the Measure of Active Engagement and Transactional Supports (MAETS; see Appendix 2) at baseline through 36 months of age. Specifically, these home observations will be completed monthly during the 9 month intervention period and then quarterly through the child's 36 month birthday. It is also hypothesized that the measures available through Projects I and II, of social visual and vocal engagement, are mediating variables, and will be examined in relation to the MAETS and outcomes on dependent variables for children in the two treatment conditions.

Moderator Variables

Demographic Information. Parents will be asked to provide demographic information about race, ethnicity, and socioeconomic level as possible moderators of treatment effect. (see CAC)

Baby Siblings Research Consortium Intervention History Form. The number of hours of other intervention outside of ESI will be documented and updated by a parent monthly. This form documents the hours in psychosocial or educational treatments and whether the child is receiving alternative treatments (e.g., diet, chelation). The total number of hours per week of combined therapies and intervention multiplied by the number of weeks received will be calculated. (see Appendix 2)

Parent Questionnaires about Family Functioning. Parents will complete the following questionnaires at baseline and every 6 months until 36 months of age: *ESI Home and Community Activities* form to measure how many activities the parent participates in and how their child with ASD impacts their participation. *Family Impact Questionnaire* to measure parent's perception of the impact of their child on the family; *Family Resource Scale* to measure the adequacy of physical and human resources available to the family; *Parenting Daily Hassles* to measure minor daily stresses experienced by parents in routine tasks involving child rearing; *Parenting Sense of Competence* (see CAC) to measure parents' sense of competence with their child; and *Parenting Stress Index* to measure parent-child problem areas; and a form with questions about parent's impression of child change. (see Appendix 2)

Intervention Procedures

Children will be randomly assigned to one of two parent interventions— an information, education and support (**Group**), or Group plus parent-implemented intervention (**Individual**). A treatment manual with detailed procedures and fidelity measures are provided in the Appendix. Following is a brief description of each condition.

Group Procedures. Group is organized for families to receive information about social communication, emotional regulation, play development, and behavioral challenges in toddler playgroups in a relaxed, supportive, child-friendly setting that provides the opportunity to talk with a professional and meet other parents. Group is designed to provide parents with resources and supports for their child through weekly small parent group meetings using a curriculum to help parents focus their attention on their child's developmental needs. Handouts with activities for the parents and children to participate in during the month will be provided and samples are included in the Appendix. Group is different than Individual because it does not provide individualized intervention, does not provide direct instruction to the parent in the home on how to implement strategies and supports, and does not ensure treatment fidelity or the level of intensity. Up to 12 families will attend each group, with a blend of children with early risk for ASD ranging in age from 12 to 24 months. The groups are guided by an interventionist from psychology or a related discipline and meet for 9 months during the intervention period and monthly follow-up sessions with parents through the child's 36 month birthday. Information is provided to families through discussion and handouts, answering questions, describing scenarios, and making suggestions. Little documentation on generalization of group education training for parents is available. Kaiser and colleagues concluded that while there was variability in the speed and consistency of learning that occurred by parents, it took an average of 20 individualized clinical sessions prior to generalized use of the procedures in the home setting. In a large-scale review of empirical studies of parent implemented interventions for young children with communication disorders, including ASD, Hancock and Kaiser identify generalization of the intervention strategies by parents into the home environment as key. Thus, we have designed Group to provide helpful information and support to families; however, we do not anticipate that families will generalize the use of intervention strategies to activities at home from the education meeting.

The playgroup will consist of children enrolled in this study as well as community volunteers. Community volunteer children will be typically developing. We will not collect any data on the volunteers and their parents/caregivers will be advised of the time commitment if they would like to participate. If a research staff member deems it appropriate, the community volunteer may be referred for services outside of the study.

Individual Procedures. Individual teaches parents how to support their child's communication, social, and play skills in everyday routines, activities, and places. The clinician meets with parents for 2 home visits per week for 9 months. Individual is organized by phases, beginning with the initial home visit, a month of program planning, 6 months of intervention implementation, and 2 months of generalization. The initial home visit is designed to provide an overview of Individual to the family and to discuss the importance of intensive intervention, defined as active and productive engagement for 20-25 hours per week for children with ASD. The program planning phase entails completing the SCERTS Assessment Process (SAP), which is a curricular-based assessment using parent report and observation for children with ASD [60] to identify goals and objectives for the child and teaching strategies and supports for the parents. The program planning phase is completed by mapping out which objectives will be targeted in which routines and activities to total 5 hours a day, 5 days a week. Some assessment forms are included in the Appendix, others have been added to the IRB Smartform. The parent who is the primary caregiver will be the focus of Individual training. If both the mother and father or an extended family member share caregiving, then they can participate as long as they can attend Individual sessions regularly and are available for the home observation. In the implementation phase, the 2 weekly sessions will include the following three components: 1) setting the stage to briefly review and revise the agenda for that visit and gather updates; 2) intervention implementation with the following steps: a) review the objective, b) use modeling, guided practice, or video review to teach the strategy, c) provide feedback to the parent, and d) problem solving and plan for next time; steps a-d are repeated for 3 to 5 activities per session; and 3) summarize plans for parent implementation between sessions and data collection using ESI Daily Intervention Log. During generalization, the clinician meets with the family in a variety of community settings to teach the parent how to implement strategies in new settings.

Measures/Handouts/Guides

Parent Questionnaires Completed Monthly from 12-36 Months	
	Baby Siblings Research Consortium Inventory History Form
Parent Questionnaires Completed Monthly every 6 Months from 12-36 Months	
	ESI Home and Community Activities Family Impact Questionnaire
	Family Resource Scale
	Parenting Daily Hassles
	Parenting Sense of Competence
	Parenting Stress Index-Short Form
Intervention Planning and Monitoring Forms (Individual)	
	Routines-based Family Interview
	SCERTS Assessment Process (SAP)—SAP Report, SAP Observation, and SAP Summary Forms

	ESI Weekly Intervention Log
	Home Visit Notes
	Building Support from the Bottom Up: Promoting Your Child's Active Engagement
	Keeping an Eye on Weekly Progress: How's it going? Where do we go from here?
	Home Observation Feedback Form
Fidelity of Delivery by Interventionist: Interventionist Fidelity Forms (Individual & Group)	
	Interventionist Fidelity Form for Parent-Implemented Intervention (Individual)
	Interventionist Fidelity Form for Information, Education, & Support (IES)
Fidelity of Receipt by Parent: Completed Weekly by Interventionist & Parent from 12-21 months (Individual)	
	Reflection Questions on Weekly Progress
	Caregiver Involvement Scale
	Caregiver Diary
Fidelity of Enactment: Parent Implementation of Intervention Strategies at Home (Individual& Group)	
	About Transactional Supports
	Everyday Activities of Toddlers and Their Families: Making Every Moment Count
	Instructions for Home Observation from 12 to 36 months
	Measure of Active Engagement and Transactional Support (MAETS)
	Identifying Priority Intervention Outcomes
Intervention Satisfaction Forms Completed by Parents (Individual & Group)	
	ESI Family Evaluation Survey for Individual
	ESI Family Evaluation Survey for Group

Fidelity and Program Evaluation Procedures

Three components of intervention fidelity—***delivery***, ***receipt***, and ***enactment*** and parent satisfaction will be measured and are included in the Appendix 2. Fidelity of ***delivery*** will be measured bi-weekly for Individual and bimonthly for Group to monitor whether the clinician delivered or implemented the intervention to the parent as intended from a video of an intervention session. The intervention coordinators from FSU will rate the clinicians using the Clinician Fidelity Review Form for Individual or Group and give feedback on any deviations from the intervention procedures on an ongoing basis. Fidelity of ***receipt*** will be measured only during Individual by interventionist rating of the parent's receipt of information that week and ability to implement the strategies and supports that they are learning using the Clinician Reflect Questions filled out weekly by the interventionist, the Caregiver Diary filled out weekly by the parent to monitor the parent comfort and buy-in to the treatment, and the Caregiver Involvement Scale filled out weekly by the interventionist to rate parent comfort and buy in to the treatment. These measures were developed by UCLA and are used in the AIR-B network and in the ESI ongoing RCT. The clinician will then make adjustments and give feedback to the parent on an ongoing basis. Fidelity of ***enactment*** will be measured for both Individual and Group from the monthly home observation using the MAETS to monitor whether the parent enacts the intervention strategies in natural situations when the clinician is not present. ***Parent Satisfaction*** in intervention will be measured using the Individual and Group Family Evaluation Survey. Each survey solicits information about the parent's satisfaction with many aspects of the intervention as well as their sense of competence in supporting their child's development.

Expected Impact

With the infrastructure available for the Emory ACE Center, in collaboration with the FSU Autism Institute, this new collaborative team will be able to implement a large-scale treatment study of one of the youngest samples of children with diagnostic features of ASD. The expected impact of this study will: 1) document improved outcomes for the youngest sample of children with ASD receiving a manualized, cost efficient, appropriate, and effective intervention that is implemented in community-based settings; and 2) substantiate that individualized intervention beginning by 12 months of age leads to better outcomes, providing evidence that early detection of autism is crucial to enable access to early intervention.

6. Statistical Analysis

Data Analyses and Power

Data Analytic Strategy. The main research aims and hypotheses will be analyzed using a series of mixed models, focusing on Growth Curve Modeling (GCM) and Random-Effects Regression (RER) as more powerful alternatives to repeated measures ANOVA, and estimates of effect sizes will be obtained. We anticipate that effect size estimates will be conservatively derived from simple inspection of observed differences in treatment versus control means divided by the appropriate standardizer (either the control standard deviation or the pooled standard deviation, depending upon whether the treatment is inducing group differences in variances or not). The research aims compare growth trajectories (or residualized change, or outcome only, depending on the dependent variable of interest) for children in the treatment and control groups. It is hypothesized that children receiving the Group plus Individual condition will show significantly faster growth trajectories or change on the MAETS, which will mediate social communication, autism symptoms, developmental level, and adaptive behavior outcomes. Unconditional models that vary in complexity will be used to determine the most parsimonious models for estimating growth in this sample. After fitting the overall model, we will perform fixed-effects contrasts to test for cross-sectional differences between the two groups at points along the curve. Aims 2 and 3 build upon these models to investigate potential mediator and moderator variables that may predict response to treatment. Moderator variables such as initial level of child or parent performance and measures of family functioning will be interacted with treatment group to investigate potential moderating relationships. To investigate potential mediators of treatment effectiveness such as MAETS, we will follow standard strategy for testing mediational effects in a multilevel design where fidelity is conceptualized as a level 1 mediator that can vary by time. Finally, we will consider the possibility that the mediated relation may be stronger in one subgroup than the other (moderated mediation), either because treatment fidelity is accomplished to a greater extent in one subgroup than another or because the link between treatment fidelity and outcome is stronger in one subgroup than another (e.g., treatment fidelity predicts outcome only in individuals with sufficient cognitive abilities). In addition to existing GCM/RER analyses, in synergy with Projects I & II we will repeat our analyses using Functional Data Analysis, a new approach that significantly improves both the detection of common features in trajectory shape as well as the identification of individual spurts or delays relative to the group. Project III will rely on the Data Management and Analysis Core for data storage, management, and transmission to NDAR.

Attrition Analyses. All analysis will be done using an intention to treat approach. That is, every subject in the study will be considered in the analysis as a member of the treatment group to which s/he was assigned. We will conduct a series of analyses to examine attrition and its potential effect on the results [69], including examining the differential attrition rates for the two treatments and for child and parent characteristics of those completing and those who did not complete one or both treatment conditions, different definitions of dropout, different outcome measures, and treatment-correlated attrition. For the HLM analyses with multiple time points, missing data are not a concern, but differential attrition by treatment group would be. If differential attrition appeared to be a problem, then we would conduct multiple imputation of missing data [95] to attempt to estimate the appropriate effect sizes and confidence intervals.

Power Analyses. Power for growth curve modeling was estimated using a power estimation program developed for HLM models [61]. When estimating power in growth curve models, there are a number of factors that need to be considered. In addition to alpha level, number of subjects, and anticipated effect size, power can also vary as a function of the number of observations employed and the duration of the study. For these power analyses, we set alpha at .05 and we anticipated as few as 5 and as many as 25 observations per child (per measure). Additionally, we estimated that there would be approximately 10 times as much within person variability than between person variability (the ICC for the person level effect would be .10). Using these estimates, we anticipate that 92 subjects would give us a power=.90 to detect an effect of d=.50 (which corresponds to a medium effect) with five time points estimating linear change. For models testing treatment differences in the presence of quadratic change (with 15 or more assessments per child), power is .95. If attrition drops the sample size to 80 subjects, we will still have power equal to .86 to detect a medium-sized effect (with five assessments estimating linear change) and power=. 91 for those treatment differences tested in the presence of quadratic change. Thus, the minimum power to detect medium effects with 80 subjects is .86. We anticipate that the use of FDA and PACE will increase power.

7. Risks

Parents will be informed that at any time during their participation in this study, they will have the opportunity to refuse to participate in any procedures or withdraw from the study at any time without prejudice or effect on them and their child. The initial assessment portion of this study takes about 5 hours, there is a risk that a child may become bored or tired. To minimize fatigue, breaks will be taken whenever necessary. This amount of time is typical for an assessment with children. We will take breaks and can reschedule as necessary.
Attempts will be made to stop an assessment and/or treatment if the child seems to be reacting negatively. If a child becomes unduly upset, the assessment and/or treatment will stop immediately and attempts made to comfort the child. A follow-up phone call to the parent will be made in order to determine that the child and parent are comfortable. Participants do not have to answer any questions that they are not comfortable with. They are free to ask questions at any time during the study. Steps taken to minimize the risk to confidentiality include: (1)

keeping all data containing personal information in a locked file cabinet in a locked office to which only the research coordinators have access; (2) assigning identification numbers to all participants for tabulation of data; and (3) using identification numbers on all tests, questionnaires, and videotapes shared with other network sites. Participants will be informed that they do not have to answer any questions that may cause them discomfort. We will be as flexible as possible in scheduling assessments, and make expected time commitments clear to parents at the beginning of the study. Referrals for other treatment will be made if necessary. We have developed a specialized Microsoft Access database with tables linked by an assigned identification code to enter all of the data that will be gathered for this study. The database is housed on a web server with encrypting and password protection in compliance with HIPPA regulations. It is necessary for the project to have identifying information, including names and addresses, since clinical reports are generated from the project. Because the database is stored on a HIPPA compliant server that is accessed over the internet, if the actual project computers were stolen, the user could not access the database, thus protecting the security and confidentiality of the records. Queries are designed so that only de-identified data using the identification code will be exported and used for data analysis. Video recordings will be stored on a secure server in a password protected program.

8. Adverse Event Reporting

The procedures to be used in the study have no known hazards and are comparable with assessment and treatment procedures that have been used in psychological research for decades in infants, toddlers, and adults. During clinical and home visits, a parent will remain with the child at all times. If a child expresses displeasure due to any cause, the session will be suspended. With parental permission, treatment and/or assessment will continue when the parent deems that the child is ready. The researchers, clinicians, and research assistants who interact with the children and families have a background in child development and thorough knowledge of all experimental procedures.

All information that is collected in connection with this study will remain confidential and will only be disclosed as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Every foreseeable precaution to protect confidentiality will be taken. As in all research studies, the potential risk for a loss of confidentiality exists (i.e., computer viruses, computer hackers). However, every reasonable precautionary measure will be taken to protect confidentiality of all data. Computers will regularly be updated for virus protection.

9. Data and Safety Monitoring Plan

Although minimal risks are anticipated, a Data and Safety Monitoring Plan (DSMP) will be established and will be responsible for data and safety monitoring. The DSMP will include the PI, Project Coordinator, and the Family Resource Coordinator from each site and will be headed by the PI. The DSMP will include a monthly meeting. across-site DSMP members will meet every six months through teleconference for review of child and family progress and inspection of the reliability of assessment measures and treatment fidelity measures to ensure the validity and integrity of the data. If any adverse events are identified, an adverse event report will be provided to the IRB at Emory and FSU and the funding Institute and Center. If children show an extremely slow rate of progress or regression, parents will be encouraged to increase community resources that are available in the same way as they would be in our clinic. Other treatments will be considered as covariates of treatment effects. Although this may make interpreting the data more difficult, it would be unethical to deny children more intense treatment because of our research.

This research project proposes to manage data using Emory Amazon Web Services (Emory AWS), which is an Emory customized implementation of the Amazon Web Services on-demand cloud infrastructure for high-performance computing, data storage, database management, data sharing and hosting. Emory AWS provides investigators with access to many of the key research computing services offered by AWS. Additional security and technical controls help ensure that data are protected from unauthorized use, and that data storage and processing are conducted in a standardized, secure and HIPAA-eligible environment.

When using Emory AWS from the Emory campus, traffic flows through the Emory core network to the AWS environment, ensuring secure data transmission. Account creation is limited to Emory-authorized users and accounts are password protected, ensuring secure data access. As part of the account creation process, Emory AWS provisions a set of virtual private cloud environments that are automatically set to an approved configuration limiting user privileges and access to data and services, with appropriate levels of security and minimal risk of variations. Data stored in AWS are automatically encrypted with automatic versioning, backup, and logging, ensuring data integrity. All AWS services enabled in Emory AWS have been assessed for potential risks by the Emory Information Security team. Where applicable, the teams have built out monitoring and remediation controls to check and ensure that accounts do not implement configurations that may have unintended consequences or move them to a state of non-compliance.

For example, all storage must be encrypted; if storage is configured to be unencrypted, the monitor will notify the account owner and unmount the storage. All of these processes are automated, providing a greater level of assurance around data security, access control, firewall rules, network configurations, and environment setups. To satisfy HIPAA regulations, Emory has entered into a Business Associate Agreement (BAA) with Amazon Web Services. As a result of these precautions, Emory AWS may be used to store, manage, process and analyze data, including Emory electronic protected health information (ePHI), for the purpose of human subjects research.

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