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An Investigation of the Relationship Between Seizures and Autism Symptomology in Young Children

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AN INVESTIGATION OF THE RELATIONSHIP BETWEEN SEIZURES AND
AUTISM SYMPTOMOLOGY IN YOUNG CHILDREN

A Thesis

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Master of Arts

In

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by
Claire O. Burns
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TABLE OF CONTENTS

Abstract.....	iii
Introduction.....	1
Purpose.....	23
Method.....	25
Results.....	31
Discussion.....	36
References.....	43
Vita.....	53

Abstract

Autism spectrum disorder (ASD) is a condition that consists of deficits in social communication as well as restricted, repetitive interests or behaviors. Individuals with ASD also often have comorbid psychiatric and medical disorders. One such concern is high rates of seizures and epilepsy. Researchers have found that rates of seizures tend to be higher in individuals with ASD who also have more impaired functioning. However, few studies have examined how the presence of seizures is related to symptoms of ASD. The current study aimed to expand the extant literature by investigating whether a history of seizures is associated with ASD symptomology across different domains (i.e., Socialization/Nonverbal Communication, Restricted Interests/Repetitive Behaviors, Communication), as measured by the *BISCUIT-Part 1*. Young children with atypical development without a diagnosis of ASD or a history of seizures were found to have the lowest endorsement of overall ASD symptomology as well as across subscales. Individuals with seizures but without an ASD diagnosis had the second lowest scores, followed by individuals with both ASD and seizures. The ASD without a history of seizures group had the highest ASD symptomology scores. These results indicate that, for atypically developing individuals without ASD, a history of seizures was related to higher levels of autism symptomology. Conversely, for young children with ASD, a history of seizures was related to lower endorsement of autism symptoms than those without a history of seizures. These findings support the need for early identification of both ASD and seizure disorders, as both diagnoses have significant implications for treatment. Future directions for research are discussed.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that involves impairments in social communication as well as restricted, repetitive behaviors, interests, and activities (American Psychiatric Association, 2013; Tidmarsh & Volkmar, 2003). Although prevalence rates of ASD have increased in recent years (Baio, 2014), little is known regarding the etiology or underlying mechanisms of the disorder. Research on neurological or physiological abnormalities related to ASD have been largely inconclusive. Although the potential biological underpinnings are still under investigation, researchers have suggested that the high prevalence of seizures and epilepsy within the disorder may indicate neurological differences in individuals with ASD (Bolton et al., 2011; Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005; Frye, 2016; Levisohn, 2007; Tuchman & Rapin, 2002).

Several factors have been found to be related to risk of seizures in ASD, including intellectual functioning, gender (Amiet et al., 2008; Bolton et al., 2011), and autism severity (Gabis, Pomeroy, & Andriola, 2005). However, some researchers have suggested that cognitive functioning underlies all of these associations, as lower intellectual functioning in ASD is often related to female gender (Danielsson et al., 2005). As the mechanism behind the relationship between ASD and seizures is unknown, further investigation of factors associated with the presence of seizures in ASD may help researchers and clinicians to better understand their co-occurrence.

The aim of the present study is to further investigate differences in ASD symptom severity in individuals with comorbid ASD and seizures. Groups based on ASD diagnosis and a history of seizures were compared to further elucidate whether seizures

and seizure disorders are associated with overall ASD symptom severity and/or specific symptoms (i.e., communication, socialization/nonverbal communication, repetitive behavior/restricted interests). Further, the current study aims to expand the extant literature, which has focused primarily on children, adolescents, and adults, by investigating these differences in a sample of infants and toddlers. This will serve to further elucidate whether differences in symptomology are evident at a young age.

Autism Spectrum Disorder

History of ASD

The first reports of conditions comparable to ASD were described by Leo Kanner in 1943. Kanner (1943) described the heterogeneity of symptom presentation in 11 children, and drew parallels across the following symptoms: failure to relate to others; marked “autistic aloneness”; failure to change body posture in anticipation of being held; differences in verbal abilities; superior memory; delayed echolalia; replication of personal pronouns in speech without altering them to be grammatically correct; hypersensitivity to loud noises and sudden movements; repetitive repetition of verbalizations; need for maintenance of sameness; limited variety of spontaneous activity; and ability to maintain interest in objects. Kanner further noted that the parents of all of these children were intelligent and very few were “warmhearted”, and therefore suggested that the desire for “aloneness” may be associated with parental characteristics. He also highlighted the fact that these children seemed to have adequate or high cognitive abilities. Finally, Kanner attributed the characteristic failure to relate to others to an innate, biological deficit, describing them as “inborn autistic disturbances of affective contact (Kanner, 1943).

In a follow-up study published nearly 30 years later, Kanner revisited these 11 individuals and reported on their current status (Kanner, 1971). In childhood, the participants were described as having relatively good overall health. Although large head circumference and gross motor difficulties were noted in some, fine motor skills were not found to be impaired. Two of the children developed epileptic seizures, one in childhood and one in adulthood. In contrast to his original finding that the intellectual functioning of these children seemed to be close to average, in adulthood four were found to have extremely low IQ. In both the original and follow up study, Kanner sought to differentiate autism from childhood schizophrenia. He stated that while there were some similarities, symptoms across the two disorders differed in many ways (Kanner, 1971). Kanner further cited the fact that schizophrenia usually emerges as a change in behavior, while the symptoms reported in children with autism seem to have been present from birth (Kanner, 1943).

This view was supported by Kanner's contemporary, Michael Rutter, who outlined additional differences between schizophrenia and autism. These distinctions included sex ratio (i.e., schizophrenia has roughly equal prevalence rates in males and females, while autism is much more common in males) as well as family socioeconomic status (i.e., parents of children with autism tend to have higher intelligence and socioeconomic status [SES] than the general population, while parents of individuals with schizophrenia typically have average intelligence and SES). Additionally, a family history of schizophrenia is considered a risk factor for developing schizophrenia, while individuals with infantile autism rarely have a relative with schizophrenia. Rutter also found that individuals with autism tend to have lower than normal IQ with discrepancies

between domains, as visuo-spatial abilities tend to be high while verbal abilities are often low. Hallucinations and delusions, which are characteristic of schizophrenia, are not common in autism. Finally, Rutter maintained Kanner's assertion that autism symptoms are stable over the lifespan, while the severity of symptoms of schizophrenia may change over time (Rutter, 1968). The distinction between autism and schizophrenia was central in paving the way for autism to be recognized as a separate disorder.

While researchers consistently found support for discrepancies between autism and schizophrenia, Rutter's findings did differ from Kanner's assertions in that he found that children with autism had lower intellectual functioning than the general population (Rutter & Schopler, 1987), which is consistent with current estimates of intellectual disability in 70% of individuals with ASD (Mannion, Leader, & Healy, 2013; Matson & Nebel-Schwalm, 2007; Newschaffer et al., 2007). However, children with autism differed from individuals with intellectual disability in several ways. First, though both groups share an increased prevalence rate of seizures, seizures tend to begin later (typically in adolescence) for individuals with ASD. There are also differences regarding co-occurring genetic disorders, as well as the previously mentioned sex difference, which is not observed in individuals with intellectual disability (Rutter & Schopler, 1987).

Early research on autism therefore supported its distinction as a separate, unique disorder.

Diagnostic Criteria

Diagnostic criteria for ASD have changed significantly in recent years. ASD was first recognized as a disorder in the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III;* American Psychiatric Association, 1980), which included infantile autism, childhood-

onset pervasive developmental disorder (PDD), and atypical PDD. One of the primary differentiations between these diagnoses was that infantile autism must have onset before 30 months of age, while childhood PDD may emerge between 30 months and 12 years. Atypical PDD included those individuals who did not meet criteria for either of the other two types, but had atypical developmental in several domains.

In the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R*; American Psychiatric Association, 1987), these subtypes were reclassified as Autistic Disorder and Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS). Although Autistic Disorder included a specifier if age at onset was after 36 months, the general requirement was emergence during infancy or childhood. The three general criteria for Autistic Disorder were impairments in social interaction, impairment in verbal and nonverbal communication, and the presence of restricted activities and interests. The criteria for PDD-NOS were similar to that for PDD in DSM-III: impairment in development, but the individual did not meet full criteria for Autistic Disorder.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV*; American Psychiatric Association, 2000) represented a shift toward classification based on severity. The categories of PDD in DSM-IV included Autistic Disorder, Asperger's disorder, Rett's Disorder, Childhood Disintegrative Disorder, and PDD-NOS. The criteria for Autistic Disorder and PDD-NOS were relatively similar to the previous DSM version; however, the inclusion of Asperger's disorder represented a classification for individuals who had deficits in social interaction and exhibited restricted, repetitive, and stereotyped behavior and/or interests, but without deficits in

communication or language. Rett's disorder and Childhood Disintegrative Disorder both involved the loss of previously acquired skills, though the criteria for Rett's included more emphasis on psychomotor development and earlier regression (i.e., 5-48 months), while Childhood Disintegrative Disorder involved typical development for at least the first two years of life, followed by regression of expressive or receptive language, social skills, adaptive behavior, bowel or bladder control, play skills, or motor skills. Childhood Disintegrative Disorder also required impairments in at least two of the three areas of impairment necessary for an autistic disorder diagnosis.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*; (American Psychiatric Association, 2013) marked an important shift in both the diagnostic criteria as well as the categories for autism. A key change was that the separate disorders were combined into a singular disorder with different levels of symptom severity. Autistic Disorder, Asperger's Disorder, and PDD-NOS were merged into one diagnostic category: autism spectrum disorder. Additionally, the social and communication categories were combined into one domain of social communication and social interaction. Childhood disintegrative disorder is no longer classified as separate developmental disorder, and Rett disorder is now considered a neurologic disorder with a known genetic cause; therefore, both are not included in the most recent version of the DSM (Volkmar & Reichow, 2013).

The current criteria for a diagnosis of ASD include persistent impairments in social communication/interactions across settings and restricted, repetitive patterns of behavior, interests or activities. The diagnostic criteria also require that symptoms be present early in childhood and that they impair or limit functioning. For the social

communication and interaction category, impairments must be present in: 1) social-emotional reciprocity (e.g., impairments in initiation of social interaction, sharing of interests or emotions; social imitation); 2) nonverbal communication that is relevant to socialization (e.g., impairments in eye contact, understanding and using body language, speech intonation/volume/rhythm; affect); 3) developing and sustaining relationships (beyond those with caregivers; e.g., impairments in theory of mind, adjusting behavior based on social context, imaginative play, interest in others). In regard to the restricted, repetitive patterns of behavior, interests, or activities, at least two of the following four criteria must be met: 1) stereotyped or repetitive speech, motor movements, or object use (e.g., pedantic or formal language, echolalia, pronoun reversal, perseverative language, stereotyped or repetitive movements or use of objects); 2) excessively sticking to routines, patterns of behavior, or resistance to change (e.g., adherence to routine, ritualized patterns of verbal and nonverbal behavior, resistance to change, rigid thinking); 3) exceedingly limited, fixated interests that are unusual in intensity or focus (e.g., narrow range of interests, attachment to unusual inanimate objects; preoccupations or obsessions); 4) over-reactivity or under-reactivity to sensory stimuli or unusual sensory interests (e.g., high tolerance to pain, interest or fascination with watching movement of objects, such as spinning wheels or fans, licking or smelling objects; APA, 2013).

Although ASD is considered one singular disorder, it includes three levels of symptom severity. ASD Level 1 specifies that the functional impairments related to the disorder require support; Level 2 indicates that the deficits require substantial supports; and Level 3 reflects that the impairments require very substantial support. Several specifiers have also been included to denote comorbidities. These include: with or

without accompanying intellectual impairment; with or without accompanying language impairment; associated with a known medical or genetic condition or environmental factor; associated with other neurodevelopmental, mental, or behavioral disorders; and with catatonia (APA, 2013).

Many of the diagnostic items in the DSM-IV-TR communication category now fall under social communication or restricted, repetitive behavior, interests, and activities. Impairments in social communication and interaction must also be present in multiple settings. Furthermore, while restricted, repetitive behaviors and interests (RRBIs) were not a requirement for a diagnosis under DSM-IV, these behaviors are now a mandatory criterion for ASD. Individuals who present with deficits in social communication but do not have RRBIs instead typically qualify for Social (Pragmatic) Communication Disorder. Additional changes include: abnormal sensory responses are now included; symptoms do not have to manifest prior to age 3; dual diagnosis of comorbid conditions (e.g., ADHD) are now permitted; and historical report of behavioral symptoms can be included in the diagnostic process (APA, 2013).

Prevalence of ASD

Although autism was once considered to be a relatively uncommon disorder, occurring in as few as 3 or 5 children out of 10,000, prevalence rates have risen in recent years (Howlin, 2006). The most current estimated prevalence is approximately 1 in 68 children (Baio, 2014). Additionally, there is a well-established sex difference, as males are four to five times more likely to have ASD than females (Baio, 2014; Howlin, 2006). Some considerations that may account for recent increases in prevalence rates include an increase in awareness, changes in diagnostic criteria, improved methodology of research

studies, cultural influences, and improvements in assessment and diagnostic practice (Fombonne, 2009; Matson & Kozlowski, 2011; Volkmar, Lord, Bailey, Schultz, & Klin, 2004). ASD can potentially be diagnosed as young as 18 months of age (Chawarska et al., 2014); however, many children do not receive a diagnosis until later in childhood (Shattuck et al., 2009).

Comorbid Conditions

Psychiatric comorbidities are common in individuals with ASD. Simonoff and colleagues (2008) found that 70% of children with ASD had at least one comorbid condition and 41% had two or more. Common comorbidities include anxiety disorder, attention-deficit hyperactivity (ADHD) disorder, oppositional defiant disorder, and mood disorders (Leyfer et al., 2006; Simonoff et al., 2008). Individuals with ASD also have high rates of medical conditions, including gastrointestinal issues, sleep concerns (Mannion et al., 2013; Mazurek et al., 2012; Mazurek & Petroski, 2015) and genetic conditions such as tuberous sclerosis, Fragile X syndrome, and Angelman syndrome (Moss & Howlin, 2009). Additionally, seizure disorders are a medical comorbidity that have been widely studied within this population (Danielsson et al., 2005; Frye, 2016; Jokiranta et al., 2014; Mannion et al., 2013; Saemundsen, Ludvigsson, Hilmarsdottir, & Rafnsson, 2007). The identification and treatment of comorbid disorders in individuals with ASD is crucial, as these conditions can often exacerbate impairments in functioning (Mazurek, 2016).

Seizures

A seizure is a “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher et al., 2005). Epilepsy is

a disorder that involves a predisposition to epileptic seizures, and typically is defined as recurrent seizures (Reilly & Gillberg, 2016). Epilepsy is a common neurological disorder (Reilly & Gillberg, 2016) and Hesdorffer and colleague (2011) estimated that the lifetime prevalence of epilepsy is 1 in 26 people. The results of several studies indicate that the risk of developing epilepsy may be greater at a younger ages and decreases during puberty and into adulthood (Camfield, Camfield, Gordon, Wirrell, & Dooley, 1996; Danielsson et al., 2005).

Types of Seizures

There are several different types of seizures, all of which fall into two categories: generalized or partial/focal (Reilly & Gillberg, 2016). Generalized seizures originate within bilateral networks and the location and lateralization are not the same for all seizures. This class of seizures includes tonic-clonic, absence, myoclonic, clonic, tonic, and atonic seizures (Berg et al., 2010). Tonic-clonic seizures, also known as grand mal seizures, affect the entire body and are characterized by convulsions that cause muscle rigidity and contractions. Absence seizures often present as blank facial affect and unresponsiveness, and are classified as either typical or atypical. Typical absence seizures often have a short duration and include impaired consciousness. Atypical absence seizures have a longer duration and often include tonic, clonic, or automatic movements (Holmes, 1997). Tonic seizures are usually brief and involve increased muscle tone in extensor muscles as the muscles contract and stiffen. Consciousness is also often impaired. Clonic seizures cause muscles to spasm, which results in jerking muscle motions, while myoclonic seizures are short jerks of a muscle or groups of muscles, similar to the characteristic physical response to shock. Lastly, atonic seizures usually

involve loss of muscle tone, which can result in the person falling or in the dropping of the head or slumping of the body (McCandless, 2012). Consciousness is sometimes also impaired, and myoclonic jerks often occur after the atonic episodes. This type of seizure occurs most often in children (Holmes, 1997).

Focal or partial seizures originate in a localized region and are confined to networks within one hemisphere of the brain (Berg et al., 2010). Focal seizures include both simple and complex partial seizures. In a complex partial seizure, the individual exhibits impaired consciousness, meaning that they may not be aware or responsive. Simple partial seizures do not involve changes in consciousness, but may include some sensory auras (e.g., auditory, olfactory, visual hallucinations; McCandless, 2012).

Etiology

Theories regarding the etiology of seizures and epilepsy have evolved over the last several decades. The etiologic categorizations of epilepsy include idiopathic, symptomatic, provoked, and according to some researchers, cryptogenic. Idiopathic seizures are those that have or are thought to have a genetic origin, and therefore do not have a specific neuroanatomical or pathological cause (Shorvon, 2011). The defining characteristics of these seizures are age at onset, clinical and electrographic features, and an assumed genetic susceptibility (Berg et al., 2010). Symptomatic epilepsy has an underlying cause that is associated with anatomical or pathological abnormalities. This includes genetic disorders that are associated with pathological changes (e.g., tuberous sclerosis, West syndrome), as well as those that are acquired (e.g., head trauma, cerebral tumors or infection, neurodegenerative conditions). Finally, cryptogenic epilepsy involves seizures with an unknown or unidentified cause. Provoked epilepsy is a fourth

category used by some researchers. Provoked epilepsy is linked to a specific environmental or systemic factor that causes the seizures in the absence of anatomical or pathological irregularities (e.g., toxin-induced, drug-induced, metabolic). These factors can include genetic or acquired bases (Shorvon, 2011).

Berg and colleagues (2010) advised that the terms idiopathic, symptomatic, and cryptogenic had become too interwoven with different meanings and connotations within the field, which led to inconsistencies in their use. They therefore proposed the following alternative terms: genetic, structural/metabolic, and unknown cause. Genetic causes imply that the seizures are a direct result of either an identified or presumed genetic mutation. Structural/metabolic cause implies that there is a specific cause other than a genetic one that is directly related to the occurrence of seizures. These include structural lesions and metabolic diseases that may impair metabolism or osmolality, or introduce toxins (O'Brien, 1998). Lastly, unknown cause represents a neutral view that the underlying mechanism is unknown and may be related to an unidentified genetic correlate or another process that is not yet understood in relation to seizures (Berg et al., 2010).

However, regardless of the terminology used to describe the potential cause of seizures, an important consideration is that many cases of epilepsy have multiple causes. Often both genetic and environmental influences impact the individual's susceptibility to seizures and to developing epilepsy. As one cause is often considered the predominant mechanism, using categories of causation has clinical utility but should not obscure other contributing factors.

Assessment and Treatment

Seizures and epilepsy are typically identified and diagnosed through clinical description and the use of electroencephalogram (EEG) to detect any abnormalities in neurological activity (Manford, 2001). EEG patterns can identify epileptiform dischargers and determine whether these abnormalities are epileptic or non-epileptic paroxysmal attacks. Different types of seizures (e.g., clonic, tonic) often show discrete EEG patterns, and this distinction can aid in accurate diagnosis (Noachtar & Rémi, 2009).

The treatment for seizures depends on the type of seizure as well as individual characteristics. Provoked seizures, which are caused by an identifiable source, are treated by addressing the specific anomaly that is thought to have triggered the seizure. Seizures that are not provoked are often treated by anti-epileptic drugs (AED). Common anticonvulsants include phenobarbital, valproate, carbamazepine, gabapentin, topiramate, oxcarbazepine, clobazam, phenytoin, lamotrigine, levetiracetam, rufinamide, lacosamide, and zonisamide (McCandless, 2012). The type of AED prescribed typically depends on the type of seizure. For example, certain AEDs (i.e., valproate, lamotrigine, and topiramate) are very effective in treating absence seizures, but others can cause deterioration (i.e., carbamazepine, tiagabine; Noachtar & Rémi, 2009). Therefore, accurate assessment and diagnosis is crucial for treatment decisions.

If multiple AEDs are not effective in controlling seizures, in some cases surgery is implemented as the next step. Types of surgery include curative surgeries (i.e., resection of a seizure focus) and palliative surgeries (e.g., corpus callosotomy). Vagus nerve stimulation is also sometimes used to reduced seizure by implanting a vagus nerve stimulator under the patient's clavicle (Tarulli, 2016).

The ketogenic diet has also been promoted as a treatment for drug-resistant seizures. The ketogenic diet is high in fat, low in protein, and low in carbohydrates. This alteration in the body's sources of energy is designed to elicit biochemical changes in the brain that are associated with starvation (Freeman et al., 1998). This biochemical response causes the body to replace glucose as the brain's source of energy with ketones (Hartman, Gasiior, Vining, & Rogawski, 2007). The results of several studies support the use of the ketogenic diet to control medication-resistant seizures (Groesbeck, Bluml, & Kossoff, 2006; Kinsman, Vining, Quaskey, Mellits, & Freeman, 1992; Neal et al., 2008).

Prognosis

The impact of seizures and epilepsy on individuals is far-reaching. Researchers have found that individuals incur significant financial burden from seizure treatments. Factors that contribute to the cost of treatment include doctor visits, AEDs, tests and procedures, medical services and supplies. Other financial considerations related to seizures are cost of social services, transport to and from treatment, specific medical equipment, and absence from work or school (Baker, Nashef, & van Hout, 1997). More frequent seizures have also been found to be related to lower quality of life, as individuals with epilepsy encounter psychosocial difficulties such as higher rates of unemployment or underemployment (Smeets, van Lierop, Vanhoutvin, Aldenkamp, & Nijhuis, 2007), stigmatization, and lower self-fulfillment ratings (Baker et al., 1997). Epilepsy-related mortality rates are also a concern, as mortality is more common in those who experience more frequent seizures than those whose seizures are better controlled (Baker et al., 1997).

Seizures in Individuals with ASD

Researchers have suggested that ASD and epilepsy may share a molecular developmental mechanism. The fact that some genetic disorders such as tuberous sclerosis and Fragile X syndrome are associated with both ASD and epilepsy provides some support for this theory (Brooks-Kayal, 2010; Reilly & Gillberg, 2016). One suggested explanation is that genetic mutations or the effects of seizures at a young age can impact synaptic plasticity and may influence the presence of both ASD and epilepsy (Brooks-Kayal, 2010). Researchers have also proposed that deficiencies in GABAergic signaling may be an underlying mechanism (Kang & Barnes, 2012), though the research on this association is limited. Taken together, these studies emphasize the need for further research on the potential underpinning for atypical neurological activity and ASD.

Prevalence

Prevalence rates of seizures and seizure disorders are estimated to be higher in individuals with ASD than in the general population (Jokiranta et al., 2014). Relatedly, researchers have found that the frequency of ASD diagnoses are higher in individuals with epilepsy than those without (Reilly et al., 2014; Saemundsen et al., 2007). Researchers have estimated the prevalence rate of seizures in individuals with ASD to be between 5-40% (Danielsson et al., 2005; Gabis et al., 2005; Hrdlicka et al., 2004; Jokiranta et al., 2014; Viscidi et al., 2013). There is also evidence that prevalence may increase with age (Viscidi et al., 2013), so the differences in these rates may be due to sample characteristics of the studies, including age range, level of functioning, and definition of history of seizures (e.g., one seizure vs. diagnosis of epilepsy; Ballaban-Gil & Tuchman, 2000).

In addition to seizures and epilepsy, researchers have also investigated rate of epileptiform abnormalities in individuals with ASD. These findings indicate that in addition to higher rates of seizures in individuals with ASD than in the general population, the rates of epileptiform abnormalities are also higher (Hrdlicka et al., 2004; Kawasaki, Yokota, Shinomiya, Shimizu, & Niwa, 1997). This has important implications for the understanding of the underlying mechanism for abnormal neurological activity in ASD.

Age at onset

Several researchers have investigated the average age at onset of seizures and whether age is related to other factors, such as level of impairment. Bishop (1985) found that, in a sample of children with Landau-Kleffner syndrome, earlier the age at onset had worse language prognoses. O'Leary and colleagues (1981) reported consistent findings that children with onset of seizures prior to 5 years of age demonstrated greater cognitive impairments than those with later onset. Similar results were reported based on a comparison of age of onset prior to 2 years of age versus later in life (Vasconcellos et al., 2001), and there is also evidence that the relationship between age at onset and cognitive impairment is strongest early in life and decreases with age (Berg, Zelko, Levy, & Testa, 2012). However, contradictory findings indicate that age of onset may not be significantly related to intellectual (Ellenberg, Hirtz, & Nelson, 1984) or adaptive functioning (Berg et al. 2004).

As previously mentioned, Rutter and Schopler (1987) suggested that seizures emerge later in individuals with ASD than those with ID, and typically occur in adolescence. In a retrospective study conducted by Hara and colleagues (2007), the

authors concluded the mean age at onset was 14 years, with a range of 8 to 26 years. Similarly, Bolton and colleagues (2011) found that the average age of emergence was 13.3 years, and the majority of seizures began after age 10. Researchers have suggested that the tendency for seizures to emerge in adolescence in individuals with ASD is associated with age-related neurological development (Bolton et al., 2011).

However, Mouridsen and colleagues (1999) and Danielsson and colleagues (2005) reported younger ages as onset of 8.1 year and 7.5 years, respectively. Danielsson (2005) also found that one third of participants with ASD and epilepsy had their first seizure before 24 months of age, and suggested that the risk for epilepsy is highest in the first few years of life and decreases with age. Nomura and colleagues (2010) further investigated age at onset, and found that there were two general “peak” ages at which epilepsy began in individuals with autism: early in childhood at 3.2 years of age, and in late adolescence at 16.7 years. Similarly, researchers have suggested that seizure occurrence is highest in individuals with ASD at 5 and 10 years of age (Matson & Neal, 2009). These findings may help to explain the discrepancies in reported age at onset across studies.

Factors Associated with Seizures

Several interrelated factors are thought to be associated with the presence of seizures in individuals with ASD. The most well-established is cognitive ability. The bulk of the research on epilepsy and seizures and comorbid intellectual disability (ID) in individuals with ASD indicates that seizures are positively associated with lower cognitive or intellectual functioning (Amiet et al., 2008; Bolton et al., 2011; Danielsson et al., 2005; Gabis et al., 2005; Hrdlicka et al., 2004; Jokiranta et al., 2014; Viscidi et al.,

2013). Amiet and colleagues (2008) found that the rate of epilepsy was 21.4% in individuals with comorbid ASD and ID, but was only 8% in individuals with ASD without ID. The authors further investigated this relationship and found that this increased prevalence rate was found only for individuals with an intelligence quotient (IQ) of less than 50 compared to those with an IQ of above 70; no significant differences in rates of epilepsy were found between those with IQ between 50 and 70 and those with IQs above 70. This indicates that moderate and severe ID, but not mild ID, may be associated with increased rates of epilepsy. These rates are consistent with those reported by Mouridsen and colleagues (2011), which were seizure rates of 33.7% for those with IQs below 70 and 8.8% for those without ID.

In addition to lower cognitive functioning, Bolton and colleagues (2011) also found that individuals with epilepsy also had greater deficits in speech and language abilities, though this is in contrast to Shubrata and colleagues' (2014) outcome that there were no differences in receptive or expressive language. Although the relationship between seizures and language abilities is currently unclear, evidence of decreased cognitive functioning could be extrapolated to suggest that language impairments related to lower intellectual functioning may be associated with seizures and seizure disorder.

The second factor is severity of ASD symptomology. Researchers have found that individuals in the more impaired range of autism symptoms have higher rates of abnormal electroencephalograms and epilepsy (Gabis et al., 2005). Shubrata and colleagues (2014) also found that individuals with comorbid epilepsy had lower social quotient and higher scores on measures of autism symptoms (i.e., Childhood Autism

Rating Scale [CARS]). This provides evidence that ASD symptoms may be related to the presence of epilepsy.

However, there is some evidence that this relationship may be more strongly influenced by the level of cognitive functioning than core symptoms of ASD. For instance, Viscidi and colleagues (2013) found that more severe ASD symptoms were not independently associated with epilepsy, as there was not a significant association after controlling for IQ. This indicates that intellectual functioning may play more of a role in susceptibility to seizures than ASD symptomology, and Viscidi and colleagues (2013) suggested that children with ASD may be at an increased risk for epilepsy because they are at an increased risk for ID. Interestingly, Smith and Matson (2010) reported that in a sample of adults with ID, those with comorbid ASD and epilepsy demonstrated greater impairment in social skills than those with ASD but without epilepsy. These results indicate that in a sample of individuals with diagnoses of both ASD and ID, individuals with comorbid seizures had greater deficits in social functioning. Overall, while the relationship between seizure disorders and autism symptomology independent of intellectual disability is not well established, there is some evidence of an association.

The third factor is gender, as females with ASD are more likely to experience seizures than males (Amiet et al., 2008; Bolton et al., 2011). Amiet and colleagues (2008) and Bolton and colleagues (2011) both reported prevalence of seizures in 30-34.5% of females and 18-18.5% of males with ASD. This discrepancy is consistent with the findings of Danielsson and colleagues (2005), who suggested that epilepsy was present in 58% of females and 32% of males. However, other researchers have failed to find gender differences in prevalence (Hara, 2007).

Researchers have suggested that this may be connected to lower cognitive functioning in females with ASD compared to males (Danielsson et al., 2005; Gabis et al., 2005; Reilly & Gillberg, 2016). Nonetheless, there is some evidence that these factors may be unrelated. Blackmon and colleagues (2016) further investigated this relationship by examining treatment resistant epilepsy. They found that females displayed higher rates of treatment resistant epilepsy, but also had lower overall autism symptom severity. These results suggest that females with ASD and comorbid epilepsy may represent a subtype characterized by higher risk for epilepsy phenotype and less severe ASD symptoms. This is consistent with the findings of Bolton and colleagues (2011) that the level of cognitive functioning and language skills did not differ significantly between males and females with comorbid ASD and epilepsy.

An additional factor that has been investigated is regression in young children with ASD. Previous studies have yielded inconsistent results as to whether children who experience a regression are more likely to develop seizures. For instance, some research implies that epileptiform abnormalities, paroxysmal abnormalities, and epilepsy were not associated with regression (Bolton et al., 2011; Canitano, Luchetti, & Zappella, 2005; Cuccaro et al., 2011; Kobayashi & Murata, 1998; Tuchman & Rapin, 1997). In contrast, other researchers have found that regression was more frequent in individuals with epilepsy than those without (Hrdlicka et al., 2004). Similarly, Giannotti and colleagues (2008) reported that epilepsy and epileptiform abnormalities were more common in children with ASD who regressed than those who did not. However, despite some evidence for this association, the research overall does not support a potential relationship between regression and epilepsy.

Assessment and Treatment Considerations

A diagnosis of ASD may indicate certain barriers to the identification of a seizure disorder. Core symptoms of ASD, such as lack of response to socially salient stimuli (e.g., responding to name, voices) or repetitive behaviors, may obscure seizure symptoms (Jokiranta et al., 2014; Peake, Notghi, & Philip, 2006; Reilly & Gillberg, 2016). Given the high prevalence of seizures and seizure disorders in individuals with ASD, clinicians are encouraged to consider this potential comorbidity during assessment (Matson & Neal, 2009).

Individuals with epilepsy are at risk for cognitive impairment (Berg, Zelko, Levy, & Testa, 2012) and behavioral abnormalities (Elger, Helmstaedter, & Kurthen, 2004; Vingerhoets, 2006). Baker and colleagues (2011) found that individuals with recent diagnoses of epilepsy demonstrated a distinct cognitive trajectory compared to those without epilepsy, and specifically displayed declines in memory, psychomotor speed and executive functioning over the course of a year. The use of AEDs has also been implicated in cognitive deficits, possibly due to neuronal sensitivity and excitability (Meador, 2002). Berg and colleagues (2004) also found that young children with onset of seizure before age 3 showed declines in age appropriate adaptive skills over time. As cognitive impairments and adaptive skill deficits are already present in many individuals with ASD, the presence of comorbid seizures or epilepsy have significant implications for functioning in this population. As previously mentioned, although the association between ASD and seizures is well-established, little is currently known about the mechanisms that underlie this relationship. Consequently, early identification and

effective treatment of seizure disorders are crucial steps in optimizing outcomes for individuals with ASD.

Purpose

Many individuals with ASD have co-occurring psychiatric disorders or medical concerns, and disorders such as epilepsy can complicate the diagnostic process as well as treatment planning. Although many researchers have investigated possible neurological differences between individuals with ASD and TD individuals, the relationship between ASD and neurological dysfunction (such as that characteristic of epilepsy or epileptiform abnormalities) is still unclear. However, the literature does suggest that individual with more severe ASD symptomology and cognitive impairment show higher rates of seizures or seizure disorders (Amiet et al., 2008; Bolton et al., 2011; Gabis et al., 2005). These findings indicate that there may be neurological underpinnings to ASD in some individuals (Tuchman & Rapin, 2002).

The current study aimed to examine the relationship between ASD diagnosis and a history of seizures and autism symptom severity. Although the previous literature suggests that severe autism symptomology is related to comorbid seizures (Gabis et al., 2005), very few studies have investigated specific symptoms. Additionally, few researchers have explored this association in children under the age of 3. Expanding this line of research to younger children may help to elucidate whether these differences are consistent early in life, or if they become more apparent with age. Therefore, the current study investigated differences in total symptomology as well as symptoms within specific domains (i.e., social communication, restricted repetitive interests and behaviors, and communication) in infants and toddlers with and without a history of seizures and with and without an ASD diagnosis. The extant literature on ASD and seizure disorders provides some evidence that ASD symptoms may be exacerbated in individual with ASD

and co-occurring seizures (Gabis et al., 2005; Shubrata et al., 2014). Therefore, it was hypothesized that across both total and domain scores individuals with comorbid ASD and a history of seizures would have the highest symptomology, followed by the ASD without seizures group, and the atypical group without seizures will have the lowest scores. The results of the current study may have clinical implications for assessment and treatment of ASD comorbid with a history of seizures or seizure disorder.

Method

Participants

All participants were enrolled in EarlySteps, Louisiana's statewide early intervention program under the Individuals with Disabilities Education Act, Part C. The data for this study were extracted from an existing dataset containing assessment information. Children under 3 years of age qualify for EarlySteps services if they have or are at risk for a developmental delay. Therefore, all participants included from this dataset had some form of atypical development. Only participants between the ages of 17 and 37 months at the time of assessment were included in the analyses.

Participants were assigned to groups based on whether they meet criteria for ASD and whether they had a history of seizures or a seizure disorder. Diagnoses of ASD were given by a licensed clinical psychologist based on an algorithm in accordance with the *Diagnostic and Statistical Manual, Fifth Edition (DSM-5, American Psychiatric Association, 2013)*. A classification of a history of seizures or seizure disorder was based on parental report of any seizures on the demographic subsection of the *Baby and Infant Screen for Children with aUtism Traits (BISCUIT; Matson, Boisjoli, & Wilkins, 2007)*. Participants were assigned to one of four groups: an atypical development group without a history of seizures (ATYP), an atypical group with a history of seizures (ATYP+SEIZ), an ASD only group without history of seizures (ASD), and a comorbid ASD and seizures group (ASD+ SEIZ).

A statistical power analysis program, G*POWER, was used to establish necessary samples size for the four groups in order to demonstrate adequate power. A power of .80 (Field, 2013), alpha of .05, and medium effect size of $\eta^2 = .25$ were used, as these values

(Tabachnick & Fidell, 2007). If a participant had received more than one evaluation, the most recent was included in the analyses. For the exact number of cases excluded, see Figure 1.

The total number of cases remaining was 9,410 (i.e., 8,164 ATYP, 1,024 ASD, 174 ATYP+SEIZ, and 48 ASD+SEIZ). Due to unequal sample sizes between groups, participants from each group were age and gender and gender matched to the smallest group (i.e., ASD+SEIZ). This matching procedure was used because, as previously discussed, previous research has shown that there are age and gender effects related to seizures and developmental functioning, so these demographic factors were controlled for through matching to the smallest group. This resulted in a total of 192 participants, with 48 participants in each group. For one participant in the ATYP+SEIZ group, it was not possible to match exactly for age and gender. Consequently, this case was matched with a case within one month of age (e.g., 24 months instead of 23 months). The age range for the participants was 17-35 months ($M = 25.89$, $SD = 4.59$). In regard to the total sample, 58.3% were male ($n = 112$) and 41.7% ($n = 80$) were female. With respect to participant race, 47.9% were African American ($n = 92$), 42.2% were Caucasian ($n = 81$), 4.2% were Hispanic ($n = 8$), and 5.7% were of another race ($n = 11$). Group demographic information is presented in Table 1.

Measures

Baby and Infant Screen for Children with aUtism Traits, Part 1 (BISCUIT-Part 1; Matson et al., 2007).

The *BISCUIT* is an informant-report measure designed for young children 17 to 37 months of age. This measure consists of three sections which evaluate ASD symptomology, comorbid psychopathology, and challenging behaviors. The *BISCUIT*-

Part 1 assesses ASD symptoms and consists of 62 items related to nonverbal and verbal communication, socialization, and repetitive behavior/restricted interests. Each of these items is rated based on a 3-point Likert scale that compares the child to same-aged peers. A rating of 0 corresponds to “not different; no impairment”, a rating of 2 corresponds to “somewhat different; mild impairment”, and a rating of 3 corresponds to “very different; severe impairment”. This measure includes age-based cut-off ranges for the total *BISCUIT* score; a score of 0-16 falls within the “No ASD/Atypical Development” range; a score of 17-38 falls within the “Possible ASD” range; and a score of 41-124 falls within the “Probable ASD” range. Therefore, a score of 17 or higher is classified as in the “at risk” range. The Socialization/Nonverbal Communication subscale consists of 24 items, the Repetitive Behavior/Restricted Interests subscale includes 23 items, and the Communication subscale includes 7 items.

Table 1. *Demographics*

	<i>ATYP</i> (<i>n</i> = 48)	<i>ATYP+SEIZ</i> (<i>n</i> = 48)	<i>ASD</i> (<i>n</i> = 48)	<i>ASD+SEIZ</i> (<i>n</i> =48)
Mean Age (in months)	25.88	25.90	25.88	25.88
SD (in months)	4.47	4.72	4.74	4.74
Gender				
Male	28 (58.3%)	28 (58.3%)	28 (58.3%)	28 (58.3%)
Female	20 (41.7%)	20 (41.7%)	20 (41.7%)	20 (41.7%)
Race				
African American	23 (47.9%)	18 (37.5%)	24 (50.0%)	27 (56.3%)
Caucasian	19 (39.6%)	27 (56.3%)	20 (41.7%)	15 (31.3%)
Hispanic	5 (10.4%)	0 (0%)	1 (2.1%)	2 (4.2%)
Other	1 (2.1%)	3 (6.3%)	3 (6.3%)	4 (8.3%)

The *BISCUIT-Part 1* has an estimated internal reliability of .87 and overall correct classification rate of .89 (Matson et al., 2009). The *BISCUIT-Part 1* has also

been found to have convergent validity with the *Modified Checklist for Autism in Toddlers (M-CHAT)* and the Personal-Social domain of the *Battelle Developmental Inventory, Second Edition (BDI-2)*, as well as divergent validity through small correlation with the *BDI-2*'s Adaptive and Motor domains (Matson, Wilkins, & Fodstad, 2011). The present study used the *BISCUIT-Part 1* total score and domains scores, as well as the demographic form. The demographic form is used to collect information regarding the participant's demographic variables, family history, and developmental and medical history. The *BISCUIT-1* total score were used to assess ASD symptom severity, and the subscale scores were used to assess symptomology across nonverbal communication/socialization, repetitive behavior/restricted interests, and communication.

Procedure

The Louisiana State University institutional review board and the State of Louisiana's Office for Citizens with Developmental Disabilities approved the study prior to data collection. The *BISCUIT-Part 1* were administered by service providers at the participant's home or daycare center as part of an assessment battery that included caregiver interviews and direct observation. All service providers attended trainings on the administration of the assessment measures and held a degree, certification, and/or licensure in various related fields such as occupational therapy, physical therapy, psychology, special education, and speech-language pathology. Only records collected between 2010-2016 were included in the statistical analyses.

The data used for the present study were from a research database of de-identified archival records. Consequently, the Institutional Review Board determined that the 45

CFR part 46 of the U.S. Department of Health and Human Services regulation does not apply and informed consent was not required.

Statistical Analyses

Bivariate and univariate analyses were conducted to investigate the following research questions: 1) does autism symptom severity differ based on a history of seizures or seizure disorder and 2) does a history of seizures or seizure disorder impact separate domains of ASD symptoms differently? The four groups were age and gender-matched to the smallest group, so a priori analyses of differences in these demographic variables were not included, though a chi-square analysis was conducted to assess differences in race between groups. Descriptive statistics were conducted for total scores on the BISCUIT-Part 1 and the three subscales.

An analysis of variance (ANOVA) was conducted to examine the relationship between group and total ASD symptom severity. The independent variable (IV) was group (i.e., ATYP, ASD, ATYP+SEIZ, and ASD+SEIZ) and the dependent variable (DV) was ASD symptom severity, based on the total *BISCUIT-Part 1* score. Post hoc tests were used to further examine differences between groups. A multivariate analysis of variance (MANOVA) was conducted with group as the IV and scores from the three ASD symptom subscales (i.e., Socialization/Nonverbal Communication, Repetitive Behavior/Restricted Interests, Communication) as the DVs. Post-hoc comparisons were done to further investigate differences between groups.

Results

Bivariate analyses were not conducted for age or gender because matching was applied to all group; however, the results of a chi-squared analysis revealed no significant differences between groups in regard to race, $\chi^2(9) = 14.25, p = .114$). Internal consistency for the 62 items on the BISCUIT Part-1 was estimated to be $\alpha = .97$. Prior to performing the initial ANOVA, the data were checked for outliers in total score on the *BISCUIT-Part 1*. Results indicated that there were outliers in the ATYP and ASD+SEIZ groups. A square root transformation was then applied to the score dependent variable to address these outliers because the scores were moderately positively skewed. Due to the large samples size ($n > 50$), normal distribution was assessed by Normal Quantile-Quantile (Q-Q) rather than by the Komogrov-Smirnov and Shapiro-Wilks tests (Field, 2013; Laerd, 2015). Based on visual analysis of Normal Q-Q Plots, it was determined that scores for all three subscales were normally distributed. The initial ANOVA showed significant differences in total symptom severity between groups, $F(3,188) = 90.97, p > .001, partial \eta^2 = .592$. Descriptive statistics for the total *BISCUIT-Part 1* scores across groups are provided in Table 2. Levene's Test of Equality of error variance was significant ($p = .023$), so Games-Howell post hoc tests were used. The results of Games-Howell post hoc tests indicated that all groups had significantly different total scores on the BISCUIT- Part 1 ($p < .001$).

Prior to conducting the MANOVA, the assumptions for this analysis were checked. There were univariate outliers in the data for all three subscales of the *BISCUIT- Part 1*, as determined by inspection of boxplots for values greater than 1.5 lengths from the box. Based on observation of histograms, it was determined that the

data for the Socialization/ Nonverbal communication and RRBI domains subscales was strongly positively skewed, while the Communication domain was strongly negatively skewed. Therefore, logarithmic transformations were conducted for the first two subscales and a reflect and logarithmic transformation was applied to the Communication domain. Following these transformations, there were no univariate outliers for any of the domains. Based on visual analysis of Normal Q-Q Plots, it was determined that scores for all three subscales were normally distributed. Multicollinearity was assessed through a linear regression analysis using the principle proposed by Belsley, Kuh, and Welsch (1980; from Tabachnick & Fidell, 2007). Although the final dimension had more than one variance proportion greater than .50, none of the condition indices approached 30; therefore, multicollinearity was not detected. There was a linear relationship between the Socialization/Nonverbal Communication, RRBI, and Communication as assessed by scatterplot. There were no multivariate outliers, as assessed by Mahalanobis distance ($p > .001$), using a critical value of 16.27 based on the number of dependent variables.

Table 2. *Autism symptom severity comparison between groups*

	<i>ATYP</i> <i>M (SD)</i>	<i>ATYP+SEIZ</i> <i>M (SD)</i>	<i>ASD</i> <i>M (SD)</i>	<i>ASD+SEIZ</i> <i>M (SD)</i>
<i>BISCUIT-Part 1:</i> ASD Symptom Severity	18.54 (14.92) _{bcd}	32.50 (18.75) _{acd}	75.79 (19.61) _{abd}	57.69 (21.76) _{abc}
Socialization/Nonverbal Communication	5.58 (7.99) _{bcd}	13.48 (11.32) _{cd}	33.48 (9.14) _{abd}	26.21 (12.02) _{abc}
Restricted/Repetitive Behaviors/Interests	4.06 (5.02) _{cd}	6.38 (6.18) _{cd}	23.10 (10.17) _{abd}	16.19 (9.74) _{abc}
Communication	7.13 (3.81) _{bcd}	10.23 (2.05) _{ac}	12.38 (2.01) _{ab}	11.40 (2.89) _a

- a. Significantly different from ATYP, $p < .05$ Note: *M* = Mean; *SD* = Standard Deviation.
b. Significantly different from ATYP+SEIZ, $p < .05$
c. Significantly different from ASD, $p < .05$
d. Significantly different from ASD+SEIZ, $p < .05$

A MANOVA was then conducted to evaluate scores across symptom domains (see Figure 2). There was not homogeneity of variance-covariances matrices, as assessed by Box's test of equality of covariance matrices ($p < .001$). Although the sample sizes across groups were equal and therefore a violation of this assumption is typically not considered a concern, Pillai's Trace was used rather than Wilks' Lambda as it is more robust to violations of assumptions (Field, 2013; Laerd Statistics, 2013). There was not homogeneity of variances for any of the subscales, as assessed by Leven's Test of Equality of Error Variances ($p < .001$ for Socialization/Nonverbal Communication and RRBI, and $p = .019$ for Communication). Therefore, Games-Howell post hoc tests were conducted for follow-up ANOVAs (Laerd Statistics, 2015).

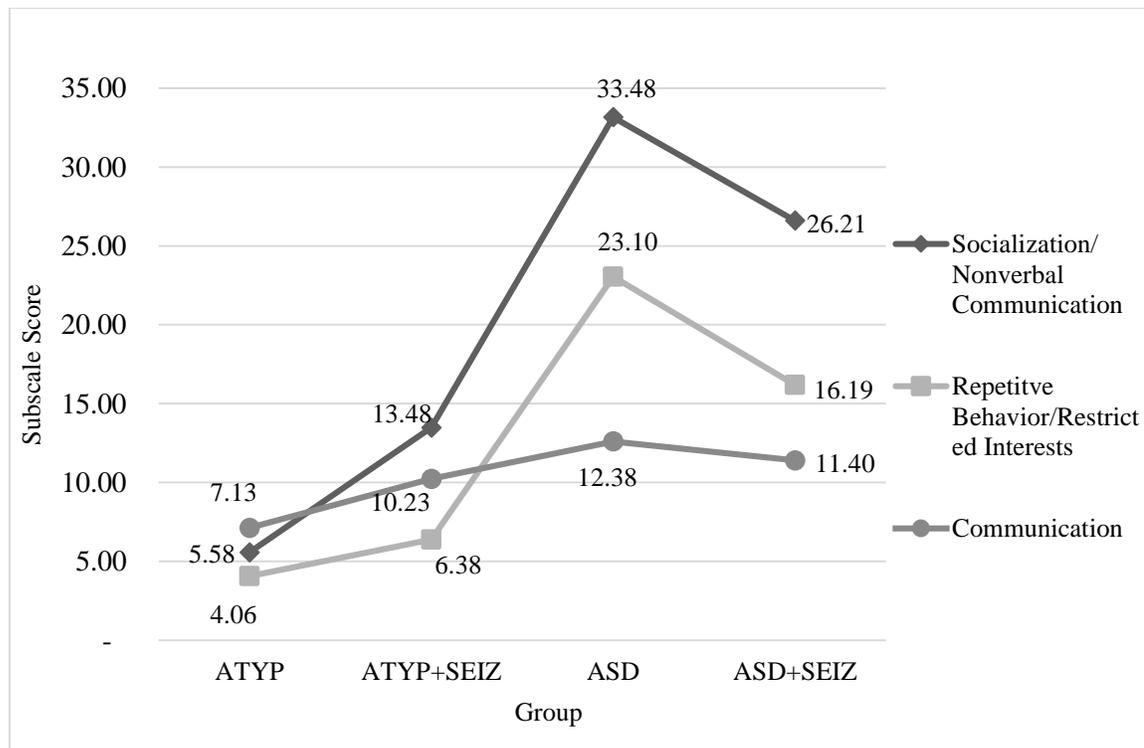


Figure 2. Mean Group Scores Across Subscales

According to Pillai's trace, there were significant differences between groups across symptoms, $V = .644$, $F(9,564) = 17.13$, $p < .001$, $partial \eta^2 = .215$. Follow-up

ANOVAs were also conducted, and a Bonferroni correction ($p < .017$) was used to account for multiple comparisons. There were significant differences between groups for all three domains: Socialization/nonverbal communication domain, $F(3,188) = 73.88$, $p > .001$, $partial \eta^2 = .541$; RRBI domain, $F(3,188) = 63.55$, $p > .001$, $partial \eta^2 = .504$, and the Communication domain $F(3,188) = 25.78$, $p > .001$, $partial \eta^2 = .292$.

Games-Howell post hoc tests were conducted to evaluate differences between groups across symptom domains because the assumption of homogeneity of variances was violated (Laerd Statistics, 2015). For the Socialization/Nonverbal communication domain, the ASD+SEIZ group had significantly higher score than both the ATYP and ATYP+SEIZ groups ($p < .001$) and significantly lower scores than the ASD group ($p = .003$). The ATYP+SEIZ group also had significantly higher scores than the ATYP group ($p < .001$) and lower scores than the ASD group ($p < .001$). Lastly, the ASD group also had significantly higher scores than the ATYP group ($p < .001$).

For the Restricted/repetitive behaviors and interest domain, the ASD+SEIZ group had significantly lower scores than the ASD group ($p = .002$) and higher scores than both the ATYP and ATYP+SEIZ groups ($p < .001$). The ATYP+SEIZ group had significantly lower scores than the ASD group ($p < .001$), but did not differ significantly from the ATYP group ($p = .094$). The ASD group also had significantly higher scores than the ATYP group ($p < .001$).

In regard to the Communication subscale, the ATYP group had significantly lower scores than all three of the other groups ($p < .001$). The ATYP+SEIZ group had significantly lower scores than the ASD group ($p = .001$), but did not differ significantly from the ASD+SEIZ group ($p = .194$). ASD group also had significantly higher scores

than the ATYP ($p < .01$) and the ATYP+SEIZ ($p = .001$) groups. Significant differences were not found for the ASD and ASD+SEIZ groups on this domain ($p = .365$).

Descriptive statistics for the *BISCUIT-Part 1* subscale scores across groups are provided in Table 2.

Discussion

ASD symptomology, as measured by the *BISCUIT-Part 1*, was compared between groups of participants with atypical development, atypical development and comorbid seizures, ASD, and comorbid ASD and seizures. Total ASD symptom scores were examined, as well as symptoms on three symptom domains: Socialization/nonverbal communication, Restricted/repetitive behaviors and interests, and Communication.

The findings of this study indicated that there were significant differences between groups for the total *BISCUIT-Part 1* scores as well as between most groups for symptom domains. Across all IVs, the ASD group had the highest scores, followed by the ASD+SEIZ group, then the ATYP+SEIZ group, with the ATYP group evincing the lowest scores. Differences were significant between all four groups for the total score and Socialization/nonverbal communication. The majority of comparisons were significant for the other two domains. Exceptions included the ATYP and ATYP+SEIZ groups for the RRBI domain and the ASD+SEIZ and the ASD and ATYP+SEIZ groups for the Communication subscale.

The general trend of these findings was that for individuals with ASD, a history of seizures indicated lower endorsement of symptoms. Conversely, for individuals without ASD, a history of seizures was related to higher overall symptomology. These results contradict some previous findings that individuals in the more impaired range of ASD (i.e., autism rather than Asperger's syndrome or PDD-NOS) demonstrate higher likelihood to experience seizures (Gabis et al., 2005), as comorbid seizures were associated with lower rates of ASD symptoms in the current study. Other researchers have found that, based on DSM-IV-TR diagnoses, epilepsy occurs at higher rates in both

autistic disorder and PDD-NOS than in Asperger's syndrome (El Achkar & Spence, 2015). Nonetheless, given that there is a well-documented relationship between seizures and ID, these results are consistent with the assumption that children with seizures may have more cognitive impairment than those without seizures. Therefore, atypically developing children with seizures and therefore potential ID may exhibit more symptoms related to ASD (e.g., language delays, motor stereotypies) than those without ASD or seizures. Further, in young children with ASD, those with comorbid seizures and possible lower cognitive functioning may have lower overall developmental functioning. This does not, however, necessarily suggest more autism-specific symptoms but rather more global impairments.

For the RRBI subscale, a history of seizures was not related to significantly higher levels of restricted, repetitive interests and behaviors in the atypically developing sample. Conversely, in the ASD sample, those without a history of seizures had significantly higher scores on the RRBI domain than those with seizures. This finding may suggest that in atypically developing children, neurological differences related to seizures may not be significantly associated with increases in restricted, repetitive interests and/or behaviors in individuals without ASD. The differences between the ASD and atypically developing groups may indicate that seizures may be more closely related to RRBI in young children with ASD, but less intertwined in children without ASD.

A history of seizures also seemed to be less robustly related to communication and language skills, as there were fewer significant differences between groups for this domain. Specifically, the Communication score in the ASD+SEIZ group did not differ from ASD or ATYP+SEIZ groups. The results for this domain indicated that the

atypically developing group had significantly less impairment in communication than the other three groups, but that those with atypical development and seizures did not have significantly fewer communication difficulties than those with ASD and seizures. Further, the ASD group did not have significantly worse communication skills than the ASD+SEIZ group. These results indicate that seizures may play more of a role in impairments in communication than an ASD diagnosis. Of note, this finding may be accounted for by the small number of items (7 as compared to 24 and 23). Given that this domain is not a diagnostic criterion for ASD according to DSM-5, and the fact that there are so few items, these findings may have less substantial implications for the field. However, because so many children with ASD do experience language delays and impairments, this subscale was included in the analyses to examine general trends between groups.

An important consideration in the interpretation of these findings is the very young age of the participants. Previous research indicates that many individuals do not develop seizures until later in childhood or adolescence (Bolton et al., 2011; Hara et al., 2007). There is substantial evidence that earlier onset of seizures may be related to greater cognitive impairment (Berg et al., 2012; O’Leary et al., 1981; Vasconcellos et al. 2001). Physical disabilities such as motor impairments may also be more prevalent in children with seizures (McGrother et al., 2006). Therefore, this sample may represent a group of children with greater global delays associated with early onset seizures, which may account for some of the observed differences between groups.

Additionally, it is likely that many of the children whose seizures had been identified at this young age were exhibiting types of seizures with more visible motor

features (e.g., tonic-clonic seizures), rather than less obvious symptoms (e.g., absence seizures), which would be more difficult to identify in younger children, particularly with communication deficits. Therefore, it is possible that some children in this sample may have had undiagnosed seizures at the time of assessment.

Overall, the evidence that a history of seizures may be significantly related to autism symptomology both in atypically developing children and those with ASD highlights the importance of early identification. In this sample, those with ASD and comorbid seizures had lower autism symptomology scores than those without seizures, and it is possible that this is due to impairments in cognitive functioning. Further, young children without ASD had higher scores of ASD symptomology if they had a history of seizures, which may indicate impairments in the three domains discussed even in the absence of a diagnosis of a developmental disability when there is abnormal neurological activity.

Although there is currently a lack of consensus in the field regarding screening procedures for epilepsy in those with ASD, this study supports the recommendations of researchers such as El Achkar and Spence (2015) that providers be proficient in differentiating ASD symptoms from potential indicators of seizures. Given the increased prevalence of seizures in the ASD population (Jokiranta et al., 2014) and the potential association with symptomology (Gabis et al., 2005) and cognitive impairments (Amiet et al., 2008; Bolton et al., 2011; Danielsson et al., 2005), providers should take additional care in considering the likelihood of seizure disorder.

Early identification of seizures in young children with ASD is crucial, as researchers have recommended that individuals with this comorbidity may evince

different patterns of symptoms and may require longitudinal follow-up throughout development to monitor the seizures (Shubrata et al., 2014). Tuchman and colleagues (2010) suggested that early recognition and diagnosis of seizures may also help identify children who may be at-risk for ASD, given the high incidence of these two conditions. Early treatment of seizures, such as medication or lifestyle changes, may help to improve outcomes for individuals with ASD (Tuchman et al., 2010). However, Reilly & Gillburg (2016) caution that consideration of potential side effects of anti-epileptic medication should be considered in this population.

Limitations

One limitation to the current study is the lack of a typically developing comparison group. Given that children were included in the EarlySteps database if their caregivers requested an evaluation due to concerns regarding their child's development, most children in this sample evinced some sort of developmental delay or medical concern. Although this allowed for a comparison between children with and without ASD and with and without a history of seizures, these results may not be generalizable to comparisons between children with ASD and typically developing children. Additionally, the *BISCUIT* demographic form is a caregiver-report measure, and therefore classification of having a history of seizures was based solely on caregiver report and was not validated through medical records. Finally, the results for the Communication subscale should be interpreted with caution due to the small number of items in this domain. This domain was still included in the analyses because many children with ASD experience language delays.

Future Directions

These findings highlight the need for additional research on how seizure disorders affect symptom presentation in children with ASD. This study provides preliminary evidence that seizures in individuals with ASD may be related to lower levels of autism-specific symptoms as compared to children with ASD alone. These results should be further investigated, both in young children as well as in older children where ID can be investigated as a variable to further elucidate the relationship between autism symptomology, intellectual disability, and seizures. The sample of participants used in this study was too young for an ID diagnosis to be used as a reliable variable in the present analyses, but it is hypothesized that the findings on a history of seizure disorders may be associated with lower cognitive functioning. Although many studies have considered comorbidity of ASD, ID, and seizure disorders, the majority have focused on cognitive functioning and few have investigated autism symptomology specifically.

As the current study relied upon caregiver-report of a history of seizures, information regarding the type or frequency of seizures was not available. Although some studies have focused on specific types of seizures (Reilly & Gillburg, 2016), additional research is warranted. Further, the demographics of this sample upheld previous research that female gender may serve as a risk factor for epilepsy in individuals with ASD (El Achkar & Spence, 2015). Despite the overall gender ratio of 4-5:1 male to female with ASD (Baio, 2014), the sample of individuals with ASD used in this study included 28 males and 20 females, which is a more even gender split than the general ASD population. Although gender was not included as a variable in this study due to the age and gender matching procedure applied to the four groups, future investigation of the

differences between males and females with comorbid ASD and seizures may help to elucidate the relationship between seizures, ASD, and ID.

Future studies involving young children should be considered to further clarify symptom patterns in very young children with a history of seizures. As the literature indicates that seizure disorders do not develop or are not diagnosed until later in childhood, additional investigation of how seizures early in development relate to ASD and associated impairments is warranted.

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Vita

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