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Developmental Regression in Children with Autism Spectrum Disorder: Associated Factors and Outcomes

Jasper Abarte Estabillo
Louisiana State University and Agricultural and Mechanical College, jestab1@lsu.edu

DEVELOPMENTAL REGRESSION IN CHILDREN WITH AUTISM SPECTRUM DISORDER: ASSOCIATED FACTORS AND OUTCOMES

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Jasper Estabillo
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Abstract

Autism spectrum disorder (ASD) is an increasingly common neurodevelopmental disorder characterized by deficits in socialization skills and the presence of restricted and repetitive behaviors. In addition to a number of medical and psychological comorbidities, ASD is associated with a complex phenomenon: developmental regression (i.e., loss of skills in developmental domains). Although present in other disorders (albeit rare), developmental regression is prevalent among individuals with ASD. Thus, interest in studying the phenomenon has grown. However, research on associated risk factors and outcomes is limited and findings have been inconsistent. The current study had two aims: (1) examine potential factors associated with developmental regression in children with ASD, and (2) compare outcomes between children with and without a history of developmental regression. Gender, race/ethnicity, maternal age, paternal age, and history of seizures were not significantly associated with developmental regression. Children who regressed were found to exhibit greater severity in ASD symptoms and adaptive deficits in the communication domain. Implications of these findings are discussed.

Developmental Regression in Children with Autism Spectrum Disorder: Associated Factors and Outcomes

Developmental regression is one of the most complex and puzzling phenomena related to autism spectrum disorder (ASD) (Al Backer, 2015; Bernabei, Cerquiglini, Cortesi, & D'Ardia, 2007; Matson & Kozlowski, 2010). Despite challenges in characterization, developmental regression has become an increasing area of research within the field of autism (Barger, Campbell, & McDonough, 2013; Wiggins, Rice, & Baio, 2009). At present, there is currently no universally accepted definition of developmental regression, but all generally describe some loss of a previously accomplished skill (Al Backer, 2015; Boterberg, Charman, Marschik, Bölte, & Roeyers, 2019). The Autism and Developmental Disabilities Monitoring Network describes developmental regression as "the documented loss of previously acquired social, communication, play, or motor areas" (Wiggins et al., 2009). The skills lost may be from a range of developmental domains; however, specifications as to how to classify and document loss are unclear. While there is no single definition used across researchers and clinicians, review of the literature indicates developmental regression is typically categorized into four types: language, social, language and social, and mixed regression (Barger et al., 2013).

Language Regression

Language regression is the loss of previously attained vocalizations (Al Backer, 2015; Barger et al., 2013; Bernabei et al., 2007). These language skills range from early verbalizations (e.g., babbling) to functional use of words (Barger et al., 2013). Across developmental regression types, parents most frequently report loss of language skills (Al Backer, 2015), and language regression is typically considered to be the most salient aspect of developmental regression in core ASD features (Bernabei et al., 2007; Shinnar et al., 2001). Although ASD is

characterized by deficits in both socialization and communication, parents may be more likely to report regression in early language skills without loss in socialization skills (Baird, Charman, et al., 2008). This may be due to the emphasis put on achievement of language milestones such as first words or the tangible nature of language (e.g., number of words in a child's vocabulary). Perhaps because of the saliency of language, loss of language skills may be a useful red flag for ASD (Lord, Shulman, & DiLavore, 2004).

Social Regression

Loss of early social interaction skills is also reported by parents (Al Backer, 2015). These skills typically include pre-verbal social skills such as eye contact, social smiling, joint attention, and use of gestures (e.g., pointing), but may also include social interests such as play (Barger et al., 2013). Regression in socialization skills may be more difficult to characterize than language loss due to the qualitative nature of social skills. Whereas parents may report the number of words their child previously used compared to their current vocabulary size, social skills are more likely to be described in broad qualitative terms, such as performing a behavior less frequently than in the past. As such, loss of social communication behaviors may occur much more often than reported in the literature (Ozonoff et al., 2010).

Language and Social Regression

Most individuals who experience regression exhibit losses in both language and social skills (Kalb, Law, Landa, & Law, 2010; Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008). Loss of language is often accompanied with regression in non-verbal communication skills (e.g., gestures, eye contact) and social withdrawal. Any loss of language skills is often associated with more global regression in skills and behaviors, which have serious implications for a child's functioning (Shinnar et al., 2001). Moreover, it is uncommon for a child to regress

in language but continue to exhibit age appropriate social skills with the same quality and quantity that would be expected. Therefore, while language regression is more frequently reported by parents, this loss is more commonly associated with additional losses in social communication behaviors.

Mixed Regression

Mixed regression refers to the documented loss of skills in domains other than language or socialization (Barger et al., 2013). These skills may include motor abilities, such as walking, and adaptive skills, such as self-feeding and toileting. Although less commonly reported, some parents do report loss in fine motor skills (e.g., manipulation of small objects), psychomotor retardation, and dyskinesia (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Moretti et al., 2008). In a research report by IAN (Interactive Autism Network, 2008), parents were asked to state what skill was affected most if their child regressed. Of the children who regressed, 3% of children with autism, 2% of children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), and 5% of children with Asperger's syndrome were affected most in the motor skills domain. When examining daily living skills, 2% of the autism group, 3% of the PDD-NOS group, and 9% of children in the Asperger's syndrome group exhibited the most significant losses in adaptive behaviors. This suggests that regression in motor and adaptive skills may be less prevalent, but are areas of concern, as losses in these domains may be severe. Overall, loss of skills in motor and adaptive domains are typically experienced in conjunction with regression in language and/or socialization skills (Barger et al., 2013).

Developmental Regression and ASD

ASD is a neurodevelopmental disorder characterized by pervasive impairments in social communication skills (e.g., social-emotional reciprocity, nonverbal communication skills, deficits in developing and maintaining age appropriate relationships) and the presence of restricted, repetitive behaviors, interests, and/or activities (e.g., stereotyped speech or motor movements, rigid thinking, fixated interests, sensory abnormalities) (American Psychiatric Association, 2013). Onset of ASD symptoms is gradual through a child's earlier years, and symptoms become more apparent as social demands exceed one's abilities (Werner, Dawson, Munson, & Osterling, 2005).

Developmental regression may be one of three onset patterns for ASD (Rogers, 2004). These patterns are: (1) no period of typical development (i.e., child has consistently atypical or delayed development); (2) developmental plateau (i.e., child develops typically then stops achieving new skills); and (3) developmental regression (i.e., child develops typically then loses skills) (Ozonoff et al., 2008; Rogers, 2004). Although regression is typically conceptualized as the loss of skills following typical development, regression following a history of developmental delays has been found to be more prevalent among individuals with ASD (Kalb et al., 2010; Werner & Dawson, 2005; Wiggins et al., 2009). Research is limited on how children who regress present ASD-associated deficits prior to onset of regression; however, some data suggest that core ASD symptoms are present in some form (Matson & Kozlowski, 2010). Additionally, although language and social skills are the most common and salient skills lost, it is in the context of other atypical behaviors and core ASD-features that developmental regression must be studied (Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). As such, there is limited

understanding on the nature of developmental regression, but it may be a presenting feature that can lead to early diagnosis of ASD in some children (Parr, 2017; Shattuck et al., 2009).

More recent literature suggests that developmental regression may be more subtle than previous reports (Ozonoff & Iosif, 2019; Pearson, Charman, Happé, Bolton, & McEwen, 2018). Interest in studying developmental regression and increased prospective studies have found that skills loss may not appear as a clear-cut loss of skills that parents in retrospective studies may report (Pearson et al., 2018).

Although relatively common in ASD, developmental regression is rare in other neurodevelopmental disorders (Williams, Brignell, Prior, Bartak, & Roberts, 2015). For children without ASD who regress, their skill loss is typically associated with some neurological condition (Baird, Charman, et al., 2008). Other disorders, such as Landau Kleffner syndrome and Rett syndrome, are characterized by regression in developmental skills. Landau Kleffner syndrome, also referred to as acquired aphasia with convulsive disorder or acquired epileptiform aphasia, is a disorder characterized by regression in language comprehension and expression that is associated with severely abnormal EEG and seizures (Stefanatos, 2008). Onset for Landau Kleffner syndrome is between ages three and eight years. Some children with Landau Kleffner syndrome may exhibit behavioral problems; however, social impairments are typically not as significant as the deficits seen in individuals with ASD. Importantly, when the seizures in Landau-Kleffer is treated effectively, ASD symptoms diminish (Besag, 2017). Rett syndrome is characterized by regression in language, coordination, and other behaviors around 18 months (Besag, 2017). The disorder occurs almost exclusively in females. Though phenotypically very similar to symptoms of ASD, Rett syndrome is caused by mutations in the MECP2 gene, which is important for the production of proteins in the brain necessary for normal neuronal functioning

(U.S. National Library of Medicine, 2017b). Though the genetic cause of Rett syndrome has been identified, it is unknown how this dysfunction results in the specific features of the disorder (U.S. National Library of Medicine, 2017b). Continued research on other neurodevelopmental disorders that are characterized by developmental regression may help elucidate developmental regression in ASD.

Childhood disintegrative disorder (CDD) is a rare condition in which children dramatically lose a range of developmental and adaptive skills between ages two and seven (Mehra et al., 2018). Loss of skills is dramatic and occurs over the course of days to eight weeks (Mehra et al., 2018). Previously listed in the DSM as a diagnosis under pervasive developmental disorders, CDD has been under the umbrella of ASD since the DSM-5 (American Psychiatric Association, 2013). Some researchers state that because children with CDD demonstrate such phenotypical similarities to ASD, CDD is part of the spectrum (Hendry, 2000; Mouridsen, 2003; Mouridsen, Rich, & Isager, 1999). However, children with CDD also exhibit distinct characteristics (Fombonne, 2009; Matson & Mahan, 2009). In contrast to the varying developmental trajectories observed in ASD, children with CDD typically meet developmental milestones within normal limits (Kurita, Kita, & Miyake, 1992; Malhotra & Gupta, 2002; Mehra et al., 2018). After regression onset, children with CDD likely do not regain previous achieved skills. Additionally, the regression that occurs in CDD is characterized by acute anxiety, aggression, hyperactivity, and some features of psychosis (e.g., muttering, gesturing to the air) (Hiroshi Kurita & Inoue, 2013). Compared with children with ASD and history of developmental regression, children with ASD have been found to exhibit higher prevalence of loss of toileting skills, anxiety, and epilepsy (Mehra et al., 2018). Despite these distinct features, there is not enough data to conclude that CDD is a separate condition from ASD at this time.

Moreover, clinicians have not been able to differentiate between CDD and ASD in clinical settings (APA, 2013). Findings from a recent review indicated that individuals with CDD had more severe intellectual impairment, high rates of mutism, and increased prevalence of epilepsy and seizure activity (Mehra et al., 2018). Because CDD is characterized by developmental regression, it would be of interest for researchers to continue studying this subset of individuals with ASD.

To further complicate the issue, regression in skills may also be seen in typically developing children (Brignell et al., 2017). Approximately 14% of typically developing children regress in eye gaze and showing emotions during toddlerhood. The reasons why typically developing children decline in these socialization skills is unknown, but it is possible that as children develop, they may stop showing skills they once mastered (at least for a short period of time). However, typically developing children are more likely than children with ASD to make up for those losses in skills and compensate through other behaviors. Children with ASD who regress lose skills and are less able to compensate for their regression.

Theories

The mechanism underlying developmental regression is unknown; however, dysfunction in neurological processes may be the cause. Researchers suggest that ASD may be due to impaired mechanisms in the anatomical remodeling of the brain during the process of synaptic growth and pruning in a child's second year of life (Fombonne, 2009; Matson & Mahan, 2009). Thus, developmental regression may be due to overly aggressive synaptic pruning (Thomas, Knowland, & Karmiloff-Smith, 2011). This disruption in neuronal connectivity may then result in loss of previously acquired skills. Studies examining this theory are limited; however, it is a promising area of research with the field of ASD. Particularly because other conditions

characterized by regression have identified neurological components, continued studies of the possible neurological basis of ASD and developmental regression are warranted. At present, the specific underlying mechanism of developmental regression in ASD is unknown, and additional research on possible genetic bases and neurobiological causes are needed (Nordahl et al., 2011; Thomas et al., 2011; Xi et al., 2007).

Developmental History

Parent report is the most commonly used method to establish the presence of developmental regression (Barger et al., 2013; Matson & Kozlowski, 2010; Ozonoff & Iosif, 2019; Pearson et al., 2018; Werner & Dawson, 2005), which can vary from formal criteria to a parent's response to the question if their child has ever lost skills without additional follow-up questions. The most common formal criteria used in the literature is based on a parent's answer to various questions on the Autism Diagnostic Interview-Revised (ADI-R) (Barger et al., 2013; Ozonoff, Li, Deprey, Hanzel, & Iosif, 2018; Rogers, 2004; Werner & Dawson, 2005). Several questions on the ADI-R provide evidence of developmental regression. One question asks if the child had at least five words that they used spontaneously, meaningfully, and communicatively for at least three months before being lost for at least three months. However, if the child does not meet these criteria, then they would not be classified as having experienced developmental regression. There are additional concerns with these strict criteria for developmental regression, as many children with ASD are delayed in achieving milestones and may not have had a verbal repertoire of at least five words established for at least three months before onset of developmental regression. Use of a single question (e.g., "Did your child ever experience regression in skills?") and parent surveys are also used in research (Barger et al., 2013); however, without further probes, the presence of developmental regression is unclear.

As stated by Barbaresi (2016), concern regarding use of parent report is not only related to difficulty recalling age of onset and what skill(s) may have been lost, but also if the definition of developmental regression actually translates with parents. For example, parents may affirm that their child lost words, but when asked follow-up questions, it may be revealed that these words were not used communicatively, pragmatically appropriately, and/or were solely imitation. As such, Barbaresi argues that these reports do not truly meet the requirement that there is a loss of previously acquired, functional skills.

There are some concerns that although use of parent report is practical, there may be under-reporting of not only ASD-associated symptoms, but developmental skills broadly, leading to under-reporting of regression (Ozonoff et al., 2010). Because most studies on developmental regression utilize parent report, it is possible that there is a "telescoping effect" when determining age at onset (Ozonoff, Li, Deprey, Hanzel, & Iosif, 2018). "Telescoping effect" refers to parents of older children reporting later onset of symptoms and symptom recognition than parents of younger children (Lord et al., 2004). This may affect studies on age at regression onset due to parents of older children tending to report later ages at onset and symptom emergence (Barger et al., 2013). These factors are a major concern when studying the phenomenon of developmental regression; however, the most important concern may be the difficulty in separating the child's age at regression onset from the child's age at parents' recognition of skill loss (Goldberg et al., 2003). Use of videotape recordings has been utilized to provide additional evidence of regression onset. However, videos are typically not made in replicable contexts or of all possible behaviors. Although videos may be useful in providing some detail of skills attained, the difficulty lies in the availability of videos for all possible skills a child may display (Lord et al., 2004). Additional records such as medical charts and baby

books can be helpful in providing information but are rarely comprehensive enough in describing the skills achieved and skills lost. As such, use of parental report for developmental history continues to be the most widely used method of studying developmental regression.

Prevalence

Developmental regression occurs in a significant subgroup of individuals with ASD; however, there is variability in the prevalence reported across current studies. These differences in rates have been related to type of developmental regression studied, study methodology, sampling method, and child's age at assessment. Overall, estimates suggest that around one-third of individuals with ASD regress in some developmental skills during childhood (Parr et al., 2011). However, other researchers have suggested up to 63% of children with ASD regress (Thurm, Manwaring, Luckenbaugh, Lord, & Swedo, 2014). Results from recent studies indicate that developmental regression may be more prevalent than previously thought and may be considered part of the trajectory of ASD (Ozonoff & Iosif, 2019; Pearson et al., 2018).

Regression type. A meta-analysis by Barger and colleagues (2013) found that 32.1% (confidence interval [CI]: 29.5-34.8) of children with ASD regress in some skill domain. When looking at specific developmental areas, rates of developmental regression differed based on the type of skill lost. Language regression occurred in 24.9% of children with ASD, language and social regression in 38.1%, mixed regression in 32.5%, and unspecified regression in 39.1% (Barger et al., 2013). The majority of the literature has examined language regression and has found prevalence rates ranging from 15% to 37%, with most studies reporting rates between 20% to 25% (Davidovitch et al., 2000).

Study methodology. There have also been differences in the prevalence rates of developmental regression in ASD dependent on study methodology. Retrospective studies,

which utilize parent report (i.e., developmental interview) to determine if the child had a history of developmental regression, have found prevalence rates around 30% (Davidovitch et al., 2000; Goldberg et al., 2003; Hoshino et al., 1987; Oslejskova, Dusek, Makovska, & Rektor, 2007; Siperstein & Volkmar, 2004). Parent report is important and widely used in developmental assessments because parents are able to provide information about the child's general development and ASD concerns. Researchers indicate that using both parent report to obtain developmental information in conjunction with direct observational measures give the most accurate results for diagnostic assessments (Lemler, 2012). Rates based on parent reports tend to find lower rates than studies aimed at specifically examining the prevalence of developmental regression. Although widely used in studies of developmental regression, retrospective studies are limited to the bias of parent report. Thus, there is a need to develop better methods to assess for developmental regression (Barbaresi, 2016).

Prospective studies, which include high-risk infant sibling studies in order to track development over time prior to diagnosis of ASD, have on average reported higher rates. Prospective studies allow researchers to monitor development at multiple time points and assess for changes in behaviors as they emerge. In one study, approximately half of children later diagnosed with ASD were found to have typical development until about 14 months, followed by a period of change characterized by some developmental regression (Lemler, 2012). As researchers are able to monitor for ASD symptoms and behavior changes through the use of prospective studies, recent literature has suggested that developmental regression may be more common and subtle than previously thought (Ozonoff & Iosif, 2019; Pearson et al., 2018).

Sampling method. Differences in prevalence rates were also found based on sampling method. In population-based studies, the rate was 21.8% (Barger et al., 2013). Clinic-based

prevalence was found to be 33.6%, and prevalence in parent-survey studies was found to be much higher at 40.8% (Barger et al., 2013).

Age at assessment. The age of the child at the time of assessment has also been found to be associated with higher prevalence rates, such that parents of children who were evaluated closer to the age at regression onset were more likely to report loss of skills compared to parents of children being evaluated at older ages (Tuchman & Rapin, 1997). In a study comparing children older and younger than age three at time of evaluation, only 28% of children older than three were reported to have regressed compared to 40% of children younger than three years (Tuchman & Rapin, 1997).

Age at Onset

Overall, studies indicate that developmental regression occurs sometime between age two and three years, with the average age at regression onset around 20 months (Oslejskova et al., 2007; Ritvo & Freeman, 1977; Tuchman & Rapin, 1997). Meta-analysis findings indicated that the mean age at onset was 1.78 years (CI: 1.69-1.89) (Barger et al., 2013). A study by Rogers (2004) reported a wide range of age at onset. Almost 50% of children in the study regressed between 12 and 24 months, 30% between 24 and 36 months, and 15% regressed after 36 months.

Regression type. There have been disparate findings regarding age at onset and type of skill lost. Wilson and colleagues (2003) reported language regression to occur at 21.2 months, and similarly, Shinnar and colleagues (2001) reported language regression onset at 22.8 months. Goldberg and colleagues (2003) had different results. While language regression was reported at approximately 21 months, non-language regression was reported to occur earlier, at around 18 months (Goldberg et al., 2003). Broader definitions of developmental regression, such as those

that include all developmental domains, may have older average age at onset (i.e., around 27 months) (Matson, Wilkins, & Fodstad, 2010).

Gender differences. There is some evidence of gender differences in age at onset of developmental regression. Wiggins and colleagues (2009) found that there was a significant gender difference in age at onset, such that males regressed at much younger ages than girls. Alternatively, Kobayashi and Murata (1998) found no significant difference in mean age at onset; however, in their study, all cases with onset prior to age one were female and significantly more males were found to regress after age three. Additional research must be conducted to further examine possible gender differences in age at onset of developmental regression.

Course of Developmental Regression

While some studies report an abrupt change in the child's development and behavior, others report a gradual change over the course of several weeks (Baird, Charman, et al., 2008). According to Matson, Wilkins, and Fodstad (2010), loss of skills occurred over a 3-month period. This period of skill loss is typically followed by regaining of skills, but the rate of acquisition is variable (Baird, Charman, et al., 2008). Some recovery in skills was reported (e.g., 61% of children in a study by Wilson and colleagues (2003) and 57% of children reported by Shinnar and colleagues (2001); however, this improvement in skills was more likely in children who did not experience developmental delays prior to regression (Wilson et al., 2003).

Factors Associated with Developmental Regression

This section will discuss research on various factors related to developmental regression in ASD. Researchers have focused on a range of associated genetic, biological, environmental, and developmental variables, and studies have found varying results. At present, much like the etiology of ASD, the cause of developmental regression is currently unknown. Findings across studies indicate that there is a continued need to research variables associated with developmental regression in ASD.

Gender

While there is a well-established significant gender difference in ASD, such that the gender ratio is approximately 4 male:1 female (Constantino & Charman, 2012; Giarelli et al., 2010; Rinehart, Cornish, & Tonge, 2011; Zwaigenbaum et al., 2012), studies have not found a significant difference in the risk for developmental regression between genders (Barger et al., 2013; Kern, Geier, & Geier, 2014; Lord et al., 2004; Luyster et al., 2005; Scott, Shi, Andriashek, Clark, & Goez, 2017). Of the children who regress, approximately 24% were female (Scott et al., 2017).

Race and Ethnicity

Disparities between racial groups in the recognition of ASD have been researched (Mandell, Listerud, Levy, & Pinto-Martin, 2002; Mandell et al., 2009; Tek & Landa, 2012). When examining rates of developmental regression across racial groups, studies have shown inconsistent results. One study did not find differences between racial/ethnic groups (Kern et al., 2014); however, other researchers have found minority children to experience higher rates of developmental regression (Spinks-Franklin & Swanson, 2014). In one study, African American children were twice as likely to regress than White children, and Hispanic children were 1.5

times more likely than White children to regress (Spinks-Franklin & Swanson, 2014). Identification of why minority children may be more likely to experience developmental regression is unknown. Additionally, more research is needed to confirm these data, because as suggested by the study authors, minority children tend to exhibit more severe symptoms before receiving an ASD diagnosis (Spinks-Franklin & Swanson, 2014). Thus, developmental regression may be over-represented in minority children because they may be demonstrating more severe symptoms before getting evaluated and diagnosed.

Parental Age

Parental age has been linked to an increased risk for ASD; however, there is currently very limited research examining if parental age is associated with developmental regression. Davidovitch and colleagues (2001) did not find a significant difference in parent age between groups. Zhang and colleagues (2012) examined maternal age and did not find a significant relationship. No other studies were found that specifically examined parental age as a factor for developmental regression.

When studying autism broadly, researchers have found that older parents are more likely to have children diagnosed with ASD (Croen, Najjar, Fireman, & Grether, 2007; Durkin et al., 2008; Idring et al., 2014; Michaelson et al., 2012; Parner et al., 2012; Reichenberg et al., 2006; Weiser et al., 2008). Sandin and colleagues (2015) found that older fathers (i.e., over 50 years) were found to be 66% more likely than fathers in their 20s to have children with autism. Fathers in their 40s were 28% more likely to have children with ASD. Maternal age indicated a different pattern, such that teenaged mothers were 18% more likely to have a child with autism than a mother in her 20s, and mothers in their 40s were 15% more likely than mothers in their 20s. Age differences between mothers and fathers was also found to be a risk factor. Fathers in the 35-44

years group who had an age difference of greater than 10 years with their partner were also at an increased risk. Taken together, these studies indicate that parental age is a risk factor for ASD. Although the specific mechanism is unclear, the association between parental age and autism is likely due to the accumulation of genetic variations in older parents' sperm and egg cells (Michaelson et al., 2012). Much like continued research on how genetics and parent age may be associated with autism, additional research to identify how maternal and paternal age may be related to onset of developmental regression is needed.

Family History of ASD

Studies of at-risk siblings and family history of ASD are common in the field, as they elucidate insight into the emergence of the disorder. Similar to studies of ASD symptoms in at-risk children, researchers have examined history of developmental regression. Retrospective reports of developmental regression in children in multiplex families have found similar (i.e., about 24%) or lower rates than in simplex families (Parr et al., 2011). Although there may be concerns due to parent report (i.e., parents with a child with ASD may be more astute observers of their subsequent children's development and likely to recognize skills loss), parents in multiplex families have been found to under-report regression (Landa et al., 2013; Ozonoff & Iosif, 2019).

Genetic Variations

Studies on genetic variations and developmental regression are limited. Davidovitch and colleagues (2000) reported that all children in their study (both those who regressed and those who did not) who had genetic tests completed had normal results. However, results in clinical tests are limited and do not provide the same information that may be available in research studies. Molloy and colleagues (2005) found some evidence linking developmental regression

with genetic variations on chromosomes 7q and 20q. In a study utilizing data from the Simons Simplex Collection, children with ASD who had mutations in genes that encode postsynaptic density proteins were more likely to experience developmental regression (Goin-Kochel, Trinh, Barber, & Bernier, 2017). Variations on these loci may contribute to susceptibility to developmental regression in ASD, but additional research is needed to explore these relationships. As the field of genetics rapidly progresses, continued studies examining possible genetic variations associated with developmental regression are highly necessary.

Socio-economic Status

Rates of ASD diagnosis have been found to vary across socioeconomic status (SES) levels (Delobel-Ayoub et al., 2015; King & Bearman, 2011; Thomas et al., 2012), but studies have not shown developmental regression to be more prevalent among any one SES group (Christopher, Sears, Williams, Oliver, & Hersh, 2004; Davidovitch et al., 2000; Hansen et al., 2008). Because SES may be associated with additional factors that may be related to developmental regression (e.g., prenatal factors, education level, parental age), additional studies are needed to examine this relationship.

Birth Order

Studies on birth order have found varying results. Birth order has not been found to be associated with developmental regression in ASD in some studies (Meilleur & Fombonne, 2009; Oslejskova et al., 2007; Parr et al., 2011). However, there is limited evidence that birth order may be associated with developmental regression when examining specific skills. Though no effect of birth order was found on parents' reports of word loss, a higher percentage of firstborn children were described to lose early vocalizations (Lord et al., 2004). Thus, birth order may be associated with loss of early vocalizations.

Pregnancy Complications

Prenatal complications have been associated with higher risk of ASD (Larsson et al., 2005; Williams & Ross, 2007; Zerbo et al., 2013). However, pregnancy complications, including maternal hypertension, infections, teratogen exposure, and gestational diabetes, were not found to be associated with greater risk for developmental regression in children with ASD (Scott et al., 2017). At present, due to limited research, it is unclear if pregnancy complications may contribute to increased risk for developmental regression.

Birth and Peri-Natal Complications

Delivery Complications. Davidovitch and colleagues (2000) reported no difference in delivery complications between children who did and did not regress. Rates of various delivery complications (e.g., emergency cesarean section, instrumental delivery) were reportedly similar in both groups; however, children who regressed were found to have epidural anesthesia used more frequently. Although use of epidural anesthesia was found to be higher in children who regress, the relationship between epidural anesthesia and developmental regression, as well as how its use may contribute to possible later regression, is unknown.

Mode of Delivery. When comparing children who had and had not regressed, mode of delivery was not found to be a significant risk factor for developmental regression (Zhang et al., 2012). Children who were born via cesarean section were not more likely than children born via natural delivery to experience developmental regression.

Premature birth and low birth weight. Premature birth and low birth weight are also factors that have been associated with ASD (Atladóttir, Schendel, Henriksen, Hjort, & Parner, 2016; Kerstjens, De Winter, Bocca-Tjeertes, Bos, & Reijneveld, 2012; Lampi et al., 2012; Schendel & Bhasin, 2008). Being born preterm and/or small for one's gestational age have been

associated with greater risk for autism (Hultman, Sparén, & Cnattingius, 2002). However, when examining the relationship between prematurity and developmental regression, preterm delivery was not found to be associated with an increased risk (Scott et al., 2017). Birth weight also was not found to be associated with increased risk for developmental regression (Zhang et al., 2012). Additional research is needed to examine these findings, as well as the possible relationship between low birth weight and risk for developmental regression.

Peri-natal Complications. Researchers have also studied the possible role of postnatal complications as risk factors for developmental regression in children with ASD. Early postnatal complications, including requiring oxygen and a stay at the NICU, were not associated with developmental regression (Scott et al., 2017). APGAR scores were also similar between children who regress and those who do not (Davidovitch et al., 2000). There is limited research examining postnatal complications as a risk factor for developmental regression, and at present, complications do not appear to result in higher risk for children with ASD.

Achievement of Developmental Milestones

Researchers have also examined timing of achievement of various developmental milestones in children who experience developmental regression. Of note, developmental concerns have been commonly reported prior to regression onset (Wiggins et al., 2009)

Motor. Motor delays were commonly reported prior to regression, with 24% noting deficits in this area (Wiggins et al., 2009). In a small study, children who regressed began walking earlier than children who did not regress (Wiggins et al., 2009). The mean age at first steps for children who regressed was 13.18 months, while children who did not regress reportedly walked at 17.66 months. This finding suggests that children who regress may achieve motor milestones earlier; however, why this may put a child at-risk is unclear. In contrast, other

researchers have also found no differences in age at achievement of motor milestones between children with and without regression (Bernabei et al., 2007; Jones & Campbell, 2010).

Communication. Researchers have found disparate results regarding language milestones and developmental regression. Some studies have found that children with ASD who regress develop language earlier than children who do not regress (Baird, Charman, et al., 2008; Lord et al., 2004; Pickles et al., 2009). However, parents have also reported children with developmental regression to have significantly more language delays overall (Wiggins et al., 2009). Other researchers have found that children who regress have higher levels of social and language development at age one, but not at age two (Werner & Dawson, 2005). Others have found that 94% of children who regress only had single word vocabularies prior to regression, 7% had several single words, and 3% of children who regressed had phrase speech prior to language regression (Kurita, 1985). Prior to regression in language, 87% of children were reported to only use single words and have a vocabulary lexicon of less than five words and only 28% were able to speak in two- or three-word phrases (Malhi & Singhi, 2012). However, some studies have found no difference in achievement of first words between children who regress and those who do not (Baird, Charman, et al., 2008). The majority of studies have found that children who regress in language achieve first words within normal limits (Baird, Charman, et al., 2008; Christopher et al., 2004; Jones & Campbell, 2010; Lord et al., 2004; Meilleur & Fombonne, 2009). Given the varying results across studies, additional research is needed to explore the possible relationship between language milestones and developmental regression.

Social. Children with history of developmental regression have also been reported to show early delays in social-communication skills. Prior to regression onset, 45% of children with ASD were found to also demonstrate deficits in joint attention, showing, and social games

(Ozonoff, 2005). Similarly, Luyster and colleagues (2005) found that children who regressed before 24 months showed impaired preverbal communication behaviors (e.g., actions with objects, communicative gestures, games). However, when compared to children with ASD and no regression, children who regress have been found to exhibit significantly more early social-communication behaviors such as use of gestures, participation in social games, and receptive language (Luyster et al., 2005; Ozonoff, 2005).

Medical Conditions

Although specific causes of autism are unknown, many researchers support the conclusion that immune system dysfunction and neuroinflammation are common characteristics of ASD (Ruggiero, 2017; Scott et al., 2017; Theoharides, Tsilioni, Patel, & Doyle, 2016). Therefore, researchers have also examined how immune dysfunction may play a role in the etiology of developmental regression. These researchers have also suggested that developmental regression has an altogether different etiology than ASD (Scott et al., 2017).

Febrile illness. A history of febrile illness, particularly in the six months prior to first concerns, was found to be significantly higher in children with regression, such that around 30% of the children who experienced regression also had a history of febrile illness (Scott et al., 2017). Therefore, febrile illness may be associated with increased risk for developmental regression in children with ASD.

Mitochondrial disease. Additionally, a number of mitochondrial diseases show regression with fever. Patients with mitochondrial disease are at increased risk of neurologic regression associated with stressors such as fever, infection, and dehydration (Shoffner et al., 2010). Developmental regression occurred in 60.7% of children with ASD in one study of 28 children with mitochondrial diseases (Shoffner et al., 2010). Of those children, 70.6% regressed

with fever and 29.4% regressed with no identifiable link to fever or vaccines. Although fever was associated with regression, the duration of fever in this study was unknown. Mitochondrial disease may be related to developmental regression due to the impaired function of oxidative phosphorylation, which is an essential component of metabolism in which energy is produced. The study researchers concluded that fever may be a risk factor for developmental regression in a subgroup of children with ASD and mitochondrial disease.

Autoimmune disorders. Children with ASD who regress have been found to have significantly higher levels of proinflammatory and regulatory cytokine production, resulting in excessive immune responses than children who did not experience regression (Jyonouchi, Sun, & Le, 2001). It has been suggested that these excessive immune responses may be related to ASD symptomatology and regression of skills (Jyonouchi et al., 2001).

Some studies have also documented developmental regression due to autoimmune anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis (Hacohen et al., 2016; Scott et al., 2014). Autoimmune anti-NMDAR encephalitis is an immunological syndrome characterized by expressive dysphasia, mutism, and psychosis (Hacohen et al., 2016; Scott et al., 2014). For a subset of patients, prodromal regression in language and communication skills may also be seen (Hacohen et al., 2016). Hacohen and colleagues (2016) described two females, aged two years, who experienced acute regression (i.e., over 3-4 weeks) in their social communication skills (e.g., initiation of social interaction, loss of words) and were found to have NMDAR receptor antibodies (NMDAR-Ab) in their serum and cerebrospinal fluid. Both children were treated with intravenous methylprednisolone, a corticosteroid typically used to treat severe allergic reactions, rheumatic diseases, gastrointestinal diseases, and lupus (U.S. National Library of Medicine, 2017a). Following treatment, one child regained all lost skills and did not exhibit any behavioral

or psychiatric concerns. The other child made improvements in her language but was reported to exhibit continued behavioral concerns. The authors concluded the N-methly-D-aspartate receptor antibodies may be tests in children who regress in language and communication skills, particularly children who also experience additional neurological problems.

Similarly, Scott and colleagues (2014) described a 33-month-old male who regressed in language and social skills, as well as exhibited abnormal motor movements (e.g., toe walking, repetitive wringing of left hand) following an infection in his upper respiratory tract with fever. After his infection was treated, the child continued to regress in skills, and one month after onset of regression, the child met criteria for ASD. Reacquisition of language and social skills (e.g., use of single words, eye contact) were noted beginning on day three of treatment with intravenous immunoglobulins. After two-week treatment, the child continued to gain language skills (i.e., use of multiple short phrases) and no longer exhibited manual stereotypy. Although promising, it should be noted that these children were developing typically prior to onset of regression. Given that most children with ASD experience some developmental delays prior to regression of skills, it is possible that there may be separate underlying etiologies (Hacohen et al., 2016).

Familial autoimmune disorders. Rates of familial autoimmune disorders have been found to be higher in children with regression (Scott et al., 2017). This was particularly true for the prevalence of maternal autoimmune disorders, with significantly greater children with regression having an affected mother (Scott et al., 2017). Additionally, a higher rate of familial type 1 diabetes and autoimmune thyroid disease was found in children with regression (Scott et al., 2017). As such, there is some evidence that immune activation is related to the etiology of developmental regression in autism.

History of Seizures

Several researchers have examined the relationship between seizures and developmental regression. A significant number of children with ASD who regress have been found to also experience seizures, with the prevalence of seizures ranging from 15%-86% (Kobayashi & Murata, 1998; Moretti et al., 2008; Wilson et al., 2003).

When examining this relationship further, seizures were found to be more common in children who regressed after age three (Shinnar et al., 2001). Researchers have found that there may be bimodal peaks of epilepsy onset in ASD during infancy and adolescence (Besag, 2017). It has been suggested that ASD and epilepsy result from genetic and environmental variables which predispose an individual to both conditions (Besag, 2017). However, it is unclear whether epilepsy plays a role in the onset of developmental regression for children with ASD (Besag, 2017).

Children with ASD and regression were more likely to have epilepsy and atypical epileptiform electroencephelograms (aeEEG) than children who did not regress, with an odds ratio of 1.29 for aeEEG and 1.59 for epilepsy (Barger, Campbell, & Simmons, 2017). In this study, type of regression was not related to group differences. This suggests a relatively weak, but significant relationship between a history of seizures and developmental regression in ASD. Additional data are needed to confirm these results.

In a small study by Baird and colleagues (2007), no significant difference in epileptiform activity was found between children with and without history of developmental regression; however, a trend toward more abnormalities was shown in children who regressed. In their sample, approximately 61% of the participants experienced developmental regression while about 31% had aeEEGs.

Vaccinations

Although some researchers and the general public have postulated the role of vaccinations in autism (Wakefield et al., 1998), studies have failed to support an association between regressive autism and vaccines (Baird, Pickles, et al., 2008; DeStefano, Bhasin, Thompson, Yeargin-Allsopp, & Boyle, 2004; Richler et al., 2006). It has been suggested that autism may be caused by developmental regression shortly after a child receives the Measles-Mumps-Rubella (MMR) vaccination (Wakefield et al., 1998). However, the prevalence of developmental regression did not significantly increase during the years since the introduction of the MMR vaccine in London (Taylor et al., 2002). Researchers have concluded that there is no support for an MMR-associated variant of autism with developmental regression.

Though researchers have continued to find no association between autism and vaccinations, concerns persist. These concerns may related to the several possibilities: (1) vaccines may damage intestinal lining, allowing encephalopathic proteins to enter, (2) the presence of thimerosal in vaccines, which is toxic to the central nervous system, and (3) current vaccination schedules which call for administration of multiple vaccines at once, which may overwhelm or weaken one's immune system (Gerber & Offit, 2009). The logical link between autism and vaccines may be due to the temporal nature, as both occur in early childhood years. Because children receive immunizations at early ages, parents may be likely to use medical visits and receiving vaccines as key events to create a developmental timeline. This timeline may then be skewed to be interpreted as receiving vaccines as causal to the child's autism or developmental regression. As it stands, there is no evidence to support that MMR vaccines cause autism or developmental regression in children.

Outcomes

Results from studies on the prognosis of children who regress versus those who do not have been mixed. A few studies have found no significant difference in outcomes between groups (Kobayashi & Murata, 1998; Shumway et al., 2011), but other researchers have reported that children who regress eventually have more severe deficits in ASD symptoms, language skills, social skills, challenging behaviors, IQ scores, and adaptive behaviors than children who do not regress (Baird, Charman, et al., 2008; Hoshino et al., 1987; Kobayashi & Murata, 1998; Kurita, 1985; Luyster et al., 2005; Matson et al., 2010; Rogers & Dilalla, 1990; Wiggins et al., 2009; Wilson et al., 2003). Lord (2004) also reported that some children may never regain lost skills. Researchers have established relationships between ASD severity, symptoms, cognitive functioning, challenging behaviors, and adaptive skills (Cervantes & Matson, 2015; Cervantes, Matson, Williams, & Jang, 2014; Davis et al., 2011; Goldin, Matson, & Cervantes, 2014; Jang & Matson, 2015; Tureck, Matson, Cervantes, & Konst, 2014), and developmental regression may further exacerbate these difficulties.

Studies on cognitive functioning of children who regress differ in their results. Some data indicate that IQ scores are not significantly different between children who regress and those who do not, but others state that developmental regression may be associated with greater cognitive impairment (Gadow, Perlman, & Weber, 2017; Wiggins et al., 2009; Wilson et al., 2003). When specifically examining the lower range of IQ, there is a greater percentage of children who regress in the moderate to severe range of intellectual disability compared to children who do not regress (Kobayashi & Murata, 1998; Rogers, 2004).

There has been some evidence that adaptive skills are also more severely affected in children who experience developmental regression (Gadow et al., 2017; Wilson et al., 2003).

However, Kobayashi and Murata (1998) did not find a significant difference in adaptive skills at age six, with no significant difference in the number of children with poor, fair, or good adaptive skills across groups. Additional research is needed to confirm these data, as the study utilized clinical physician evaluations to determine adaptive level rather than standardized measures.

When examining only children who regressed, age at onset was not been found to be significantly related to an individual's cognitive functioning, adaptive skills, or ASD symptom severity (Baird, Charman, et al., 2008). As such, there is currently no evidence that age at onset may be associated with greater impairment in various outcomes.

It has been suggested that differences between children who regress and those who do not may become more significant over time, which highlights the importance of longitudinal studies on developmental regression (Bernabei et al., 2007). While no significant differences were seen between groups at age two, differences in receptive language and expressive language became more significant after age four, and differences in play activities became more apparent after age five (Bernabei et al., 2007). For example, at four years, children who regressed were found to understand only contextual orders and did not continue to improve in receptive language, while children who did not experience regression continued to develop skills. With respect to expressive language, at age six, children who did not regress achieved three-word phrases including a subject, verb, and object, while children who regressed primarily spoke in single words. Regarding play, children who did not regress displayed representational play with objects (i.e., pretend play with objects used in appropriate ways to represent their world), while children who regressed were limited to functional object use (i.e., appropriate use of play objects with self). Therefore, the magnitude of difficulties that children who regress exhibit become increasingly apparent over time.

For clinical treatment, there is currently no difference in treatment approaches for children who regress from those who do not (Williams et al., 2015). Treatment for ASD is typically individualized and based on behavioral principles; interventions typically target the impairments (i.e., language, socialization, challenging behaviors) that the individual experiences (Dawson et al., 2010; Matson & Smith, 2008; Romanczyk & Gillis, 2005). There are no specific recommendations for children who regress; however, if regression in skills is reported by parents, then clinicians should also consider the possibility for comorbid seizure disorder, metabolic disease, and/or genetic causes (Williams et al., 2015).

Purpose

The purposes of the current study were to: (1) conduct an examination of factors that may be associated with the onset of developmental regression in children with ASD and (2) compare outcomes of children with ASD with and without a history of developmental regression. Given the varying results across studies on this topic, additional research is needed to further explore how different factors may be related to developmental regression, as well as outcomes for individuals who regress.

The study contributes to the field's understanding of developmental regression in children with ASD. Findings from this study add to the literature on developmental regression and identify possible variables that may be related to the phenomenon. Although researchers have examined various factors, studies are limited, and results are inconclusive at this time. Some variables (e.g., mitochondrial disease; Shoffner et al., 2010) may result in increased risk for developmental regression; however, there is a paucity of research on the current variables of interest (e.g., gender, race/ethnicity, parental age, history of seizures). These variables were chosen for different reasons. Gender was of interest due to the significant difference observed in diagnosis of ASD, as well as increasing understanding of where gender differences lie among individuals with autism. Regarding race/ethnicity, only one previous study was found that examined its potential relationship with developmental regression, highlighting the need to conduct additional research. Parental age was of interest due to the increasing trend within the field of ASD examining the role of parental factors (e.g., age, education level, SES, medical and psychiatric history, broad autism phenotype) associated with the prevalence of ASD in children. Lastly, history of seizures was included in this study to examine the role of medical history in developmental regression. Therefore, the present study aimed to examine these various

relationships. Despite studies on how the variables of gender, race/ethnicity, parental age, and history of seizures may be related to ASD broadly, less is known regarding the relationships between these factors and developmental regression (Canitano, 2007; Croen et al., 2007; Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2014; Lee, Smith, & Paciorkowski, 2015; Levisohn, 2007; Mandell et al., 2002; Mannion & Leader, 2014; May, Cornish, & Rinehart, 2013; Rivet & Matson, 2011; Sandin et al., 2015; Shattuck et al., 2009). It is possible that these variables may result in increased risk for developmental regression in children at varying degrees.

Additionally, this study focused on outcomes of children who have a history of developmental regression. At present, results from studies examining various outcomes of children who have a history of developmental regression have been inconsistent. Given these disparate results, additional research is needed to study potential differences between children with and without a history of developmental regression. By examining ASD severity, data on possible differences in overall severity between children with and without history of developmental regression was obtained. Skills in broader developmental domains were also compared to study potential disparities in adaptive behavior skills. Continuing to increase our understanding of developmental regression and its implications for an individual's symptoms and prognosis is vital, and results from this study add to our understanding of this phenomenon in the ASD population.

Hypotheses

Based on previous literature, hypotheses were be made regarding the results of the proposed studies. Although studies that examine the variables of interest are very limited, there is some evidence to indicate that gender and parental age are not associated with increased risk for developmental regression in children with ASD (Barger et al., 2013; Davidovitch et al., 2000; Lord et al., 2004; Luyster et al., 2005; Scott et al., 2017; Zhang, Xu, Liu, Li, & Xu, 2012). Alternatively, there is some evidence that race/ethnicity and seizures may be associated with increased risk (Barger et al., 2017; Kobayashi & Murata, 1998; Moretti et al., 2008; Shinnar et al., 2001; Spinks-Franklin & Swanson, 2014; Wilson et al., 2003). These relationships were examined in the current study, as well as analysis of the relative risk associated with each factor.

Hypotheses were also postulated regarding outcomes for children who regress. A few studies have found no significant differences between children with and without a history of developmental regression (Kobayashi & Murata, 1998; Shumway et al., 2011); however, the majority of studies indicate that children who regress exhibit greater impairments in ASD core symptoms of socialization, communication, and restricted and repetitive patterns of behaviors (Baird, Charman, et al., 2008; Hoshino et al., 1987; Luyster et al., 2005; Matson et al., 2010; Wiggins et al., 2009), as well as adaptive behavior skills (Baird, Charman, et al., 2008; Bernabei et al., 2007; Hoshino et al., 1987; Matson et al., 2010). As such, the present study hypothesized that children with ASD and a history of developmental regression would consistently experience greater deficits in ASD severity and adaptive behaviors (e.g., communication, daily living skills, socialization, motor skills).

Methods

Procedure

The study was approved by the Louisiana State University (LSU) Institutional Review Board (IRB)prior to initiation of data collection. Data were obtained from psychodiagnostic evaluations conducted by doctoral level graduate students in the LSU clinical psychology program supervised by a licensed clinical psychologist who specializes in the assessment of intellectual and developmental disabilities. Although a number of doctoral clinicians conducted assessments over the course of several years, all cases were staffed with the same licensed clinical psychologist and each case was discussed in supervision to determine diagnosis and other clinically relevant details. Informed consent for participation in research was obtained from all parents/legal guardians and children (when appropriate). Data obtained from clinical evaluations were later entered into an archival database than continues to expand with ongoing assessments. The version of the database used in this study included children assessed between September 2006 and March 2019.

During assessments, parents/legal guardians provided demographic information and developmental history for the child and completed various rating scales, and clinicians completed a battery of measures and behavioral observations. Demographic information included gender, medication history, and parent information (e.g., age, education level, occupation). Clinical interview conducted by the clinicians included discussion of the child's developmental history and developmental concerns. To assess for history of developmental regression, parents/legal guardians were asked, "Was there a period of time during development that your child lost skills?" If parents/legal guardians said yes, there were asked additional questions to clarify if the child was functionally utilizing skills and met criteria for

developmental regression. Parents/legal guardians were then asked the following questions: (1) "What types of skills were lost?" and (2) "At what age did this skill loss occur?" Interview was utilized because it has been suggested that this method may be a more valid mode of discerning history of developmental regression compared to surveys or questionnaires because the interviewer can further probe and utilize clinical judgement to determine if the parents are truly reporting skills loss indicative of developmental regression (Boterberg et al., 2019).

As part of the protocol for psychodiagnostic evaluations, several clinical measures were completed. These measures included assessments completed by clinicians, as well as rating scales filled out by parents/legal guardians. Clinical measures included in this study were the Childhood Autism Rating Scale, Second Edition (CARS2) (Schopler, Van Bourgondien, Wellman, & Love, 2010) and Vineland Adaptive Behavior Scales, Second Edition (Vineland-2) (Sparrow, 2011). The CARS2 was completed by the clinician based on direct observation of the child. The clinicians administered the Vineland-2 to parents/legal guardians in interview format. Measures are described in detail in a following section.

Information obtained from evaluations (e.g., developmental history, demographics, scores on clinical measures) was then de-identified and entered into a database utilized for research purposes. Per LSU IRB, data from evaluations are to be used for research on ASD and developmental disabilities (see Appendix).

Participants

The participants were children who received an evaluation from the LSU Psychological Services Center's Developmental Disabilities Clinic. All children were referred to the clinic due to concerns with developmental delays. Diagnoses were made based on clinical judgment, developmental history, parent rating scales, clinical assessment measures, and in-clinic

observation. Children received various diagnoses including ASD, Global Developmental Delay, Intellectual Disability (ID), Attention-Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, Specific Learning Disorders, and/or anxiety and mood disorders. Other children may have received no diagnosis.

The total sample consisted of 821 children. For the purposes of the current study, only children who received a diagnosis of ASD were included (N = 538). This sample of 538 children was composed of 82.5% males (N = 444) and 17.5% females (N = 94). The children were 7.02 years old (SD = 3.79). Of the children with ASD, 11.5% were African American, 61.9% were White, and 26.6% identified as Other ethnicities. See Table 1.

Table 1. Study sample demographics.

	Total (N = 538)
Gender	
Male	82.5% (N = 444)
Female	17.5% (N = 94)
Age M (SD)	7.02 (3.79)
Ethnicity	
African American	11.5% (N = 62)
White	61.9% (N = 333)
Other	26.6% (N = 143)

Measures

CARS2. The Standard Version Rating Booklet (CARS2-ST) and High-Functioning Version Rating Booklet (CARS2-HF) are clinical rating scales used by clinicians to identify children with ASD (Schopler et al., 2010). The measures are comparable for research use. The CARS2-ST is used for children younger than six years or with an estimated IQ deemed to be below average, while the CARS2-HF is for children older than six years and an IQ above 80. Clinicians answer questions pertaining to the child's behavior based on parent report and clinical observation. The measure is composed of 15 items covering ability to relate to people; imitation

skills (ST) or social-emotional understanding (HF); emotional response (ST) or emotional expression and regulation of emotions (HF); body use; object use (ST) or object use in play (HF); adaptation to change (ST) or adaptation to change/restricted interests (HF); visual response; listening response; taste, smell, and touch response and use; fear or nervousness (ST) or fear/anxiety (HF); verbal communication; nonverbal communication; activity level (ST) or thinking/cognitive integration skills (HF); level and consistency of intellectual response; and general impressions. Items are rated on a 4-point scale based on the frequency and intensity of the behavior. The total score indicates severity with cut-offs for "minimal-to-no symptoms of ASD," "mild-to-moderate symptoms of ASD," and "severe symptoms of ASD" ranges.

Vineland-2. The Vineland Adaptive Behavior Scales, Second Edition (Vineland-2) (Sparrow, 2011) is a measure of an individual's adaptive behavior. The measure is validated for individuals from birth to 90 years old, and it is widely used in assessments for individuals with intellectual and developmental disabilities. The form is administered by a clinician to parents/caregivers as a semi-structured interview, where reporters provide responses regarding the individual's behavior. Responses are rated on a 3-point scale based on the individual's ability to perform certain behaviors. Scores for the domains of Communication, Daily Living Skills, Socialization, and Motor Skills are provided, with an overall Adaptive Behavior Composite and optional Maladaptive Behavior domain. For the purposes of the present study, the Communication, Daily Living Skills, Socialization, and Motor Skills domains were used.

Statistical Analyses: Study 1

Operational Definitions of Variables

Developmental Regression. The dependent variable of interest in the study is if the child experienced developmental regression. For the purposes of the present study, developmental regression was coded as the parent/legal guardian's response to the question, "Was there a period of time during development that your child lost skills?" This study utilizes the broad definition of developmental regression, which includes skills loss in any developmental domain (e.g., language, social, motor, adaptive, etc.). This variable was coded as 0 = no history of developmental regression and 1 = history of developmental regression.

Gender. The child's gender was based on the demographic information provided during the assessment. Male gender was used as the reference category, such that 0 = male, 1 = female.

Race/ethnicity. Information on the child's race was obtained during the assessment. Response categories included White, African American, Hispanic/Latino, Multiracial, and Other. Due to the small percentage of children coded as Hispanic/Latino, Multiracial, and Other, these categories were subsequently collapsed into one "Other" category. These data were recoded into 1 = African American, 2 = White, and 3 = Other.

Maternal Age. Maternal age at the child's birth was obtained during the assessment on the child's demographic information form. This was entered into the logistic regression model as a continuous variable.

Paternal Age. Paternal age was also obtained during the assessment on the child's demographic information form. Paternal age was entered into the model as a continuous variable.

Seizures. Information on history of seizures was also obtained during the assessment. Parents/legal guardians indicated if the child had a history of seizures by answering the question, "Does the child have a history of seizures/epilepsy?" This variable was coded as 0 = no history of seizures and 1 = history of seizures.

Sample size

General recommendations state that there should be at least 10 events per variable for a necessary sample size in logistic regression; however, other researchers have suggested that this may be a conservative estimate (Steyerberg, Schemper, & Harrell, 2011; Vittinghoff & McCulloch, 2007). Although a conservative estimate, the study's sample size (N = 538) meets the suggested criterion.

Data Analyses

All statistical analyses were performed using SPSS 25.0. Data analyzed were the variables listed above (i.e., history of developmental regression, gender, race/ethnicity, maternal age, paternal age, history of seizures). Descriptive statistics were first run in order to determine the percentage of children in the sample with a history of developmental regression. Descriptive statistics were also conducted to determine the average age at onset and prevalence of each type of developmental regression (e.g., language, social, language and social, mixed).

The data were then analyzed to determine if the assumptions of logistic regression were met (Field, 2013), and a binary logistic regression model was created. First, the dependent variable must be measured on a dichotomous scale. The dependent variable in the model is the presence of developmental regression (i.e., yes or no); therefore, this criterion was met. Second, there must be one or more predictor variables that are categorical or continuous. All predictor variables of interest in this study were categorical (e.g., gender, race/ethnicity, history of

seizures) or continuous (e.g., maternal age, paternal age). Third, there must be independence of observations and the dependent variable must have mutually exclusive categories. Because each case represented one child, each case was independent; no re-evaluations were included in the study sample. The dependent variable has mutually exclusive categories in that a child either has or has not experienced developmental regression; there is no overlap between groups. Lastly, there must be a linear relationship between any continuous predictor variable and its logit transformation. This assumption was checked by running the logistic regression including predictors that are the interaction between each continuous variable (i.e., maternal age, paternal age) and the log of itself (i.e., ln_maternal age, ln_paternal age); the interaction predictors of maternal age by ln_maternal age and paternal age by ln_paternal age were included. Neither interaction terms were significant in the model, $p > .05$. Therefore, the assumption of linear relationships between continuous variables and its logit transformation was met.

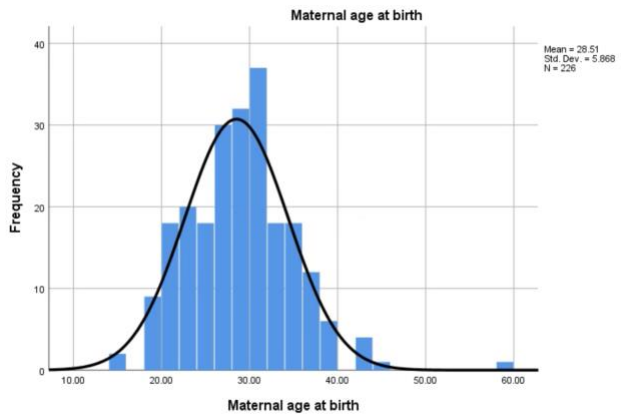

Figure 1. Distribution of maternal age.

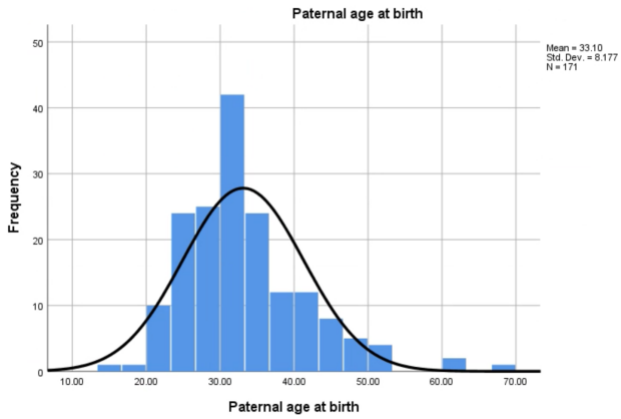

Figure 2. Distribution of paternal age.

Multicollinearity was also tested by examining statistics of tolerance and VIF. Tolerance values less than 0.1 and VIF values greater than 10 are concerning. For the variables of gender, dummy code for African American, dummy code for Other, maternal age, paternal age, and seizures, both criteria were met. For the dummy code for White, the tolerance value was less

than 0.1, indicating an issue of collinearity. Additional collinearity diagnostics indicated collinearity problems, as demonstrated by examination of Eigenvalues and condition indices, which were not fairly similar across dimensions. In analyzing the variance proportions, maternal age and paternal age had high proportions on the same small eigenvalue, indicating dependency between these variables. Although there is some concern regarding this dependency, maternal and paternal age are likely to be related, as parents are typically of similarl ages. The distributions for maternal and paternal age can be seen in the histograms (Figures 1 and 2); maternal age was found to be moderately positively skewed (0.651), while paternal age was highly positively skewed (1.10). As stated by Field (2013), once collinearity is identified, there is not much to be done about it (e.g., no statistical support for omitting one variable over another). Field asserts that the safest remedy is to acknowledge the unreliability of the model. Therefore, the logistic regression model may be unreliable and these results should be interpreted with caution. These analyses may be re-done in the future with a larger sample size to see if multicollinearity may be lessened.

To analyze the possible relationships between the variables of interest and developmental regression, a binary logistic regression model was created. All variables were entered into the model utilizing the enter method. The race/ethnicity variable was entered with the Other category as the reference group. Analysis of the adjusted odds ratios of the variables of interest demonstrated their relationship to the outcome variable of developmental regression.

Statistical Analyses: Study 2

Operational Definitions of Variables

Presence of Intellectual Disability. Presence of ID was coded dichotomously based on if the child received a comorbid diagnosis of ID. This variable was coded as 0 = no comorbid ID diagnosis and 1 = comorbid ID diagnosis.

ASD Severity. ASD severity was measured as a continuous variable, calculated as the child's total score on the CARS2. Scores between 15-29.5 place the child in the minimal-to-no symptoms range, 30-36.5 are in the mild-to-moderate symptoms range, and scores 37 and above are in the severe symptoms range.

Communication Skills. Communication skills was measured as a continuous variable as calculated on the Vineland-2. This domain is a measure of a child's expressive, receptive, and written (when appropriate) language skills. Communication skills are reported as a standard score with a mean of 100 and standard deviation of 15.

Daily Living Skills. Daily living skills were measured as a continuous variable as calculated on the Vineland-2. This domain is a measure of a child's ability to perform practical and everyday tasks in the home and community. Daily living skills are reported as a standard score with a mean of 100 and standard deviation of 15.

Socialization Skills. Socialization skills were also measured as a continuous variable as calculated on the Vineland-2. The socialization domain is a measure of a child's ability to function in social situations. Scores as standardized such that the mean is 100 and standard deviation is 15.

Motor Skills. Motor skills were also measured as a continuous variable reported from the Vineland-2. This domain assesses a child's gross and fine motor abilities. As with the above

variables, scores on this subdomain are standardized with a mean of 100 and standard deviation of 15.

Sample Size

Suggested sample size for an independent samples t-test and multivariate analysis of variance (MANOVA) were checked utilizing G*Power (Faul, Erdfelder, Buchner, & Lang, 2009). For the t-test, with the parameters of a medium effect size (d = .5), alpha error probability of .05, and power of .8, the recommended minimum total sample size is 102; the study sample size met this criterion. For the MANOVA with 2 groups and 4 variables in the composite dependent variable and utilizing the parameters of a medium effect size (V = .06), alpha of .05, power of .8, the recommended minimum total sample size is 196. The sample size also met this criterion.

Data Analyses

All analyses for outcomes were also conducted in SPSS 25.0. Bivariate analyses were first conducted to examine potential differences between groups. An independent samples t-test was run to determine if groups were significantly different in age.

Intellectual disability. Chi-square analyses were conducted to determine if groups differed in prevalence of comorbid ID.

ASD severity. To compare ASD severity, scores on the CARS2 were compared between groups. This analysis was performed using an independent samples t-test with CARS2 total score (i.e., ASD severity) as the dependent variable.

Adaptive behavior skills. Analyses were also conducted to compare groups on adaptive behavior skills. Assumptions for a MANOVA were first checked. Observations should be independent, and the data should be a random sample. Because the observations represent one

child, they were independent. The MANOVA also assumes that the dependent variables together have normality within the groups. Lastly, there must be homogeneity of covariance matrices. In addition to the variances in each group being approximately equal, the correlation between any of the dependent variables must also be the same in all groups. Thus, Levene's test was conducted to test homogeneity of variance, as well as Box's test for homogeneity of the covariance matrices. Box's test of equality covariance results indicated covariance matrices of the dependent variables were equal across groups, Box's M = 6.07, $F(10, 48429.69) = .59$, $p > .05$ (i.e., the assumption of equality of covariance matrices was met). Levene's tests of equality error variances were not significant for any of the Vineland-2 domains, which indicated that the error variance of the dependent variables was equal across groups.

The MANOVA was then run with group (e.g., ASD or ASD+developmental regression [DR]) as the predictor variable and the Vineland-2 domains (e.g., Communication, Daily Living Skills, Socialization, Motor) as the composite dependent variable. Following a significant MANOVA, post hoc comparisons were run to determine differences between groups on each of the Vineland-2 domains.

Results: Study 1

Of the 538 children with ASD, 20.4% were reported to have a history of developmental regression (*N* = 109). See Table 2. The average age at onset for developmental regression was 19.84 months (*SD* = 10.59), with a range of two to 74 months.

Table 2. Demographics separated by developmental regression type.

	All ASD+DR (*N* = 109)	Language (*N* = 77)	Social (*N* = 5)	Language+Social (*N* = 24)	Mixed (*N* = 3)
Gender %					
Male	85.3	86.8	100	87.5	66.7
Female	14.7	13.2	0	12.5	33.3
Age at DR					
M(SD)	19.84 (10.59)	19.09 (8.64)	27.50 (21.75)	17.22 (5.29)	41.67 (30.66)
Range	2-74	2-42	14-60	6-28	13-74

Of the children with a history of developmental regression, 70.6% (*N* = 77) were reported to have language regression, 4.6% (*N* = 5) had social regression, 22% (*N* = 24) reported to have language and social regression, and 2.8% (*N* = 3) were reported to have mixed regression. Parents often reported loss of "speech," "babbling," and the various sounds and/or words that child stopped saying. Social skills included eye contact, "interest in others," and "engagement with people." Skills lost for the children with mixed regression included crawling and toileting.

Table 3. Demographics separated by ASD or ASD+ DR group.

	Total (*N* = 538)	ASD (*N* = 429)	ASD+DR (*N* = 109)
Gender			
Male	82.5% (*N* = 444)	81.8% (*N* = 351)	85.3% (*N* = 93)
Female	17.5% (*N* = 94)	18.2% (*N* = 78)	14.7% (*N* = 16)
Age M(SD)	7.02 (3.79)	7.29 (3.77)	5.98 (3.70)
Ethnicity			
African American	11.5% (*N* = 62)	11.9% (*N* = 51)	10.1% (*N* = 11)
White	61.9% (*N* = 333)	61.1% (*N* = 262)	65.1% (*N* = 71)
Other	26.6% (*N* = 143)	27% (*N* = 116)	24.8% (*N* = 27)
Seizures	2.8% (*N* = 15)	2.6% (*N* = 11)	3.7% (*N* = 4)
Parental age M(SD)			
Mother	28.51 (5.87)	28.65 (5.77)	28.18 (6.03)
Father	33.10 (8.18)	32.43 (8.00)	34.18 (8.31)

To determine if there were differences between the ASD and ASD+DR groups on various factors, several chi-square analyses were conducted. A significant difference was found between the ASD group (M = 7.29, SD = 3.77) and ASD+DR group (M = 5.98, SD = 3.70) on age, $t(504) = 3.20$, $p < .001$. An additional analysis was conducted to determine if there was a gender difference in age at regression onset. Although males were found to regress at a slightly younger age (M = 19.20, SD = 8.71) than females (M = 22.57, SD = 18.27), this difference was not found to be significant, $t(97) = -1.11$, $p > .05$. Demographics based on ASD and ASD+DR groups are in Table 3.

Due to the significant difference in age between ASD and ASD+DR groups, additional analyses were conducted to further examine the prevalence of developmental regression by age group. See Table 4 for the percentage of participants with developmental regression by age.

A chi-square test was conducted to assess for differences between prevalence of developmental regression by age. Results of the chi-square test showed significant differences between ages, $\chi^2(41) = 60.84$, $p < .05$. Overall, a higher percentage of young children were found to have history of developmental regression compared to older children. When dividing the participants into groups younger and older than six years, a significant difference in prevalence of developmental regression was found, $\chi^2(1) = 10.15$, $p < .001$. A higher percentage of children younger than six years (27.7%) were found to have history of developmental regression compared to children older than six years (15.9%).

Additionally, children younger than six years were found to have regressed at a younger age (M = 17.16, SD = 7.11) compared to children older than six years (M = 22.61, SD = 13.13) at the time of assessment, $t(93) = -2.57$, $p < .05$. This finding suggests that children who are

younger at the time of assessment were reported to experience regression earlier than children older at time of assessment.

Table 4. Prevalence of developmental regression by age.

Age	% Developmental Regression	
	No	Yes
2 (*N* = 46)	54.3	45.7
3 (*N* = 68)	73.5	26.5
4 (*N* = 40)	75	25
5 (*N* = 73)	86	14
6 (*N* = 47)	85.1	14.9
7 (*N* = 49)	89.8	10.2
8 (*N* = 37)	78.4	21.6
9 (*N* = 28)	78.6	21.4
10 (*N* = 19)	84.2	15.8
11 (*N* = 23)	82.6	17.4
12 (*N* = 19)	73.7	26.3
13 (*N* = 19)	100	0
14 (*N* = 9)	77.8	22.2
15 (*N* = 13)	92.3	7.7
16 (*N* = 12)	83.1	16.7

To evaluate the relationships between factors of interest and developmental regression, the variables were entered into the logistic regression model utilizing the enter method. Examination of Cook's distance showed all values to be less than one and standardized residuals did not indicate any values above two.

Table 5. Results of logistical regression analyses for variables predicting developmental regression.

Variable	B (SE)	Odds Ratio	95% CI for Odds Ratio		*p*-value
			Lower	Upper	
Constant	-1.25 (.987)	.286			$p > .05$
Gender	-.514 (.456)	.598	.245	1.461	$p > .05$
African American	.053 (.688)	1.054	.274	4.061	$p > .05$
White	.628 (.548)	1.874	.640	5.487	$p > .05$
Other					$p > .05$
Maternal age	-.051 (.036)	.950	.885	1.020	$p > .05$
Paternal age	**.056 (.026)**	**1.058**	**1.005**	**1.113**	$\mathbf{p < .05}$
Seizures	-.496 (.879)	.609	.109	3.409	$p > .05$

Note: R^2= .042 (Cox & Snell), .058 (Nagelkerke). Model $\chi^2(6) = 7.35$, $p > .05$

The logistic regression model was not found to be significant, $\chi^2(6) = 7.35$, $p > .05$. See Table 5. Collinearity between variables (i.e., maternal and paternal age) should be considered when interpreting the logistic regression results. The result of the Hosmer and Lemeshow Test showed the model to be a good fit for the data, $\chi^2(8) = 6.44$, $p > .05$. The classification table indicated an overall classification of 61.8%, with 91.5% correctly classified as no history of developmental regression but only 12.5% correctly predicted to regress.

Although the full model was not found to be significant, paternal age was a significant variable in the model. In the full model, paternal age was found to have an odds ratio of 1.058 [CI: 1.005-1.113, $p < .05$]. This small, but significant odds ratio was further explored by creating an additional logistic regression model excluding maternal age and only including gender, ethnicity, paternal age, and history of seizures. However, the updated model was not found to be significant, $\chi^2(5) = 5.77$, $p > .05$, $R^2 = .033$ (Cox & Snell), .045 (Nagelkerke). Within the model, none of the variables were found to be significant.

As prior researchers in the broader ASD literature have found that the relationship between maternal and paternal age may increase risk for ASD, a composite variable of maternal and paternal age was created (i.e., maternal age x paternal age). This model was run; however, it was also not significant, $\chi^2(7) = 7.80$, $p > .05$, $R^2 = .045$ (Cox & Snell), .061 (Nagelkerke). None of the variables within the model were significant.

Results: Study 2

Intellectual Disability

A chi-square test showed no significant difference between groups for the presence of comorbid ID, $\chi^2(1) = 0.01$, $p > .05$. Participants with comorbid ID were found to have IQ scores of 56.71 (*SD* = 17.06). In comparison, children without comorbid ID were found to have IQ scores of 86.41 (*SD* = 19.04).

Of the 42 participants with ID (*M* = 9.48 years, *SD* = 3.35), 76.2% were male (*N* = 32) and 23.8% were female (*N* = 10). Regarding ethnicity, 16.7% were African American (*N* = 7), 73.8% were White (*N* = 31), and 9.5% were Other (*N* = 4). The average CARS2 score was 33.17 (*SD* = 7.06). Vineland-2 scores were all below average with Communication (*M* = 65.26, *SD* = 15.84), Daily Living (*M* = 75.84, *SD* = 16.85), Socialization (*M* = 71.42, *SD* = 21.01), and Motor (*M* = 80.20, *SD* = 19.63) scores all greater than one standard deviation below the mean.

CARS2

An independent samples t-test showed a significant difference between groups on total CARS2 severity, $t(162) = -2.31$, $p < .05$. The ASD+DR group (*M* = 34.10, *SD* = 7.44) had significantly higher scores than the ASD group (*M* = 31.49, *SD* = 7.05). See Table 5.

Vineland-2

In the total sample, Vineland-2 scores were all below average, with Communication (*M* = 69.92, *SD* = 16.88), Daily Living (*M* = 79.24, *SD* = 14.94), Socialization (*M* = 74.29, *SD* = 12.37), and Motor (*M* = 84.22, *SD* = 15.92) domains all greater than one standard deviation below the mean. Overall, these scores indicate participants experienced delays in adaptive living skills. Deficits in Communication skills were particularly apparent, as evidenced by an average score greater than two standard deviations below the mean.

To compare ASD and ASD+DR groups on adaptive skills, a MANOVA was conducted with a composite dependent variable created from Vineland-2 domains of Communication, Daily Living, Socialization, and Motor skills. There was a statistically significant difference in adaptive skills between groups, $F(4, 131) = 2.63$, $p < .05$, Wilk's $\Lambda = .93$, partial $\eta^2 = .074$.

Because the results from the MANOVA were significant, follow-up analyses were conducted to explore possible differences between groups on each of the Vineland-2 domains. When comparing groups on Vineland-2 domains, Communication skills were found to be significantly different between groups, $F(1) = 4.66$, $p < .05$, partial $\eta^2 = .034$. Scores on Daily Living, Socialization, and Motor skills were not found to be significantly different between groups, $p > .05$. See Table 6.

Table 6. Outcomes separated by ASD or ASD+DR group.

	Total (N = 538)	ASD (N = 429)	ASD+DR (N = 109)	p-value
ID	7.8% (N = 42)	7.7% (N = 33)	8.3% (N = 9)	$p > .05$
CARS2 Total score M(SD)	32.20 (7.23)	**31.49 (7.05)**	**34.10 (7.44)**	***p* < .05**
Vineland-2 scores M(SD)				
Communication	69.92 (16.88)	**72.21 (16.85)**	**65.80 (16.28)**	***p* < .05**
Daily Living	79.24 (14.94)	79.69 (14.80)	78.42 (15.31)	$p > .05$
Socialization	74.29 (12.37)	74.38 (12.21)	74.12 (12.78)	$p > .05$
Motor	84.22 (15.92)	84.40 (16.58)	83.90 (14.81)	$p > .05$

Discussion

Prevalence

In this study, 20.4% of the children with ASD had a history of developmental regression. This prevalence is similar, but lower than previous research, which has estimated the prevalence to be approximately 30% (Barger et al., 2013; Parr et al., 2011). Although the study's conceptualization of developmental regression included a broad definition and would be expected to have a higher percentage, results demonstrated otherwise. This prevalence may be due to utilization of retrospective parent report, which tends to find lower rates than prospective studies (Barger et al., 2013). Differences in prevalence rates were also found between different age cohorts; a greater percentage of younger children were reported to have a history of developmental regression (27.7% of children younger than six compared to 15.9% of children older than six). The varying prevalence rates can be attributed to the telescoping effect, in which parents of older children may under-report symptoms (Lord et al., 2004). Prospective studies may better estimate the prevalence of developmental regression among individuals with ASD. Additionally, this prevalence is lower than findings of other studies utilizing clinic-based prevalence (33.6%) (Barger et al., 2013) or with older children (28%) (Tuchman & Rapin, 1997). Differences in prevalence rates highlight the challenge of studying this phenomenon and continuing to refine methods to better characterize developmental regression.

Age at Onset

The age at onset for developmental regression was similar to prior researchers, with children found to regress at 19.84 months (Barger et al., 2013; Oslejskova et al., 2007). Consistent with other studies on this topic, developmental regression appears to emerge between the first and second years of life in individuals with ASD. This period in toddlerhood is the time

that children are achieving milestones and beginning to consistently show behaviors, and parents may be more likely to notice changes or losses in skills. Therefore, because children have been exhibiting skills more consistently by this age (i.e., establishing a baseline), parents may be more likely to recognize any potential changes or declines in behavior. It appears that not only do ASD-associated symptoms emerge between ages one and two, but regression in developmental skills also has onset during this time. Emergence of impairments in social communication skills and restricted behaviors, coupled with losses in developmental skills, can create challenges in understanding the trajectory of a child's development.

Notably, there was a significant difference in age at regression onset between children older and younger than age six. When examining age groups, children younger than six years were found to regress earlier (M = 17.16, SD = 7.11) than children older than six (M = 22.61, SD = 13.13). This difference in age at onset may be attributed to telescoping effect, in which parents of older children report later onset of symptoms. Based on this result, it is possible that the overall age at regression onset may be skewed by estimates from parents of older children.

For the current study, it is important to note that the children in the ASD+DR group (M = 5.98, SD = 3.70) were found to be significantly younger than the ASD group (M = 7.29, SD = 3.77). Moreover, more children under age six were reported to have a history of developmental regression compared to children over age six at the time of assessment. These differences between age groups may be due to onset of regression leading parents to seek an evaluation for their child. While ASD symptoms emerge in early childhood, it is likely that the onset of developmental regression further influences parents' concerns. It can be difficult for parents to understand atypicalities in development; however, witnessing a child gain and lose skills may create a sense of urgency for parents to seek an assessment. Thus, the younger age of the

ASD+DR group may be due to regression leading parents to obtain an assessment for their child. Furthermore, as developmental regression is associated with more severe ASD symptoms, children who regress appear to exhibit greater ASD severity at younger ages. This may be considered when assessing children with history of regression, as well as conveying to parents that young children who regress may demonstrate more impacting symptoms.

Developmental Regression Types

Similar to other researchers, participants in this study most commonly endorsed regression in language skills, followed by loss of language and social skills, social skills only, then other areas of developmental functioning (i.e., mixed regression). Loss of language skills is likely the more commonly reported domain of regression due to the saliency of skills loss for parents. Regressing in language skills is much more noticeable and quantifiable than regressing in other skills. For example, parents are able to monitor the number of words achieved and this concrete information provides a comparative data point for parents should their child regress in language. Regression in language and social skills was the second most common type of developmental regression reported. Changes in social behaviors may be subtle, and during preverbal communication development, they are likely to be closely associated with early language skills. This relationship between language and social skills in infancy and toddlerhood may create challenges for parents in determining where the regression is primarily occurring. However, during these early ages, it may not be necessary to distinguish between these skills, as they are often occurring in conjunction with each other. Regression in social skills only was less frequently reported. As social skills are closely integrated with expressive and receptive communication, regression in solely this domain may be challenging to observe or differentiate from other behaviors. Lastly, mixed regression was the least common type reported. Although

less common, loss of skills in the domains of motor and adaptive skills were still reported. Regardless of the domain of skills loss, regression in skills can be extremely challenging and confusing for parents to experience. Therefore, provision of psychoeducation, close monitoring, and supports is warranted to assist parents with understanding the phenomenon of developmental regression, their child's development, as well as prognosis.

In examining the participants who regressed, some differences were observed between regression type. The average age at regression was found to be older for the mixed regression group (M = 41.67, SD = 30.66). Because of the type of skills lost in mixed regression (i.e., adaptive skills, motor skills), older ages are expected. Adaptive skills are more complex behaviors that are achieved at older ages; thus, loss of skills in this domain would be expected to be later (Matson & Kozlowski, 2010). Interestingly, children with language+social regression were found to have the earliest regression onset (M = 17.22, SD = 5.29), followed by language regression (M = 19.09, SD = 8.64) and social regression (M =27.50, SD = 21.75). From the current study, it is unclear why language+social regression may occur earlier; however, previous researchers have also found similar results (e.g., Goldberg et al., 2003 also found that non-language regression occurred earlier than regression in language).

To better understand the phenomenon of developmental regression, future researchers should closely monitor development of children and assess for skills loss. Due to the somewhat elusive nature of developmental regression, as it may manifest in as many heterogeneous ways as autism does, broad assessment of functioning across various domains of development may be necessary. Additionally, children may be losing multiple skills simultaneously, which may convolute monitoring and assessment. For children who may regression in multiple domains, more severe losses in one domain may overshadow losses in other domains.

Study 1: Associated Factors

The full model of variables was not found to be significant, which revealed that gender, race/ethnicity, maternal age, paternal age, and seizures were not risk factors for developmental regression. Each of the variables is discussed in the following sections.

Gender. Gender was not found to be a significant factor for developmental regression. Although there continues to be a higher prevalence of males diagnosed with ASD, gender does not appear to be a risk factor for developmental regression. This result was consistent with previous researchers (Barger et al., 2013; Lord et al., 2004; Luyster et al., 2005; Scott et al., 2017). Because previous research examining the role of gender in developmental regression was limited, the current study's finding added to the literature base and supported prior findings. The hypothesis that gender was not associated with increased risk for developmental regression was supported.

An additional analysis was conducted to determine if there was a gender difference in age at regression onset. Males were found to regress at a younger age (M = 19.20, SD = 8.71) than females (M = 22.57, SD = 18.27), but this was not a significant difference. This result suggests that gender is not a risk factor for regression, nor is it associated with younger age of regression onset.

As researchers examine gender differences within ASD, it is important to continue understanding how gender may play a role in the early emergence of the disorder, including developmental regression. In the current study, the gender ratio was fairly consistent between ASD (i.e., 81.1% male and 18.2% female) and ASD+DR (i.e., 85.3% male and 14.7% female) groups. However, in the broader ASD literature, the estimated gender ratio is 3 males: 1 female (Loomes, Hull, & Mandy, 2017). It is unclear why the present study's gender ratio was much

higher, but this difference does highlight the challenge of identifying females with ASD. As females are believed to be underdiagnosed, it is necessary to continue research to understand where gender differences in ASD symptoms, onset, and outcomes may lie.

Race/ethnicity. Race/ethnicity was also not a significant factor for developmental regression. In contrast to a previous finding by Spinks-Franklin and Swanson (2014), the present study did not find that minority children were more likely to have regressed than White children. These previous researchers suggested that developmental regression may be over-represented in minority children; however, the present study did not find similar results. As such, the hypothesis that race/ethnicity may be associated with increased risk was not supported by these findings.

In terms of race/ethnicity representation, the proportion of children in the African American, White, and Other groups was consistent between ASD and ASD+DR groups. Despite consistent percentages across groups, minority children were under-represented in this sample; in Louisiana, where the study was conducted, the racial demographics differ significantly from the demographics of the study. The most recent population census determined the racial diversity of Louisiana to be approximately 63% White, 32% African American, 2% multiracial, 2% Asian, 1% Other, and <1% Native American (U.S. Census Bureau, 2010). Although the current study had a similar proportion of White children, representation of minority children was not consistent with the state, particularly for African American children. Collapsing non-White and non-African American children into an Other group also did not allow for specific analyses of developmental regression among minority groups. Given the dearth of studies examining the relationship between race/ethnicity and developmental regression in ASD, continued research is needed.

Parental age. Maternal and paternal age were also not found to be associated with increased risk for developmental regression. Although parental age has been associated with increased risk for ASD, studies examining the relationship between parental age and developmental regression were very limited (e.g., Davidovitch et al., 2001; Zhang et al., 2012), and parent age was not found to be related to developmental regression. Results from the current study support the hypothesis that parent age was not associated with increased risk for developmental regression in children with ASD.

In the first logistic regression model created, paternal age was a significant variable; however, the odds ratio was very small (i.e., 1.058). This result suggests that paternal age may have a slight relationship with developmental regression, but additional research is needed. Additional logistic regression models were created in an attempt to elucidate the relationships between maternal and paternal age and developmental regression. When paternal age alone was entered into the model, it was no longer significant. As the relationship between maternal and paternal age may account for some of the variance in the original model, a composite variable was created, and an additional model was run. However, the updated model was not found to be significant, and none of the variables, including the interaction term, were significant.

Based on study results, parental age overall was not found to be associated with increased risk for developmental regression. The small, but significant relationship between paternal age in the original model suggests there may be some small relationship; however, additional research must be conducted to confirm this result.

Seizures. History of seizures was also not found to be a risk factor for developmental regression. Firstly, the overall prevalence of seizures in the study sample was 2.8%, which is significantly less than the established estimates of 30% (Jeste & Tuchman, 2015; Matson &

Neal, 2009; Tuchman & Rapin, 1997). Of the children who regressed, only 3.7% were also found to experience seizures. This prevalence is much lower than previous estimates of between 15-86% (Kobayashi & Murata, 1998; Moretti et al., 2008; Wilson et al., 2003). Because history of seizures was not significant in the study analyses, the hypothesis that seizures were associated with developmental regression was not supported; however, additional research is needed to confirm these results.

In the current study, the low prevalence of seizures may be due to several study factors. First, the low prevalence of seizures may be attributed to the young age of the sample. As suggested by Besag (2017), onset of seizures in individuals with ASD may be bimodal, with peaks during infancy and later in adolescence. It is possible that a proportion of children in the sample may not experience seizures until later in life; therefore, the seizure prevalence in this study may be an underestimate. Additionally, seizures may be more common among children who regress after age three (Shinnar et al., 2001). Given the young age of many of the participants, many of whom may not have experienced regression at the time of assessment, seizures may also have later onset. Additionally, seizures are more common among individuals with ID (Jeste & Tuchman, 2015). Because the current study also had a low prevalence of ID (see Study 2 results), lower rates of seizures may be related the sample. It is curious that the present study had such a low proportion of children who experienced seizures, and therefore, additional research is needed to better understand the relationships between seizures, developmental regression, and ASD.

Study 2: Outcomes

Intellectual Disability. ID was not found to be more common among children with a history of developmental regression. This finding suggests that although a history of

developmental regression (i.e., losing skills) may be associated with greater impairment in skills, co-occurring ID may not be more likely given a history of regression. This may also be interpreted that ID affects individuals with ASD separately from a history of regression.

In the broader ASD literature, approximately 50% of individuals on the spectrum have comorbid ID (Barger et al., 2013; Lord et al., 2004; Luyster et al., 2005; Scott et al., 2017). In the current study sample, 9.79% of the children with ASD were found to have comorbid ID (N = 42). The lower prevalence of ID among this study sample may be attributed to the young age of many children included, as they may not have been diagnosed with ID at the time of assessment. Future researchers should continue to examine the prevalence of comorbid ID among individuals with ASD and how the co-occurring conditions may mask, interact, and exacerbate both ASD and ID symptomatology. Furthermore, ID is associated with greater risk for additional psychopathology, as 40% of individuals with ID have at least one co-occurring psychiatric condition (Kozlowski, Matson, Sipes, Hattier, & Bamburg, 2011). As such, if developmental regression is associated with higher rates of ID, then individuals who regress may be more likely to experience additional psychopathology influencing their functioning and requiring treatment.

CARS2. Children with developmental regression were found to have significantly greater impairments in ASD symptoms compared to children without regression. This finding supports previous findings (Baird, Charman, et al., 2008; Estabillo, Matson, & Cervantes, 2018; Luyster et al., 2005; Matson et al., 2010; Wiggins et al., 2009), indicating that children who have regressed also evince greater impairments in ASD-associated symptoms. Although developmental regression appears to impact ASD symptoms, how regression may do so is unclear at this time. It is possible that developmental regression may be caused by neurological components which also impact ASD behaviors more severely. This relationship should continue

to be studied to better understand how developmental regression may relate to later ASD symptoms.

Although a statistical difference was found between groups, it should be noted that the scores for both groups well within the mild-moderate range on the CARS2 (i.e., 30 to 36.5). Therefore, although the children who regressed may demonstrate greater impairments in ASD symptoms, their level of impairment is still considered to be in the mild-to-moderate range, and within the same range that children without a history of developmental regression were in. Clinically, children with a history of developmental regression may exhibit slightly more severe impairments in ASD symptoms; however, they may not be distinguishable from children without regression. In terms of overall ASD symptom severity, children who regress do not appear to be functioning in a different range from children without regression.

In addition to overall ASD severity, researchers should continue to look for differences between ASD+DR and ASD groups on ASD symptom domains (i.e., communication, social interaction, restricted and repetitive behaviors). Because both groups continued to fall within the mild-to-moderate range, analyses of symptom domains may further elucidate where differences in symptomatology may lie. Because the CARS2 utilizes items to calculate overall impairment and does not group items into symptom domains, such analyses were not conducted in the current study. Therefore, additional studies utilizing other measures to capture symptom domains may be useful. Researchers may also be interested in examining relationships between which developmental domain(s) individuals regressed in and the severity of ASD symptom domains. For example, studies may analyze if individuals with history of language regression experience more significant challenges in verbal communication compared to nonverbal communication skills or restricted and repetitive behaviors.

Regarding ASD symptoms, prior researchers have found differences between groups on domains of nonverbal communication/socialization, verbal communication, and social relationships but not insistence on sameness/restricted interests (Estabillo et al., 2018). Previous findings indicate that differences between ASD+DR and ASD groups may lie in symptoms that fall into the social communication and interaction impairments associated with ASD rather than the restricted, repetitive patterns of behaviors and interests (i.e., those with history of regressed demonstrate greater social communication deficits). It is unclear how developmental regression may differentially affect these symptom domains. To build upon these data, future studies should continue to examine where these possible differences in ASD symptoms be emerge. Although overall symptom severity may not differ between groups, identifying where possible symptoms may differ may be beneficial in understanding how developmental regression affects ASD symptoms, as well as prioritizing treatment targets.

Vineland-2. In addition to differences in ASD severity, children with developmental regression were also found to differ in adaptive skills, specifically in the Communication domain. Previous researchers have found some evidence that children who regress experience more severe deficits in adaptive skills (Gadow et al., 2017; Wilson et al., 2003); however, this finding has not been consistent across studies (Baird, Charman, et al., 2008; Kobayashi & Murata, 1998). The difference in scores on the Communication domain may be related to deficits associated with ASD (i.e., social communication skills). However, the children were not found to have significantly different scores on the Socialization domain, which would also be expected to be related to ASD symptoms. Based upon these results, developmental regression may influence one's adaptive communication skills; although, this difference may be attributed to the challenges with communication associated with regression in language. Because of

language regression was the most common type identified in the sample, these deficits in Communication skills may be related to the regression in this domain that these children experienced.

Greater impairments in ASD symptoms are associated with more severe deficits in adaptive skills (Kozlowski, Matson, Sipes, et al., 2011). The lack of significant difference across adaptive skills may be attributed to our sample. Although ASD and ASD+DR groups were found to be significantly different in ASD severity, this difference may not have been large enough to show significant differences between groups across adaptive skills. Moreover, challenges with adaptive skills may become more significant over time (Bernabei et al., 2007); given the young age of many children in the current study sample, long-term follow up may indicate greater deficits in adaptive skills.

Additionally, while deficits in adaptive skills are common among individuals with ASD, they are not diagnostic to the disorder; impairments in domains of adaptive behaviors (as well as cognitive deficits) are diagnostic to ID. The present study did not find differences in rates of ID between groups, and the lack of significant difference in adaptive behaviors may therefore be related to the study's absence of comorbid ID.

Although consistent differences were not found between groups on adaptive skills, it is important to recognize that the participants in this study continued to demonstrate substantial challenges in their adaptive behaviors. Impairments in adaptive skills are well documented in individuals with ASD (Bradshaw, Gillespie, Klaiman, Klin, & Saulnier, 2018; Farmer, Swineford, Swedo, & Thurm, 2018; Szatmari et al., 2015, 2015; Tillmann et al., 2019), and these findings are consistent with previous literature. These impairments should be highlighted, as they represent an individual's practical application of skills in their everyday life and indicate

substantial difficulties in an individual's daily functioning. Understanding an individual's adaptive behavior deficits are critical in creating behavior plans to teach them necessary skills for independent living, to whatever extent possible in the future.

The ASD+DR group demonstrated greater impairments in ASD symptoms and Communication skills, but not in other domains of adaptive behaviors. These findings support previous studies showing that children who regressed exhibit greater deficits in ASD core symptoms of socialization, communication, and restricted and repetitive patterns of behaviors (Baird, Charman, et al., 2008; Hoshino et al., 1987; Luyster et al., 2005; Matson et al., 2010; Wiggins et al., 2009). However, in contrast to previous research (Baird, Charman, et al., 2008; Bernabei et al., 2007; Hoshino et al., 1987; Matson et al., 2010), the current study did not find significant differences in adaptive behaviors. These differences in results may be attributed to differing methodologies (e.g., definitions of developmental regression, retrospective versus prospective studies), which further highlights the need for continued research in this area.

Limitations

Use of parent report has been suggested to be a more valid method of determining a history of developmental regression than questionnaires (Boterberg et al., 2019); however, they can be biased, and their limitations should be considered when conducting research on developmental regression. By using parent report, researchers and clinicians are dependent on parents' memories to reconstruct events rather than monitor behaviors as they occur. Parents can under- or over-report of symptoms, which is a particular concern when clinicians are unable to directly observe the behavior(s) of interest. Some parents may be better able to report on regression of skills but evaluating for a history of regression can be complicated when parents have difficulty reporting on their child's development and how changes have emerged over time.

During evaluations, clinicians typically spend several hours with the child and are able to assess for current level of functioning; however, clinicians are unable to directly observe if a child has regressed in skills due to the evaluation process. Therefore, in evaluation settings, utilization of parent report continues to be necessary, as parents are able to monitor achievement of milestones, as well as the child's behavior across settings. Thus, it is important for clinicians to ask follow-up questions to obtain additional information about the child's previous functioning level, understand what the parent describes as a loss, and to determine of the child meets criteria for their operational definition of developmental regression. Some suggested methods to improve reporting have included use of video in addition to screening instruments, asking parents to consult previous records (e.g., baby books, medical records, intervention progress notes) prior to completing developmental interviews, and linking reporting to major life events to establish a detailed timeline and context to discuss specific behaviors (Ozonoff et al., 2018).

Despite concerns with parent report, this method was utilized in the current study because of the importance and value of parent report of their child's developmental history. Parents are vital in recognition of developmental delays and autism symptoms, and addressing their concerns has been a critical component of early identification (De Giacomo & Fombonne, 1998; Fujiwara, Okuyama, & Funahashi, 2011; Kozlowski, Matson, Horovitz, Worley, & Neal, 2011; Talbott, Nelson, & Tager-Flusberg, 2015). Inclusion of follow-up questions, such as in the current study, can clarify if the child meets criteria for having a history of developmental regression. As suggested by other researchers, interview methods may be improved by helping parents establish timelines or key events to provide a context of remembering achievement of skills (Ozonoff et al., 2018; Rogers, 2004; Werner & Dawson, 2005). To improve on the current study method, clinicians could have consistently established a developmental timeline with parents to provide a

point of reference for achievement and loss of skills. In the future, longitudinal studies in which parent report is utilized in conjunction with researchers and clinicians who are able to assess and closely observe developmental skills at numerous timepoints may mitigate this challenge.

Developmental regression may also emerge later in some participants. Because some regressive trajectories are characterized by typical development in the first few years of life prior to sudden regression onset, children who may have been assessed and did not meet criteria for ASD would not have been included. The younger children who were found to have ASD, although exhibiting ASD symptoms, may not have yet regressed in skills. Moreover, from the CDD literature, children may develop typically and then regress between ages two and seven. Additionally, children who were typically developing would not have been referred to be evaluated for ASD. Because of this subtype, it would be interesting to note if children who later regress exhibit early signs of ASD prior to onset of regression.

Additionally, given the difficulty identifying skills loss and tracking progress, it is possible that children who lost multiple skills simultaneously were under-reported. Losing skills in multiple domains can be difficult to characterize if losses in certain domains are more severe than others, as the severe losses can overshadow more subtle regression on other areas. For example, although it is likely that children regress in both language and social skills, this type of developmental regression is reported as less common that regression in language alone. Due to this challenge in characterizing and tracking losses in multiple developmental domains, it is unclear if the child solely lost skills in the identified domain or if they lost multiple skills and their parent was only able to report on one domain. Future studies should more closely examine this phenomenon to determine what skills children may regress in first, what skills follow, and how losses in these various domains appear alongside ASD symptoms.

Given the young age of many of the participants, they may not have been diagnosed with ID. The average age of the sample was 7.02 years and because cognitive functioning is not typically considered stable under age five, the younger participants in this study were likely not assessed for or diagnosed with ID. Children under the age of five who were experiencing delays across multiple domains of development would have been diagnosed with Global Developmental Delay (American Psychiatric Association, 2013). Individuals meeting criteria for Global Developmental Delay fail to meet expected developmental milestones in several areas of intellectual functioning, and the diagnosis is applied to those who are unable to receive comprehensive assessment of intellectual functioning (i.e., children who are too young to participate in standardized testing) (American Psychiatric Association, 2013). As the individual ages, it is necessary to reassess cognitive abilities to determine if they later meet criteria for ID. Of the study participants, 50.5% were under age six, which indicates that half of the children may have unidentified or later identified with ID. Additionally, the prevalence of ID among individuals with ASD is approximately 50% (Charman et al., 2011; Newschaffer et al., 2007; Russell et al., 2019), which indicates that the study sample is likely underestimating the presence of ID.

It is also unknown from this study if the individuals who regressed regained skills or what their developmental trajectory appeared to be after they regressed. Better understanding of the prognosis and developmental trajectory of children who experience developmental regression is needed. Although children who regress were found to experience greater ASD severity and more impaired adaptive communication skills, it is unknown how skills progressed over time after regression. Researchers have found varying results on the outcome of achievement of skills post-regression; therefore, more research is needed in this area.

In terms of data analyses, our data was found to have issues with multicollinearity. Although there is not much to be done once multicollinearity has been identified (Field, 2013), this is a concern that should be addressed when interpreting these results. Findings from this study can be used as preliminary results that highlight the importance of continuing to study this phenomenon. Although most of the factors of interest were not found to be significant in this study, paternal age was found to be associated with a small, but significant risk for developmental regression. Further research should be conducted to better understand the relationship between paternal age and developmental regression, as well as the other factors in this study. In the future, these analyses may be conducted again with a larger sample size to see if multicollinearity may be lessened.

Future Directions

Given the lack of consensus regarding how to define developmental regression, and subsequent challenges in characterization, identification of risk factors, and examination of outcomes, there is a need to first better operationalize this phenomenon. Researchers have utilized different definition across studies, which affects estimates of prevalence and creates variability in how to interpret findings (Barger et al., 2013; Stefanatos, 2008). It is clear that developmental regression occurs in a significant number of individuals with ASD, and as such, continued research in this area is warranted. Because of the complex nature of developmental regression, a broader definition may be necessary to better capture the subtleties of this phenomenon.

Future researchers should examine if there are possible relationships between the type of regression and symptomology. Closer analysis of the specific differences across ASD symptoms is needed to better understand how developmental regression may influence ASD-related

impairments. For example, in addition to differences in overall ASD severity, future researchers should analyze potential differences in ASD domains of social-emotional reciprocity, nonverbal communication skills, development of relationships, stereotypical behaviors, rigidity, restricted interests, and atypical sensory behaviors.

To better understand the nature of developmental regression, it would be of interest to conduct a longitudinal study of at-risk children monitoring their development across various domains of language, socialization, motor, and adaptive skills. As suggested by Ozonoff and Iosif (2019), researchers conducting prospective studies must ensure they are measuring developmentally appropriate behaviors across the ages being examined, as well as behaviors that are robust and occur with high frequency in early child development. Therefore, when studying possible preverbal behaviors that may be associated with later ASD and developmental regression, it is suggested that these behaviors include socio-communicative skills such as gaze to faces and another's eye, shared affect, and social engagement. Continual tracking of progression through skills by researchers and clinicians would allow for better understanding of possible skills loss. Similar to previous studies examining achievement of developmental milestones and later onset of developmental regression (Baird, Charman, et al., 2008; Christopher et al., 2004; Jones & Campbell, 2010; Kurita, 1985; Malhi & Singhi, 2012; Meilleur & Fombonne, 2009; Werner & Dawson, 2005), studies examining children's developmental trajectory will further elucidate the emergence of ASD symptoms, as well as possible onset of developmental regression. Given the varying results from previous studies, future researchers should look at how children develop to better under the varying onset patterns within ASD. Due to the difficulty in categorizing developmental regression, continual study of at-risk children

provides researchers and clinicians with the ability to study skills over time, how they develop, and their relationships with the onset of ASD symptoms.

A longitudinal study may also monitor additional factors that may be associated with onset of developmental regression including medical conditions. Although the factors of interest in the current study were not found to be significant, additional research should be conducted to assess the relationships between additional possible risk factors and developmental regression. Importantly, continued research examining the relationships between medical and neurological conditions with developmental regression are needed. As hypothesized, ASD and developmental regression may be due to over-active synaptic pruning during early development (Thomas et al., 2011). Medical and neurological conditions that may affect one's brain development should be studied to better understand possible mechanisms of developmental regression.

Similarly, additional research ruling out various medical factors is needed. Although researchers have concluded that vaccines do not cause autism or developmental regression, this controversial issue persists (Gerber & Offit, 2009; Richler et al., 2006; Ruggiero, 2017; Uchiyama, Kurosawa, & Inaba, 2007). The purpose of vaccines is to expose an individual to a viral disease in order to enable the body to increase its immune response, but there is some suspicion that in some cases, injection of a live virus may result in chronic disease (Ewing, 2009). Additional concerns are related to vaccination schedules which introduce high numbers of foreign proteins and possible resulting in long-term immune dysfunction by altering the structure and function of DNA (Ewing, 2009). Despite these concerns, results across studies continue to state that vaccines do not cause autism or developmental regression.

The Advisory Committee on Immunization Practices recommends that children should receive routine vaccination against 14 serious illnesses by 24 months. At present, the number of

unvaccinated children is rising, likely due to parent hesitancy or mistrust of vaccines and ease in the protocol of obtaining exemptions (Mellerson et al., 2018). Lack of access to healthcare also continues to be a barrier to receiving vaccinations; however, parental choice remains the most common factor for children being unvaccinated (Dyer, 2018; Hill, Elam-Evans, Yankey, Singleton, & Kang, 2018). Recent estimates have found that approximately 1.3% of toddlers are unvaccinated, which is a significant increase (i.e., quadrupled rate) from 0.3% of toddlers in 2001 (Mellerson et al., 2018). The prevalence of unvaccinated children varies based on region, which some areas having vaccine exemption rates as high as 7.6% and rising (Mellerson et al., 2018). Although most identified areas with high numbers of unvaccinated children are in rural regions, urban areas have had an increase in school vaccine exemptions and the anti-vaccine movement has been active in many areas (Dyer, 2018). The increasing prevalence of unvaccinated children is a pressing concern due to recent outbreaks of once eliminated diseases, such as measles. The continued occurrence of such outbreaks emphasizes the importance of ensuring that children are protected and receive vaccinations (Hill et al., 2018).

Researchers and clinicians working with families should discuss parents' concerns; however, it is imperative that the field continue to educate parents that vaccines do not increase risk for ASD or cause autism in susceptible children (Hviid, Hansen, Frisch, & Melbye, 2019; Jain et al., 2015). Vaccines are safe and necessary to protect the population, particularly for vulnerable groups such as young children (Institute of Medicine, 2012). The ongoing controversy of the anti-vaccination movement despite lack of evidence highlights the need to continue researching possible causes of autism and developmental regression. Identifying the factors and neurological mechanisms that are involved in ASD and developmental regression would conclude the debate and emphasize the need to immunize our children against preventable

diseases. In light of the increasing prevalence of unvaccinated children and rates of disease outbreaks, autism researchers and clinicians play an important role in educating families and the public.

Conclusion

The current study explored possible associated factors and outcomes of developmental regression in children with ASD. Although there is much more to be researched on the topic, this study allowed for further understanding of the nature of this phenomenon in autism. Developmental regression is relatively common among individuals with ASD; however, it has been quite difficult to categorize, study, and identify in research. Given these challenges, it is important for researchers to continue studying this phenomenon. Prospective studies have shown that ASD involves declines in key communication and social behaviors within the first years of life for most children with the disorder, and better understanding of developmental regression and its role in the development of ASD is necessary. Continuing research on how ASD emerges in early childhood is needed to elucidate how early developmental differences to allow for early identification and provide insight into how the course of ASD may be altered (Estes et al., 2015).

In addition to increasing understanding of developmental regression for researchers and clinicians, it is important to better support families and their experience. The loss of skills can be devastating and confusing for families to witness. Variations in development can be challenging to discuss with parents, but loss of skills can be especially difficult to comprehend and process. The developmental trajectory for individuals with ASD can vary significantly across individuals, and the uncertainty of development post-regression can add to this stress. Parents of children with ASD have been found to experience high levels of stress (Baker-Ericzén, Brookman-Frazee,

& Stahmer, 2005; Davis & Carter, 2008; Duarte, Bordin, Yazigi, & Mooney, 2005; Estes et al., 2009), and the added experience of developmental regression may further exacerbate this stress. As found by Davidovitch and colleagues (2000), mothers of children who regress were more likely to express feelings of guilt regarding their children's autism compared to mothers of children with ASD who did not regress. As such, better supports for these individuals and families are needed. Psychoeducation can be helpful but is limited; therefore, additional means such as support groups and therapy may be encouraged to facilitate coping with the stress of raising an individual with a developmental disability.

Results from this study provided insight into possible risk factors and outcomes for individuals who experience developmental regression. Findings from this study indicated that gender, ethnicity, parental age, and history of seizures are not significant risk factors for developmental regression. Although previous research has been limited in identifying risk factors for developmental regression among individuals with ASD, the current study found similar results as prior studies. Additionally, individuals with ASD who have a history of developmental regression were found to experience greater severity of ASD symptoms and adaptive communication skills. While it is unknown how and why individuals who regress evince more interfering symptoms, this finding supports the need to continue targeting skills in these domains.

Implications of these results are applicable to our understanding of developmental regression within the context of ASD. One theory of the cause of autism and developmental regression is synaptic over-pruning (Thomas et al., 2011). Based on the findings of this study, various factors of gender, ethnicity, parental age, and seizures, may not be related to the neurological mechanisms involved in developmental regression. However, it appears that the

brain processes associated with developmental regression particularly influence behaviors related to social communication skills, as evidenced by increased severity in ASD symptoms and impairments in adaptive communication behaviors. Additional research on the possible neurological mechanisms involved in ASD and developmental regression is needed.

Results from the current study also provide implications for treatment of individuals with ASD. Given that individuals with ASD with a history of developmental regression were found to be more impacted by ASD symptoms, considerations for treatment may be made. Intervention based on the principles of applied behavior analysis (ABA) has been shown to be the strongest at treating the behavioral deficits and excesses associated with ASD (Matson & Smith, 2008; Peters-Scheffer, Didden, Korzilius, & Sturmey, 2011; Roane, Fisher, & Carr, 2016). In particular, ABA therapy is effective at increasing cognitive abilities, communication skills, expressive and receptive language skills, and adaptive behaviors (Makrygianni, Gena, Katoudi, & Galanis, 2018). These treatment gains have been found to maintain over time (Estes et al., 2015; Sigafoos & Waddington, 2016). Review of the literature on intervention outcomes for individuals with developmental disabilities with history of developmental regression indicate positive outcomes (Sigafoos & Waddington, 2016). At this time, specific intervention practices may not be identified as best practice; however, behavioral and educational interventions are indicated in improving outcomes for individuals (Sigafoos et al., 2019). Much of this area of research focuses on the domains in which the regression has occurred. There are no current studies on intervention addressing developmental regression in individuals with ASD (Sigafoos et al., 2019). Important considerations in treatment are determining whether the focus should be in restoring lost skills (i.e., regaining) or compensating by developing new skills (e.g., utilizing alternative communication devices rather than vocal language) (Sigafoos et al., 2019). This may

be related to the severity of regression and level of pre-regression skills. At this time, it is unknown what individual factors lend one to be more or less responsive to treatment, which can complicate treatment decision making. The broader ASD literature supports individual comprehensive treatment based on ABA; however, with the growing evidence base for various interventions, future researchers should focus on identifying variables associated with treatment responders, active ingredients of interventions, and improving measurement of outcomes (Pellecchia et al., 2015; Smith & Iadarola, 2015).

As suggested by Ozonoff and Ionif (2019), regression in ASD may be the rule rather than the exception. The discrepancy in the prevalence of developmental regression in ASD between retrospective and prospective studies indicates that prospective studies may be better able to capture earlier, subtle changes that may be difficult for parent to distinguish at early ages. Interestingly, Ozonoff and Ionif (2019) posited that all individuals with autism lose some skills; however, this loss occurs at different ages across individuals which may contribute to the difficulty in detecting skills loss. This loss may be more apparent for older children who have achieved more skills and displayed them for longer periods of time compared to infants whose changes in development may be more different to identify. This establishment of a behavioral baseline may influence a parent's ability to recognize regression in skills.

Children with ASD likely lose skills in some developmental domains, but what skills they lose, how many they lose, or when the regression occurs varies across children. Most importantly, this regression may be exceedingly subtle and challenging to note when it is occurring. Therefore, for researchers and clinicians in the field of autism, shifting our understanding of developmental regression as the rule rather than the exception may be indicated, as developmental regression is likely a process rather than a discrete event (Ozonoff &

Iosif, 2019). ASD is understood as a highly heterogenous disorder and attempting to classify individuals into binary categories can be reductive to understanding an individual's clinical presentation. As suggested by other researchers, history of developmental regression may be included as a specifier within the diagnosis of ASD (First, 2008). Based upon the findings of this study, it is possible that children who *noticeably* regress, whether in language, social, or other developmental domains, continue to exhibit greater impairments in ASD-associated behaviors and adaptive communication skills. Incorporating the child's regression into their presentation and conceptualization of their areas of need is important to best support their development. Additionally, conveying to parents that developmental regression is a process associated with autism, rather than an event with a single identifiable cause, is necessary to aid in facilitating their understanding of their child's developmental progression.

Given the multitude of ways autism presents, ASD and its onset may be conceptualized as a kaleidoscope—rather than many different manifestations, it is one disorder that emerges and presents differently among those affected (First, 2008). Part of this kaleidoscope is developmental regression and how it emerges and impacts ASD symptoms. Moving away from a dichotomous understanding of developmental regression is needed to better conceptualize this phenomenon, as well as to conduct research and clinical work that captures how regression arises. Although this perspective on ASD highlights the challenges in studying the disorder, this kaleidoscope conceptualization can be reflected in a statement frequently used within the field of ASD: if you have met one person with autism, you have met one person with autism.

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Appendix. IRB Approval

ACTION ON PROTOCOL CONTINUATION REQUEST

Institutional Review Board
Dr. Dennis Landin, Chair
130 David Boyd Hall
Baton Rouge, LA 70803
P: 225.578.8692
F: 225.578.5983
irb@lsu.edu
lsu.edu/research

TO: Johnny Matson
Psychology

FROM: Dennis Landin
Chair, Institutional Review Board

DATE: November 13, 2017

RE: **IRB#** 2609

TITLE: Developing the Autism Spectrum Disorder (ASD)

New Protocol/Modification/Continuation: Continuation

Review type: Full ___ Expedited _X_ **Review date:** 11/13/2017

Risk Factor: Minimal ___X___ Uncertain _____ Greater Than Minimal_____

Approved_____X_____ **Disapproved**_____

Approval Date: 11/13/2017 **Approval Expiration Date:** 11/12/2018

Re-review frequency: (annual unless otherwise stated)

Number of subjects approved: 2000

LSU Proposal Number (if applicable):

Protocol Matches Scope of Work in Grant proposal: (if applicable)

By: Dennis Landin, Chairman _____

PRINCIPAL INVESTIGATOR: PLEASE READ THE FOLLOWING –
Continuing approval is CONDITIONAL on:

1. Adherence to the approved protocol, familiarity with, and adherence to the ethical standards of the Belmont Report, and LSU's Assurance of Compliance with DHHS regulations for the protection of human subjects*
2. Prior approval of a change in protocol, including revision of the consent documents or an increase in the number of subjects over that approved.
3. Obtaining renewed approval (or submittal of a termination report), prior to the approval expiration date, upon request by the IRB office (irrespective of when the project actually begins); notification of project termination.
4. Retention of documentation of informed consent and study records for at least 3 years after the study ends.
5. Continuing attention to the physical and psychological well-being and informed consent of the individual participants, including notification of new information that might affect consent.
6. A prompt report to the IRB of any adverse event affecting a participant potentially arising from the study.
7. Notification of the IRB of a serious compliance failure.
8. **SPECIAL NOTE: Make sure to use bcc when emailing more than one recipient.**

**All investigators and support staff have access to copies of the Belmont Report, LSU's Assurance with DHHS, DHHS (45 CFR 46) and FDA regulations governing use of human subjects, and other relevant documents in print in this office or on our World Wide Web site at http://www.lsu.edu/irb*

Vita

Jasper A. Estabillo is from San Diego, California. After receiving her bachelor's degree in Human Development and Psychology at the University of California, San Diego (UCSD), Jasper worked as a Research Coordinator at the Autism Discovery Institute at Rady Children's Hospital-San Diego and UCSD Department of Psychiatry on a genetics study focused on identifying variations associated with ASD and related neurodevelopmental conditions. During her time at LSU's clinical psychology doctoral program, Jasper worked under the supervision of Dr. Johnny L. Matson specializing in assessment and treatment of ASD and developmental disabilities. While at LSU, she also completed the course sequence for board certification in behavior analysis and obtained extensive experience providing ABA therapy. She is currently completing her predoctoral internship at the UCLA Semel Institute for Neuroscience and Human Behavior in the Autism and Neurodevelopmental Disabilities track. Following her anticipated graduation in August 2019, Jasper will continue working in the field of ASD as a postdoctoral scholar at the UCLA Department of Psychology conducting implementation science research aimed at developing and testing methods to improve use of evidence-based treatments for ASD.