FAMILY STUDIES OF SENSORIMOTOR DISTURBANCES

IN AUTISM SPECTRUM DISORDER

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ABSTRACT

Sensorimotor impairments are prevalent in individuals with autism spectrum disorder (ASD) and among the earliest emerging features, yet the pathophysiological mechanisms underlying these deficits remain poorly understood. Family studies are one approach to better understand these pathophysiological mechanisms by identifying sensorimotor impairments that are present in both individuals with ASD (probands) and their unaffected biological family members. Previous studies have identified reduced saccade accuracy and increased variability of saccade in probands as well as analogous deficits in unaffected relatives. We also have recently demonstrated reduced accuracy and increased variability of precision gripping in ASD. Accuracy of ocular and manual motor behaviors is controlled by *feedforward* motor control processes responsible for guiding initial motor output prior to available visual feedback as well as *feedback* processes that use visual feedback information to compensate for any systematic error. Thus, previous findings

implicated disruptions of *feedforward* and *feedback* mechanisms in ASD. Here, we characterized saccade and precision gripping abnormalities in probands and their unaffected biological parents, and determined the extent to which these abnormalities are familial by studying family trios (proband, biological mother, biological father). Our results demonstrated that probands show reduced accuracy of rapid ocular and manual motor responses as well as increased variability of sustained manual motor behaviors, suggesting that cerebellar-mediated *feedforward* and *feedback* motor control processes are disrupted in ASD. Biological parents demonstrated a similar pattern of sensorimotor abnormalities to individuals with ASD. Further, impaired saccade dynamics and variability of sustained gripping inter-correlated among probands and their parents indicating that these deficits may be familial. Oculomotor and manual motor abilities were relatively independent in controls, whereas these abilities were correlated in both probands and parents suggesting reduced differentiation of these motor control systems in ASD. Sensorimotor deficits also were related to core diagnostic features in probands as well as to sub-clinical phenotypic features in parents, suggesting that deficits in sensorimotor behaviors may share pathogenic mechanisms with core symptoms. Overall, our findings provide support that sensorimotor impairments are highly prevalent in ASD, and that they may be familial, suggesting their use as intermediate phenotypes and potential biological markers of risk in ASD.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficits-Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
ApEn	Approximate Entropy
ASD	Autism Spectrum Disorder
BAP	Broad Autism Phenotype
BAP-Q	Broad Autism Phenotype Questionnaire
CNV	Copy Number Variants
CoV	Coefficient of Variation
DSM	Diagnostic and Statistical Manual of Mental Disorders
EOG	Electro-oculagraphy
ES	Effect Size
fMRI	Functional Magnetic Resonance Imaging
FT	Family Trio Sample
GABA	Gamma-Amino Butyric Acid
GWAS	Genome-Wide Association Studies
IQ	Intelligence Quotient
LTD	Long-Term Depression
M1	Primary Motor Cortex
MRI	Magnetic Resonance Imaging
MVC	Maximum Voluntary Contraction
NVIQ	Nonverbal Intelligence Quotient
PFC	Prefrontal Cortex
SCQ	Social-Communication Questionnaire

SD	Standard Deviation
SMA	Supplementary Motor Area
SNP	Single Nucleotide Polymorphism
SOLAR	Sequential Oligogenic Linkage Analysis Routines
VGS	Visually-Guided Saccade

CHAPTER ONE
Introduction

FAMILY STUDIES OF SENSORIMOTOR DISTURBANCES IN AUTISM SPECTRUM DISORDER

Statement of the Problem

Autism spectrum disorder (ASD) is a neurodevelopmental disorder affecting 1 in 68 children (Center for Disease Control and Prevention [CDC], 2014). It is characterized by social-communication deficits and the presence of restricted, repetitive behaviors (American Psychiatric Assocation [APA], 2013). The clinical presentation of ASD varies substantially across individuals due in part to the heterogeneity of its core symptoms as well as the wide range of medical and psychiatric features associated with the disorder. Among these associated features, which include cognitive and language deficits, psychological comorbidities (e.g., depression, anxiety), sleep and gastrointestinal issues, seizure disorders, and genetic conditions (e.g., Fragile X, tuberous sclerosis), sensorimotor impairments appear to be the most ubiquitous (for review see Gillberg, 2014; Mosconi, Takarae, & Sweeney, 2011) and earliest emerging (Baranek, 1999; Bryson et al., 2007; Elison et al., 2013; Estes et al., 2015; Landa & Garrett-Mayer, 2006; Loh et al., 2007; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998).

Dyspraxia (Dziuk et al., 2007; Hughes, Russell, & Robbins, 1994; Jones & Prior, 1985; Ming, Brimacombe, & Wagner, 2007; Minshew, Goldstein, & Siegel, 1997; Rogers, Bennetto, McEvoy, & Pennington, 1996), reduced postural stability (Fournier et al., 2010; Minshew, Sung, Jones, & Furman, 2004; Morris et al., 2015), and gross and fine motor impairments (Cook, Blakemore, & Press, 2013; David et al., 2009; David, Baranek, Wiesen, Miao, & Thorpe, 2012; Glazebrook, Elliott, & Lyons, 2006; Mari, Castiello, Marks, Marraffa, & Prior, 2003; Vernazza-Martin et al., 2005) are commonly reported in individuals with ASD. Despite consensus that sensorimotor abnormalities are common in ASD and that they may impact multiple behaviors (Mosconi & Sweeney, 2015), the motor control processes underlying these deficits remain unclear. One possibility is that these impairments reflect alterations in *feedforward*

and *feedback* control processes. During *feedforward* control, an internal action representation guides the initial motor output prior to sensory feedback being available for corrective adjustments (Ghez, Hening, & Gordon, 1991). In contrast, *feedback* control compensates for systematic error by transforming sensory information about the ongoing movement and comparing it against the original motor plan (Chen-Harris, Joiner, Ethier, Zee, & Shadmehr, 2008; Kawato, Furukawa, & Suzuki, 1987; Stein, 1986; Takagi, Zee, & Tamargo, 1998). Thus, optimal control of motor behaviors depends on *feedforward* and *feedback* control processes and their interaction with each other. The extent to which *feedforward* and *feedback* motor control processes each are compromised in ASD has not yet been systematically assessed.

Rapid eye movements, or saccades, are highly dependent on *feedforward* and *feedback* motor control systems. Saccades are completed prior to sensory feedback regarding their spatial position, and thus they rely on *feedforward* control mechanisms to ensure their accuracy. *Feedback* control is then responsible for determining whether adjustments need to be made to correct for spatial errors and to adjust internal models used to guide subsequent eye movements. Studies of saccadic eye movements in ASD have documented reduced accuracy and increased accuracy variability across trials implicating both *feedforward* and *feedback* motor control systems (Johnson et al., 2012; Luna, Doll, Hegedus, Minshew, & Sweeney, 2007b; Minshew, Luna, & Sweeney, 1999; Mosconi et al., 2013; Rosenhall, Johansson, & Gillberg, 1988; Schmitt, Cook, Sweeney, & Mosconi, 2014; Takarae, Minshew, Luna, Krisky, & Sweeney, 2004a; Takarae, Minshew, Luna, & Sweeney, 2004b, 2007). In addition, we recently demonstrated reduced accuracy and increased variability during precision manual motor force control in individuals with ASD (Mosconi et al., 2015a; Wang et al., 2014b), suggesting that *feedforward* and *feedback* processes are disrupted across multiple motor behaviors.

Studies of saccades and manual motor control in ASD each implicate cortical-cerebellar brain systems involved in *feedforward* and *feedback* motor control processes. The cerebellum is particularly important for ensuring the precision and consistency of movements by generating the internal action representations that are used during *feedforward* control (Ito, 1970, 2000, 2008, 2013). Additionally, the

cerebellum is responsible for translating sensory feedback information into adjusted motor commands during *feedback* control (Stein & Glickstein, 1992). The cerebellum consistently has been shown to be abnormal in *in vivo* anatomical studies and post-mortem brain studies of individuals with ASD (Bauman, 1991; Bauman & Kemper, 1985b; Courchesne et al., 1994; Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988; Gaffney, Kuperman, Tsai, & Minchin, 1988; Hashimoto, Tayama, Miyazaki, Murakawa, & Kuroda, 1993; Hashimoto et al., 1995; Whitney, Kemper, Bauman, Rosene, & Blatt, 2008b). Thus, studying *feedforward* and *feedback* control of ocular and manual motor behaviors may provide a unique and well-controlled approach for understanding brain mechanisms involved in ASD and identifying pathophysiological processes underlying sensorimotor impairments in this disorder.

Importantly, we identified a pattern of *feedforward* and *feedback* eye movement deficits in unaffected first-degree relatives of individuals with ASD that was similar to patterns seen in affected individuals suggesting these deficits may be familial (Mosconi et al., 2010). Studies assessing the familiality of different biological processes associated with ASD may be particularly useful for identifying intermediate phenotypes that represent alterations intermediate between genes and overt clinical manifestations (Gottesman & Gould, 2003). This approach can help identify phenotypes that are closer than clinical symptoms to the biological processes that cause the disorder. Importantly, our prior family study indicated that the severity of impairments in *feedback* and *feedforward* motor control processes were not associated with each other among ASD family members, suggesting that different forms of motor deficits may co-segregate in different families. To the extent that distinct biological intermediate phenotypes co-segregate in different families, this type of study design may be useful for resolving heterogeneity in ASD as it has done for other psychiatric and medical disorders (for examples, see Clementz et al., 2015; Kathiresan et al., 2009; Keating et al., 1991; Narayanan et al., 2015).

The present study is the first known project to examine the inter-relationship of sensorimotor dysfunctions across family trios comprised of an individual with ASD and their unaffected biological parents. By studying family trios, we will be able to precisely quantify *feedforward* and *feedback* control

of ocular and manual motor abnormalities in individuals with ASD as well as their unaffected family members and thus determine their role in the pathophysiology of sensorimotor impairments. These studies also will allow us to examine the extent to which sensorimotor abnormalities co-segregate in different families and thus may be useful for parsing heterogeneity in ASD.

Significance

ASD constitutes a major public health problem nationally and internationally with prevalence estimates over 1% (Baron-Cohen et al., 2009; CDC, 2014; Sun et al., 2015) and annual costs estimated to be over $250 billion in the United States (Buescher, Cidav, Knapp, & Mandell, 2014; Leigh & Du, 2015). Further, the level of strain placed on parents and families of individuals with ASD appears to be associated with significant risk for psychiatric and medical illness (for examples see Johnson, Frenn, Feetham, & Simpson, 2011; Karst & Van Hecke, 2012). Although behavioral interventions have been shown to provide significant benefits for social, communication, cognitive, and adaptive behavioral development (for examples see Dawson et al., 2012), a better understanding of the pathophysiology of the disorder is still needed to identify treatment targets and develop more individualized and effective therapies. Family trio studies offer a unique approach for identifying intermediate phenotypes that are closer than clinical symptoms to the biological processes that cause ASD. The proposed study therefore may enhance our understanding of pathophysiological mechanisms associated with sensorimotor impairments in ASD, and thus provide insight into the development of more targeted interventions.

CHAPTER TWO
Review of the Literature

AUTISM SPECTRUM DISORDERS

Overview

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social-communication deficits as well as the presence of restricted and repetitive behaviors. ASD affects 1 in 68 school-aged children in the United States and is four- to five-times more common among males than females (CDC, 2014). Prevalence estimates have been rapidly rising since ASD was first included in the Diagnostic and Statistical Manual, Third Edition (3rd ed.; *DSM-III*, APA, 1980) and more steadily rising since 2000 (CDC, 2014; Gurney et al., 2003; Newschaffer, Falb, & Gurney, 2005). Increased understanding and awareness of the disorder, advances in procedures for identifying children earlier in development, changes in diagnostic criteria, improved differential diagnosis procedures, and modifications in referral patterns and reporting practices all may be contributing to higher prevalence estimates in ASD; however, it remains unclear whether the disorder itself is becoming more common (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2005; Bishop, Whitehouse, Watt, & Line, 2008; Fombonne, 2009; Gurney, et al., 2003; Hansen, Schendel, & Parner, 2015; Keyes et al., 2012; King & Bearman, 2009; Polyak, Kubina, & Girirajan, 2015; Rice et al., 2012). Due to a lack of objective, biologically-based approaches for determining whether or not ASD is present, prevalence may be under- or over-estimated and true changes in prevalence rates are hard to estimate.

As the definition of ASD has expanded, it has become apparent that what we currently define as ASD likely encompasses multiple, relatively distinct clinical presentations, better referred to as "ASDs". These distinct presentations include symptoms outside of the core social-communication and behavioral symptoms on which the diagnosis is based. These associated features and comorbidities are common but also variable in terms of their occurrence and severity. Therefore, identifying patterns of comorbid

features may help improve our understanding of developmental deficits within the autism spectrum and the many pathophysiological processes that underlie these disorders.

Core and Associated Features of ASD

Core Features of ASD and Their Heterogeneity

From its earliest conceptions by Leo Kanner (1943) and Hans Asperger (1944, as translated by Frith, 1991), ASD was defined by social-communication deficits and the presence of restricted, repetitive behaviors. Social-communication deficits characteristic of ASD include impairments in social-emotional reciprocity (e.g., reduced sharing of interests and emotions, poor reciprocal communication), nonverbal communication used in social interaction (e.g., uncoordinated nonverbal and verbal communication, poor eye gaze and gesture use), and the ability to establish, maintain, and understand relationships (e.g., difficulty making friends, reduced interest in peers; APA, 2013). However, even 70 years ago, both Kanner and Asperger noted the high degree of inter-individual variability in social-communication symptoms across patients. It has been reported subsequently that some individuals may be observed to be uninterested, withdrawn, and aloof, whereas others may be highly socially motivated but impaired due to a lack of appropriate social skills or awareness (for example see Waterhouse et al., 1996). Likewise, restricted and repetitive behaviors are observed in a variety of forms and are variably present among individuals with ASD. Because of the high degree of variability of these symptoms, the DSM 5 requires only two of the following four behaviors to be observed to meet criteria within this domain: stereotyped, repetitive behaviors (e.g., hand and body mannerisms, banging objects), rigid, inflexible behaviors (e.g., difficulty with changes in routine or transitions, strict adherence non-functional routines), highly circumscribed and intense interests (e.g., preoccupation with unusual objects, perseverative and circumscribed interests), and hypo- or hyper-sensitivities to sensory stimuli (e.g., sensory aversions or interests; APA, 2013). There is evidence that restricted, repetitive behaviors may be better sub-grouped into lower-order (e.g., sensory interest/aversion, repetitive motor actions) versus higher-order behaviors (e.g., circumscribed interests, insistence on sameness; for review see Leekam, Prior, & Uljarevic, 2011),

which may help parse heterogeneity in ASD, but it is unclear whether these sub-groups also demonstrate specific social-communication or comorbidity profiles.

Although attempts have been made to clarify symptom heterogeneity in ASD, they have been largely unsuccessful. For instance, in the DSM-IV (APA, 2007), three separate diagnostic classifications were identified: autistic disorder, Asperger's disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). However, it was found that there was significant overlap in clinical features and similar efficacies of evidence-based treatments across diagnoses (Billstedt, Gillberg, & Gillberg, 2007; Lord et al., 2012a). Further, specific diagnoses tended to be clinic- and provider-specific (Lord, et al., 2012a). Thus, due to the lack of evidence supporting three separate disorders, they were subsumed under one diagnostic classification in the DSM 5 (APA, 2013). The DSM 5 also attempted to resolve issues of heterogeneity by including severity ratings to better classify affected individuals based upon their level of impairment and support needed within each symptom domain (APA, 2013). For example, an individual who demonstrates marginal impairments and requires few supports will be given a severity level of 1 in the social-communication and/or restricted, repetitive behavior domains, whereas an individual with more profound impairment who requires a significant level of support would be given a severity level of 3 in one or both of these domains. Although this provides a relatively standardized method of specifying severity across individuals, the amounts of variability over time and within one severity level remain considerable. Thus, the field remains challenged in its ability to parse heterogeneity in this disorder.

Co-Occurring Features and Comorbid Diagnoses in ASD

The heterogeneous presentation of ASD is further complicated by the variable presence of numerous developmental, behavioral, psychiatric, and medical conditions that commonly co-occur with ASD (for review see Veenstra-VanderWeele & Blakely, 2012). Overall, the prevalence of comorbid conditions in ASD is estimated to be approximately 70% for one condition and 41% for two or more

conditions (Simonoff et al., 2008). However, little is known regarding whether some of these factors are causal as opposed to co-occurring conditions with common or separate etiologies.

Language and Cognitive Impairments. Approximately two-thirds of individuals with ASD have language delay (Allen & Rapin, 1992) and one-fifth do not develop verbal speech (Lord, Risi, & Pickles, 2004). Additionally, an estimated 17-30% of individuals with ASD (Ben-Itzchak, Ben-Shachar, & Zachor, 2013; Wiggins, Rice, & Baio, 2009) demonstrate regression of their language skills, such that language development first occurs within normal limits, but then, most or all language is lost. However, even regression of language skills varies substantially across individuals in terms of age and level of regression as well as the amount of recovery (i.e., complete versus partial versus no recovery). Speech abnormalities also are observed in individuals with ASD regardless of their history of language delay. Common speech abnormalities present in this population include pedantic or overly precise language, articulation difficulties, use of idiosyncratic words, differences in volume, rhythm, and rate of speech, atypical intonation patterns, and pronoun reversals (for review see Eigsti, De Marchena, Schuh, & Kelley, 2011).

Notably, apraxia of speech, a motor disorder in which individuals have difficulty producing speech sounds due to central mechanisms rather than muscle weakness, has been implicated in ASD. In a recent study, it was suggested 63.6% of individuals who were initially diagnosed with ASD also had apraxia and 36.8% of individuals who received an initial diagnosis of apraxia also had ASD (Tierney et al., 2015). This suggests a high degree of comorbidity between ASD and apraxia as well as a potential direct relationship between core deficits and motor impairments in ASD. However, due to methodological concerns, including use of a small sample size of patients (n = 30), absence of a control group, and implementation of a 30-item checklist to confirm diagnoses as opposed to more rigorous gold-standard approaches, additional studies are warranted to determine the extent to which ASD and apraxia co-occur.

Intellectual and cognitive impairments also are variably present in ASD (Munson et al., 2008). Recent population-based studies have estimated that 18-55% of individuals with ASD meet criteria for intellectual disability (i.e., 2 standard deviations below the mean; Charman et al., 2011), though some older studies have suggested that these numbers may be even higher (Croen, Grether, & Selvin, 2002; Matson & Nebel-Schwalm, 2007; Ritvo et al., 1989). This suggests that over half of individuals with ASD may have relatively intact intellectual functioning; however, other cognitive deficits may be present among affected individuals. For example, executive dysfunction and learning disabilities have been consistently identified in ASD. Executive function refers to a set of cognitive processes related to cognitive control of behavior, including attention, planning, problem solving, and working memory (Lezak, 1995). Deficits in executive functioning skills have been widely reported in ASD; however, the prevalence and nature of executive impairments in ASD have been debated (for review see Happe, 1999; Hill, 2004). As an example, some studies have reported that inhibitory control is intact in ASD (Ozonoff & Strayer, 1997), while other studies have indicated that it is impaired in individuals with ASD (Christ, Holt, White, & Green, 2007; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Minshew, et al., 1999). Differences in how inhibitory control was operationalized and assessed across these studies may account for some of the differences in findings; however, heterogeneity of cognitive symptoms in ASD also may contribute to observed differences. Additionally, an estimated 67% of individuals with ASD meet criteria for a specific learning disability, most commonly in written expression (Mayes & Calhoun, 2007). Thus, language, cognitive, and learning impairments are highly prevalent co-occurring features in ASD.

Medical Comorbidities. Commonly reported medical comorbidities among individuals with ASD include seizure disorders, gastrointestinal issues, feeding problems, and sleep problems (Doshi-Velez, Ge, & Kohane, 2014; Mannion, Leader, & Healy, 2013). Among individuals with ASD, an estimated 20-80% have gastrointestinal issues (e.g., constipation, diarrhea; Horvath & Perman, 2002; Ibrahim, Voigt, Katusic, Weaver, & Barbaresi, 2009; Mannion, et al., 2013; Molloy & Manning-Courtney, 2003; Wang,

Tancredi, & Thomas, 2011) and 46-89% have feeding problems (e.g., gagging reflux, swallowing difficulties, food selectivity; Ibrahim, et al., 2009; Valicenti-McDermott et al., 2006). Seizures and seizure disorders (e.g., epilepsy) are present in 5-40% of individuals with ASD (Baird et al., 2008; Giovanardi Rossi, Posar, & Parmeggiani, 2000; Nicholas et al., 2008), with higher prevalence estimates in individuals with comorbid intellectual disability (Amiet et al., 2008). Sleep problems, which occur in approximately 50 to 90% of individuals with ASD (Kotagal & Broomall, 2012; Liu, Hubbard, Fabes, & Adam, 2006; Richdale & Schreck, 2009), also have a higher prevalence among individuals with comorbid intellectual disability (Richdale & Schreck, 2009). This suggests that certain co-morbid cognitive conditions (i.e., intellectual impairment) may increase risk for comorbid medical features.

A recent study identified potential clusters of comorbid conditions in ASD. Doshi-Velez and colleagues (2014) found that medical comorbidities cluster into four subgroups. The authors found that seizure disorders, multisystem disorders (e.g., gastrointestinal and sleep), and psychiatric disorders make up three distinct subgroups. However, a fourth undefined subgroup, which constituted approximately 90% of the sample, could not be further subdivided due to fewer comorbid symptoms. Thus, these results suggest that systematic assessments of the presence and severity of medical comorbidities may be used to help parse heterogeneity in ASD; however, it is not yet known how specific diagnostic features are related to these comorbid conditions.

Psychological comorbidities. Numerous neurodevelopmental, psychological, and behavioral conditions also co-occur in individuals with ASD. For instance, ADHD symptoms are present in 28-85% of individuals with ASD (Bradley & Isaacs, 2006; Leyfer et al., 2006; Nicholas, et al., 2008; Simonoff, et al., 2008). Challenging behaviors, including aggression and oppositional defiance, are present in 82-94% of individuals with ASD (McTiernan, Leader, Healy, & Mannion, 2011; Murphy, Healy, & Leader, 2009), and self-injurious behaviors manifest in approximately 50% of affected individuals (Baghdadli, Picot, Pascal, Pry, & Aussilloux, 2003; Duerden et al., 2012; Richards, Oliver, Nelson, & Moss, 2012). Comorbid intellectual disability increases the risk of challenging and self-injurious behaviors in

individuals with ASD (O'Brien & Pearson, 2004) and is associated with maintenance of these symptoms over time (Murphy et al., 2005).

Anxiety also is a profoundly impairing comorbid condition for individuals with ASD, occurring in approximately 42% of individuals with ASD (Simonoff, et al., 2008). Anxiety symptoms may take a variety of forms in ASD, including panic disorder, specific phobia, obsessive-compulsive disorder, separation anxiety, and agoraphobia; however, generalized anxiety and social phobia appear to be most prevalent (13.4% and 29.2%, respectively; Simonoff, et al., 2008). Depressive symptomology is another frequently co-occurring condition in individuals with ASD, affecting approximately 50% of individuals with ASD (Schendel et al., 2016; Simonoff, et al., 2008). An estimated 2-30% of individuals with ASD meet diagnostic criteria for depression (Leyfer, et al., 2006). Although the majority of individuals with ASD demonstrate at least one psychological comorbidity, little is known regarding risk and protective factors.

Motor Abnormalities. Initial descriptions of ASD by Kanner (1943) and Asperger (1944, as translated by Frith,1991) noted motor abnormalities, including hand and finger stereotypies, odd posturing, awkward and clumsy movements, slow reflexes and delays in walking. Although a few of these symptoms are now considered to be diagnostic features of the disorder (i.e., stereotypies, odd posturing), motor impairments have largely remained an under-recognized and under-studied feature of ASD. The DSM-IV included postural abnormalities and clumsiness as associated features of autism and Asperger's Syndrome, respectively (APA, 2007), and the DSM 5 includes motor impairments as an associated feature of ASD (APA, 2013). Yet, studies suggest that between 59–85% of individuals with ASD show definite motor impairments (based upon scores >2 standard deviations (SDs) below the mean), and an additional 10-25% of patients demonstrate moderate motor impairments (based upon scores between 1-2 SDs below the mean; Green et al., 2002; Green et al., 2009; Hilton et al., 2007; Miyahara et al., 1997). Additionally, an estimated 60-80% of individuals with ASD demonstrate developmental delays in the acquisition of critical motor skills (Provost, Heimerl, & Lopez, 2007a; Provost, Lopez, &

Heimerl, 2007b). Fournier and colleagues' (2010) recent meta-analysis of motor functioning in individuals with ASD documented significant impairments across motor studies of ASD (effect size (ES) = 1.2). Thus, motor impairments are highly prevalent and often severe in individuals with ASD, and more comprehensive examination to characterize these deficits and their underlying pathophysiology is warranted.

Pathophysiological Mechanisms Associated With ASD

Role of Genetics

Multiple types of studies have highlighted the strong role of genetics in the etiology of ASD [for review see \Miles, 2011 #2643;Freitag, 2007 #2645;Muhle, 2004 #2668]. For instance, early twin studies showed levels of heritability as high as .95, making ASD the most heritable behaviorally-defined disorder (Bailey et al., 1995; Folstein & Rutter, 1977). Family studies further support a strong heritable component to ASD, with recurrence estimates among siblings ranging from 3-50% (Bolton et al., 1994; Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Zhao et al., 2007). Additionally, using structural equation modeling, several studies found that phenotypic variance among twins with ASD was best accounted for by inherited genetic factors rather than environmental factors, suggesting aggregation within families is better explained by shared genes as opposed to shared environments (Bailey, et al., 1995; Folstein & Rutter, 1977; Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010).

Despite indications of a strong role of genetic mechanisms in ASD, the actual genetic mechanisms contributing to ASD are complex and do not follow typical Mendelian inheritance patterns. Genome-wide association studies (GWAS) have implicated chromosomes 1, 2, 4, 7, 10, 13, 15, 16, 17, 19, 22, and X, but were largely unsuccessful at identifying common variants (Miles, 2011; Muhle, et al., 2004). Thus, GWAS provided further support for the heterogeneous etiology of ASD that corresponds to its heterogeneous clinical presentation. Known genetic variations including single nucleotide polymorphisms (SNPs) associated with ASD, genetic syndromes associated with ASD, and copy number

variations (CNVs) linked to ASD cumulatively account for approximately 5-25% of ASD cases, with the remaining cases considered to be idiopathic (Devlin & Scherer, 2012; Miles, 2011).

Single gene disorders are estimated to account for approximately 5% of individuals diagnosed with ASD (for review see Freitag, 2007; Miles, 2011; Muhle, et al., 2004). The most common single gene disorders associated with ASD include fragile X syndrome, Tuberous Sclerosis, and Rett syndrome. The high rates of ASD among individuals with these genetic syndromes suggest that the genes involved in their etiology confer profound susceptibility to ASD features. Importantly, not all individuals with these genetic anomalies have a comorbid diagnosis of ASD as some demonstrate sub-threshold level ASD traits and others demonstrate few, if any, ASD symptoms (for example see Bailey, Palferman, Heavey, & Le Couteur, 1998b; Rogers, Wehner, & Hagerman, 2001; Smalley, 1998; Steffenburg, Gillberg, Steffenburg, & Kyllerman, 1996; Veltman, Craig, & Bolton, 2005). Therefore, while the genes involved in these disorders increase risk for ASD, they do not alone appear to cause the disorder and likely interact with many other genes and environmental factors that confer risk or provide protective influences.

Copy number variants (CNVSs) refer to structural variations of chromosomes that manifest as deletions or duplications. Although CNVs are present among healthy individuals and estimated to account for approximately 13% of variation in human DNA, CNVs also are associated with increased susceptibility and resistance to disease (Stankiewicz & Lupski, 2010). Both inherited and *de novo* (i.e., non-inherited) CNVs have been implicated in ASD. Candidate loci of duplication and deletions include 15q11-13, 16p11.2, 22q13, SHANK3, NRXN1, and PTCHD1 (for review see Marshall & Scherer, 2012). However, it should be noted that many of the CNVs identified in ASD also have been implicated in other neurodevelopmental and psychiatric disorders including schizophrenia, ADHD, and intellectual disability, suggesting common pathways may lead to phenotypically distinct outcomes based upon individual genetic and environmental differences (for example see Girirajan & Eichler, 2010).

Lastly, multiple rare genetic disorders caused by a single nucleotide polymorphism (SNP) also are associated with ASD. For example, Joubert syndrome is an autosomal recessive disorder involving

the *AH1* gene and characterized by partial or complete lack of development of the cerebellar vermis. In approximately one-third of patients with Joubert syndrome, ASD may be diagnosed (Ozonoff, Williams, Gale, & Miller, 1999). Neurofibromatosis 1 is an autosomal dominant disorder involving the *NF1* gene, which is responsible for cell division and may produce neurofibromas within the brain (Costa & Silva, 2002). Among affected individuals, approximately 26-63% demonstrate ASD symptoms (Payne, 2013; Plasschaert et al., 2015) and 4% meet diagnostic criteria for ASD (Payne, 2013). However, this disorder also is associated with ADHD, epilepsy, and intellectual disability (for review see Weiss, 2009). Thus, like single gene disorders and CNV gains/losses, SNPs associated with ASD may not be selectively linked to ASD and they increase the risk for other neurodevelopmental and medical conditions.

Studies of genetic conditions associated with ASD are highly translational, such that these genetic conditions can be modeled in animals in order to identify molecular mechanisms and develop potential drug treatments. For example, a recent study demonstrated the reversal of social and repetitive behavior deficits as well as neuronal organization in a SHANK3 mouse model when treated with a drug that helped restore SHANK3 functioning (Mei et al., 2016). Further, studying genetic disorders associated with ASD also may provide insight into the associated behavioral and medical features of ASD. For example, individuals with Phelan –McDermind Syndrome (PMS), a genetic disorder caused by 22q13 deletions or mutations involving the SHANK3 gene, often have epilepsy, gastrointestinal issues, kidney problems, and significant motor and speech delays in addition to ASD symptoms (Phelan & McDermid, 2012). Thus, studies of specific genetic conditions may provide critical insight into etiological mechanisms of ASD behaviors and provide models in which to test more targeted interventions.

Environmental Risk Factors

Although ASD is known to have strong genetic influences, environmental risk factors also contribute to the development of ASD (for review see Mandy & Lai, 2016; Matelski & Van de Water, 2016). For instance, several teratogens have been implicated in animal model and clinical studies of ASD, including valproic acid, lead, mercury, alcohol, and thalidomide (Bandim, Ventura, Miller,

Almeida, & Costa, 2003; Gardener, Spiegelman, & Buka, 2009; Moore et al., 2000; Rodier, 2002). Very low birth weight (Gardener, Spiegelman, & Buka, 2011), gestational diabetes, and maternal infection during pregnancy (Gardener, et al., 2009) also have been found to be risk factors of ASD. More recent evidence suggests increased risk of ASD with increased parental age (Frans et al., 2013; Reichenberg et al., 2006). Interestingly, increased *de novo* mutations are correlated with increased paternal age (Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012), suggesting that genetic and environmental factors interact to contribute to risk of ASD.

Despite these findings, genetic influences appear to confer the greatest risk for ASD. Genes known to be associated with ASD play fundamental roles in neural synapse formation and maintenance, cellular proliferation and migration, neurotransmitter signaling, and neurogenesis (Ben-David et al., 2011; Gilman et al., 2011; Pinto et al., 2010). Still, ASD cases with known genetic associations only account for a minority of total ASD cases (Devlin & Scherer, 2012). And, understanding of how these genetic mechanisms lead to clinical symptoms remains limited. Research is needed to determine how genetic mechanisms may contribute to brain abnormalities and to clinical manifestations of ASD.

Intermediate Phenotypes

One method to better understand the genetic mechanisms associated with ASD is by identifying biological markers of risk, or intermediate phenotypes, that are present in both individuals with ASD and their unaffected family members. Intermediate phenotypes can be any quantifiable trait that is biologically-based and genetically-influenced (Lenzenweger, 2013). The term “intermediate phenotype” highlights that the characteristic is intermediate between the underlying genotype and the clinical manifestations of the disorder. Thus, in ASD, an intermediate phenotype would be any heritable phenotypic trait present in an individual with ASD as well as their unaffected family members useful for indexing an underlying biological process (Gottesman & Gould, 2003). Gottesman and Gould (2003) identified several characteristics of an effective intermediate phenotype in psychiatry research that are relevant here. The authors indicated that intermediate phenotypes should: 1) be quantifiable; 2) be

measurable 3) be associated with a psychological disorder; 4) be heritable; 5) be relatively stable over time; 6) co-segregate within families with the psychological disorder; 7) be present in unaffected relatives, and; 8) have an identified or potential causal mechanism.

Current biomarkers and potential intermediate phenotypes in ASD. Although several biological markers of risk have been identified in ASD, few of these are directly related to pathophysiological mechanisms and none of these can be used to reliably diagnose ASD. One reason for this may be that current biological markers overlap with other disorders. Yet, research aimed at identifying biomarkers in ASD remains important as it may provide a more objective method for diagnosing patients and identifying pathophysiological mechanisms. Hyper-serotonemia, or elevated whole-blood serotonin, is among the first intermediate phenotypes described (Schain & Freedman, 1961) and subsequently replicated in ASD (for example see Cook et al., 1993; Mulder et al., 2004; Perry, Cook, Leventhal, Wainwright, & Freedman, 1991). Whole-blood serotonin levels are highly heritable, and genes associated with serotonin reuptake have been implicated in ASD (Cook, et al., 1993; Cross et al., 2008). It has been hypothesized that serotonin levels during fetal development may play a role in atypical neuronal migration and subsequent abnormalities in neural circuitry (for review see Veenstra-VanderWeele & Blakely, 2012). Thus, whole-blood serotonin is a relatively strong candidate for an intermediate phenotype in ASD. Other neurotransmitters and hormones also have been implicated in ASD, including gamma-amino butyric acid (GABA), glutamate, melatonin, and oxytocin (for review see Polleux & Lauder, 2004). Yet, these alterations are highly variable across patients and do not differentiate individuals with ASD from those who do not have ASD. Family studies are needed to determine the utility of atypical neurotransmitter and hormone levels as intermediate phenotypes.

Increased head circumference and brain size repeatedly have been documented in ASD and thus may be candidate biomarkers (for example see Courchesne, Campbell, & Solso, 2011; Courchesne et al., 2001; Wallace & Treffert, 2004). Researchers have suggested that ASD may be characterized by a pattern of rapid overgrowth of the brain within the first two years of life, followed by a period of

deceleration (Courchesne, Carper, & Akshoomoff, 2003; Dawson et al., 2007; Hazlett et al., 2005; Hazlett et al., 2011; Nordahl et al., 2011). Increases have been documented in whole-brain and regional grey and white matter volumes (Hazlett, et al., 2005; Schumann et al., 2010). For instance, frontal and temporal lobes (Carper, Moses, Tigue, & Courchesne, 2002; Hazlett, et al., 2005; Schumann, et al., 2010), specifically within the dorsolateral and mesial prefrontal cortices (Carper & Courchesne, 2005), cingulate gyrus (Schumann, et al., 2010), and amygdala (Mosconi et al., 2009a; Schumann, Barnes, Lord, & Courchesne, 2009) all have been implicated. Additionally, regional volumetric decreases within the corpus callosum have been observed in ASD (Frazier, Keshavan, Minshew, & Hardan, 2012; Nordahl et al., 2015). Several anatomical MRI studies have documented reduced long-range neural connectivity, but increased short-range connectivity in ASD (Barnea-Goraly, Lotspeich, & Reiss, 2010; Courchesne & Pierce, 2005; Frazier & Hardan, 2009; Shukla, Keehn, Lincoln, & Muller, 2010). Increased grey matter volume could suggest increased neuronal proliferation or reduced apoptosis, whereas white matter alterations may reflect disruptions in cell migration, synapse formation, myelination or astroglia formation. The precise mechanisms underlying morphometric gray and white matter alterations in ASD remain unclear.

More focal alterations among subcortical structures also have been identified in ASD. For example, increased caudate nucleus size (Hazlett et al., 2009; Hollander et al., 2005; Rojas, Camou, Reite, & Rogers, 2005; Sears et al., 1999), increased hippocampus size (Rojas et al., 2004) and reduced cerebellum size (for review see Fournier, et al., 2010) each have been reported in ASD. Interestingly, reductions in cerebellar volume appear to be more severe (ES = .72) than enlargements in other cortical (ES = .62) and subcortical (ES = .40) structures (Amaral, Schumann, & Nordahl, 2008; Stanfield et al., 2008b), suggesting this may be a particularly important brain region in ASD. However, our understanding of whether select anatomical brain differences in ASD may serve as useful intermediate phenotypes currently is limited by several factors. First, few studies have assessed whether these structural abnormalities are present in family members of individuals with ASD (Peterson et al., 2006;

Rojas, et al., 2004). Second, similar structural differences have been observed in other neurodevelopment and psychiatric disorders suggesting that these gross measures of neuroanatomy may not be able to identify deficits specific to the disorder(s), or that brain anatomical differences may not be specific to ASD (for review see Bradshaw & Sheppard, 2000; Giedd & Rapoport, 2010). Third, multiple brain regions have been implicated but to varying degrees, in varying patterns (e.g., under vs. overgrowth), and with variable effects across development. Further, neuroanatomical alterations vary across individuals with ASD but their linkage with clinical manifestations has not been consistently mapped. To determine the utility of brain structural differences as intermediate phenotypes in ASD, studies of their presentation across large numbers of well-characterized individuals with ASD across the full age and severity range are needed, and large-scale studies of their unaffected relatives are warranted.

Altered immunological and mitochondrial functioning also have been documented in ASD (for review see Rossignol & Frye, 2012). For instance, increased concentration of cytokines, or small proteins important for cell signaling during the immune response, have been found in individuals ASD despite patients' reduced adaptive immune reactions (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). However, other proteins associated with the immune response have been found in reduced concentrations in ASD (Warren, Burger, Odell, Torres, & Warren, 1994; Warren, Yonk, Burger, Odell, & Warren, 1995). This suggests that altered immune response may arise from a variety of potential pathways, including an underlying mitochondrial disease. Specific indicators of mitochondrial disease in ASD include abnormal concentrations of lactate, pyruvate, ubiquinone and acyl-carnitines (for review see Rossignol & Frye, 2012). Hypothesized mechanisms of mitochondrial dysfunction in ASD symptoms include increased oxidative stress (James et al., 2006; James et al., 2009) and imbalance of excitatory (i.e., glutamate) and inhibitory (i.e., GABA) neurotransmitters (Krey & Dolmetsch, 2007; Rubenstein & Merzenich, 2003; Splawski et al., 2004). However, no studies to date have been able to clarify the role of these mechanisms in ASD. Overall, findings across studies of immunological and mitochondrial

biomarkers have been inconsistent, suggesting variable presence of alterations across individuals with ASD and weak evidence for their use as intermediate phenotypes.

Together, current research indicates several potential biologically-based intermediate phenotypes in ASD. However, inconsistencies in findings, poor understanding of pathophysiological mechanisms, and unknown heritability (aside from hyperserotonemia) suggest that these biomarkers require further study. Thus, the need for quantifiable, biologically-based phenotypes that are heritable, present among unaffected relatives, and tied to potential etiological pathways in ASD remains high.

Motor Abnormalities as a Potential Intermediate Phenotype. Motor impairments are highly prevalent comorbid feature of ASD that demonstrate unique promise as an intermediate phenotype. There are numerous advantages of studying motor symptoms in ASD: 1) they are present in 59–85% of individuals with ASD (Fournier, et al., 2010) and are among the earliest features in developing infants (for example see Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013; Teitelbaum, et al., 1998); 2) they can be quantified precisely in both spatial and temporal domains; 3) paradigms used to study motor functioning place minimal demands on patients and have minimal practice effects, especially compared to cognitive and behavioral paradigms, and thus they are well-suited for studying individuals across broad ranges of age and intellectual ability (for example see Kida, Oda, & Matsumura, 2005); 4) neural systems underlying motor behaviors are well-defined by animal and human studies, especially compared to higher-order behaviors like executive function and social-communication; 5) the neural systems associated with motor behavior have been implicated by histological, neurophysiological, and neuroimaging studies in ASD (for example see Bauman & Kemper, 2005); and 6) motor impairments associated with ASD also have been identified in family members of individuals with ASD (Mosconi et al., 2010). Thus, motor impairments are important co-occurring features of ASD because they may be particularly useful for identifying brain mechanisms in ASD and determining new biological intermediate phenotypes.

MOTOR DISTURBANCES IN ASD

Motor abnormalities evident in infants with ASD may represent the earliest signs of the disorder (for example see Esposito & Venuti, 2008; Teitelbaum, et al., 1998). Motor skills mature rapidly within the first years of life, and thus it is not surprising that an early indicator of developmental delay and/or a neurodevelopmental disorder often is failure to meet motor milestones. Retrospective video and parent-report studies of individuals with ASD suggest that many individuals with ASD failed to meet early motor milestones or demonstrated atypical trajectories of motor development as early as the first months of life (Baranek, 1999; Chawarska et al., 2007; Esposito & Venuti, 2008; Teitelbaum, et al., 1998; Zwaigenbaum et al., 2005). To understand early motor signs associated with ASD as well as patterns of later occurring motor disturbances in patients, it is first important to characterize typical patterns of early motor development and describe their underlying mechanisms.

Motor Development and Theory

Developmental Milestones of Motor Skills

Sensory and motor regions of the brain are the first to develop, myelinate, and mature during infancy (Barkovich, Kjos, Jackson, & Norman, 1988; Calvert, 2001; Jernigan & Tallal, 1990; Lenroot & Giedd, 2006), coinciding with the rapid maturation of sensorimotor skills during early postnatal development (Haywood & Getchell, 2009; Johnson, 2001; Prechtl & Hopkins, 1986). Motor development progresses in a "top-down" fashion, that is, from head to toe, reflecting the maturation and myelination of neural systems and pathways responsible for controlling the movement of these body parts (Barkovich, et al., 1988; Sie, van der Knaap, van Wezel-Meijler, & Valk, 1997; Thelen, 1995). In contrast, the maturation of higher-order processes, like social, communication, and complex cognition, occur later in development and are dependent on early sensorimotor development (Bronner-Fraser, 2003; Lenroot & Giedd, 2006; Tau & Peterson, 2010). Thus, sensorimotor brain maturation and skill development is particularly important in prenatal and early postnatal periods.

During the first six months of postnatal life, infants predominantly demonstrate spontaneous, repetitive, and seemingly random movements, especially of the arms and legs (Cioni, Ferrari, & Prechtl, 1989; Piek & Carman, 1994; Prechtl & Hopkins, 1986), as opposed to voluntary, goal-directed movements. These repetitive movements, referred to as "spontaneous movements", often appear uncoordinated and jerky, yet kinematic analysis of these movements suggest they are smooth, symmetrical, and coordinated within the limb (Thelen, Skala, & Kelso, 1987). Spontaneous movements are considered to be a part of the normal developmental trajectory of motor functioning and even are present *in utero;* however, atypical kinematic profiles of spontaneous movements often are indicative of subsequent cognitive and behavioral developmental issues (Einspieler & Prechtl, 2005; Kanemaru et al., 2013; Piek & Carman, 1994). In addition to spontaneous movements during the first six months of life, infants gradually gain control of their head and necks, then hands, and finally their upper limbs (American Academy of Pediatrics (AAP), "Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening," 2006). By two months, infants are able to visually track objects, with rapid improvement in the accuracy of their tracking between two and three months (von Hofsten & Rosander, 1997). Additionally, 2-month-old infants are able to make rapid eye movements, or saccades, to targets; however, their saccades are slower and hypometric compared to older children (i.e., undershooting the target; Aslin & Salapatek, 1975; Harris, Jacobs, Shawkat, & Taylor, 1992). Furthermore, with increased limb and upper body control, infants are able to coordinate hand-eye movements and sit up with assistance around 3-4 months and without assistance around 6-8 months. Around this same time, infants learn to roll over by first turning their hands, then shoulders, and then trunk and hips (Haywood & Getchell, 2009; AAP, 2009).

In the latter half of the first year, infants continue to improve their balance and control of previously developed skills as well as gain control of their lower limbs (Haywood & Getchell, 2009; AAP, 2009; Davies, 2011). With dramatically increased strength and control of their lower limbs and trunk, infants become better able to coordinate their limb movements, which allows them to perform goal-

directed actions (Haywood & Getchell, 2009; Bertenthal & Von Hofsten, 1998; von Hofsten, 2004). For example, improved control of trunk and limbs helps the development of standing with support, which typically occurs between five and ten months, crawling, which typically occurs between six and twelve months, and standing unaided, which typically occurs between eight and seventeen months (Haywood & Getchell, 2009; Davies, 2011; AAP, 2009). Crawling and standing are important developmental milestones as they allow infants to better explore and interact with their environments. Trunk and limb control are further refined near the first birthday, culminating in the ability to walk, which typically occurs between nine and 18 months (Davies, 2011; Thelen, 1995). Beyond the second year, toddlers display more enhanced and integrated coordination of their limbs to support additional gross motor skills, like running and peddling a tricycle as well as fine motor skills, like turning a page one at a time and stacking small blocks (Davies, 2011; Haywood & Getchell, 2009). Thus, after the first six months of life when there are increases in strength, coordination and control of the limbs, motor behaviors become more goal-oriented as opposed to repetitive and rhythmic.

Developments in motor control are tightly linked to developments in sensory processing. For example, between birth and four weeks, infants develop the ability to track slowly moving objects and orient towards faces, and from four to six weeks old, infants begin making eye contact with others (AAP, 2015; Davies, 2011). These behaviors require both visual processing and the ability to control head movements. Later in development, motor behavior remains highly dependent on input from sensory processers, especially visual and proprioceptive feedback that specifies the location of objects and the body in space (Goble, Lewis, Hurvitz, & Brown, 2005; Von Hofsten, 1989). Movements are continuously adjusted both online and subsequent to their completion based on incoming sensory information regarding their accuracy. For example, when reaching for an object visual, proprioceptive, and tactile systems help guide initial motor commands and provide online information regarding the location and orientation of the body in space relative to the target object. This incoming sensory information subsequently is relayed to the motor systems to execute and refine the movement. Thus, the

development of motor and sensory systems is dependent on each other and the integration of motor and sensory information is critical for precision goal-directed motor behavior.

From this review of typical motor development, two important points should be highlighted. First, motor skills develop in a progressive fashion, such that the development of new skills is highly dependent on previously acquired skills, and this development is particularly rapid within the first year of life. Second, motor development does not occur in isolation. Rather, the maturation of motor abilities is highly inter-dependent on sensory and cognitive processes, including social, language, and executive abilities (Piek, Dawson, Smith, & Gasson, 2008; Shaheen, 2013). Thus, disturbances arising in one process may lead to downstream effects in other key developmental abilities.

Feedforward and Feedback Control of Motor Behavior

There exist multiple competing theories to explain basic principles of human movement, including dynamic systems theories (Smith & Thelen, 2003), equilibrium point theory (Latash, 2010) and optimal control theory (Diedrichsen, Shadmehr, & Ivry, 2010). Optimal control theory has been used to identify basic control mechanisms underlying human movement across development as well as determine the brain systems that are responsible for guiding distinct aspects of motor behavior. As such, this approach provides an important framework for studying and understanding patterns of motor deficit in ASD.

As described in the previous section, sensory and motor processes are continuously interacting to ensure that motor actions are accurately executed. In a relatively simple task, such as picking up a mug of coffee, these systems are working concurrently before, during, and after the motor action. First, sensory systems are responsible for receiving visual, tactile, and proprioceptive information regarding where the mug is on the table and where the hand is in space. These sensory inputs are integrated into a unified state estimate regarding task-relevant information, including the size of the mug, the distance of the mug from the hand, and the location of the arm and hand relative to the mug. Then, this state estimate is compared against the desired state (i.e., hand on mug) in order to generate a motor command that will

estimate the distance, speed, and direction that the body must move to pick up the mug of coffee. The transformation of the desired location into a motor command is completed using an *inverse model*, which also takes into account specific motor properties, like inertia and torque of the effectors (Atkeson, 1989; Kawato, 1999; Wolpert & Kawato, 1998). Once the motor command is generated, it is relayed to the appropriate effector(s) for execution (Wolpert & Ghahramani, 2000; Wolpert & Miall, 1996; Wolpert, Miall, & Kawato, 1998). Yet, because motor execution is not always completed with 100% accuracy, with errors arising in the state estimate (e.g., the mug is lighter than anticipated) or due to external perturbations, changes in the environment (e.g., the cup is moved), or inherent noise within the motor system, the motor system must dynamically adjust the outgoing command to ensure accuracy and reduce error. Two motor control processes are responsible for these dynamic adjustments: *feedforward* and *feedback* motor control.

Sensory feedback processing time (i.e., 80-200 ms; Keele & Posner, 1968) is often too slow to make initial corrective adjustments to ongoing movements, and thus the motor system must rely on alternative methods to make rapid adjustments. A copy of the motor command, known as the "efference copy", is generated prior to movement execution, which is used by a forward model to generate a prediction of the sensory consequences of the motor command, known as the corollary discharge (Guthrie, Porter, & Sparks, 1983; Ito, 1984). If the predicted sensory consequences, guided by the forward model, and actual sensory consequences are mismatched, the initial motor command will be re-calibrated via *feedforward* control to ensure accuracy of subsequent motor actions as part of motor learning. In contrast, *feedback* control relies on incoming sensory information to make corrective adjustments to ongoing movements (Todorov & Jordan, 2002; Wolpert & Kawato, 1998). Although *feedback* control is highly accurate because it updates the system with sensory information, it is at the expense of being inherently slow. After the sensory information is detected, it must be relayed to motor command centers to generate and then execute appropriate adjustments.

Both *feedback* and *feedforward* motor control mechanisms are necessary to dynamically guide and ensure the accuracy of ongoing movements. However, many movements, including rapid, ballistic eye movements, are completed too quickly to rely on *feedback* control for accuracy. Thus, forward models are critical for the accuracy of these movements. The accuracy of subsequent ballistic movements may incorporate sensory feedback regarding accuracy to update the initial forward model. In contrast, slower and more sustained movements, like the visual tracking of an object, use a combination of *feedforward* and *feedback* control to ensure movement accuracy.

Developmentally, *feedforward* and *feedback* control processes mature along different time scales. During infancy and early childhood (up to age seven years), *feedback* control is predominantly used to guide movements, whereas in later childhood and adolescence, *feedforward* strategies gradually become more prominent (van Roon, Caeyenberghs, Swinnen, & Smits-Engelsman, 2008). Voluntary motor actions involve the integration of these distinct systems. Motor disturbances, therefore, may arise as a result of any number of developmental dysfunctions involving the ability to process sensory input or use *feedback* or *feedforward* motor control mechanisms to guide goal-directed actions.

Motor Disturbances in Individuals with ASD

Evidence of Early Emerging Motor Impairments in ASD

Although ASD can be reliably diagnosed between 18-24 months, the mean age of diagnosis remains relatively high between 44-54 months (CDC, 2014; Shattuck et al., 2009). This is in sharp contrast to studies using retrospective video analysis that indicate the presence of motor abnormalities in infants who later receive an ASD diagnosis as early as three months old (Teitelbaum et al., 2004; Teitelbaum, et al., 1998). At 3- and 6-months of age, these infants demonstrated abnormalities in rolling over, sitting, crawling, and walking compared to typically developing infants. In similar studies using retrospective video analysis, infants who later received an ASD diagnosis demonstrated reduced movement (e.g., wiggling and squirming), greater head lag (i.e., indicative of difficulty controlling the head and neck), hypotonia, odd posturing, and repetitive movements during their first year of life (Adrien

et al., 1993; Flanagan, Landa, Bhat, & Bauman, 2012; Phagava et al., 2008). Retrospective parent-reports also have indicated that differences in motor development emerge prior to the second birthday in infants later receiving a diagnosis of ASD. Specifically, parents reported delays in infants' abilities to support their head without assistance, roll over, sit upright without support, prop up on their side, grasp objects, walk, and initiate movements (Chawarska, et al., 2007; Esposito & Venuti, 2008; Ozonoff et al., 2008). Similarly, studies of high-risk infants, or infants who have an older sibling diagnosed with ASD, have yielded similar conclusions regarding the presence of sensorimotor abnormalities within the first 12 months (Landa & Garrett-Mayer, 2006; Nickel, et al., 2013). Overall, these findings indicate that motor impairments often are present before social and communication symptoms (Zwaigenbaum, et al., 2005), and they may be important early indicators of ASD in infancy.

Furthermore, retrospective video analysis and chart review has identified hypotonia in infants and toddlers later diagnosed with ASD (Filipek et al., 1999; Ming, et al., 2007; Shetreat-Klein, Shinnar, & Rapin, 2014). Hypotonia refers to low muscle tone, or the amount of tension or resistance to stretch in a muscle, that may be caused by peripheral (e.g., muscle) or central (e.g., brain) mechanisms (Martin et al., 2005) and commonly results in poor reflexes, decreased strength, atypical posture, delayed and poor fine and gross motor skills, hyperflexibilty, and feeding and speech difficulties, all of which have been documented in ASD (Lisi & Cohn, 2011). This suggests that hypotonia may be an early symptom of ASD as well as a contributing factor to additional motor impairments in ASD.

In addition, several sensorimotor abnormalities that emerge within the first year of life are related to core deficits within the restricted, repetitive domain. For example, retrospective video analyses indicate that infants later diagnosed with ASD demonstrate abnormal posturing before 12 months (Baranek, 1999) and arm flapping and posturing between 12-18 months (Loh, et al., 2007). Additionally, sensory abnormalities, such as atypical visual orienting, reduced auditory responsiveness, increased mouthing of objects, and increased social touch aversions, have been documented in ASD as early as 7 months old (Baranek, 1999; Elison, et al., 2013; Ozonoff, et al., 2008; Zwaigenbaum, et al., 2005). These

sensory deficits may interact with abnormal development of motor abilities to disrupt the development of critical skills in infancy and provide foundations for the dysmaturation of more complex social and cognitive abilities.

Dyspraxia

Dyspraxia is the difficultly in the planning and execution of motor sequences, which cannot be accounted for by other primary motor or sensory impairments. *Feedforward* and *feedback* mechanisms are responsible for the accurate timing and sequencing of complex motor behavior (Exner & Henderson, 1995; May-Benson, 2004). Estimates of dyspraxia in ASD range from 34 to 75% (Ming, et al., 2007; Rapin, 1996). Numerous studies have documented that individuals with ASD have impairments in completing both simple and complex motor sequences (Dziuk, et al., 2007; Mostofsky et al., 2006; Rogers, 1996; Rogers, Hepburn, Stackhouse, & Wehner, 2003; Vanvuchelen, Roeyers, & De Weerdt, 2007a; Williams, Whiten, & Singh, 2004). Additional evidence of dyspraxia in ASD comes from studies demonstrating impaired motor learning (D'Cruz et al., 2009; Haswell, Izawa, Dowell, Mostofsky, & Shadmehr, 2009; Mosconi, et al., 2013) and motor imitation (for review see Williams, et al., 2004). Dziuk and colleagues (2007) compared performance on standardized measures of praxis and basic motor skills. Their findings indicate that after controlling for basic motor skills, individuals with ASD demonstrated abnormal praxis. Therefore, individuals with ASD demonstrate impairments in the planning and execution of motor sequences that cannot be better explained by basic motor skill deficits.

Postural Control

Postural control is supported by *feedforward* and *feedback* mechanisms via anticipatory adjustments and incoming sensory information from the visual, proprioceptive, somatosensory and vestibular systems (Drew, Prentice, & Schepens, 2004; Fitzpatrick & Day, 2004; Kennedy, Ross, & Brooks, 1982; Keshner & Cohen, 1989). The vestibular system is important for one's sense of balance and spatial orientation, and is necessary for postural control as well as coordinating more complex movements, like walking. The vestibular system is responsible for interpreting changes in the direction or

speed of movements so that corrective motor commands can be generated. It is located in the inner ear and is able to incorporate signals from visual, proprioceptive, and somatosensory systems as well as feedback from muscle spindles to ensure balance (Drew, et al., 2004; Fitzpatrick & Day, 2004; Horak & Nashner, 1986). Thus, impairments in postural control may result from dysfunction at any or all of these systems and their integration.

Early signs of vestibular impairment in ASD include abnormal posturing (Baranek, 1999), poor balance when sitting or rolling over (Teitelbaum, et al., 1998), poor stability when reaching (Bryson, et al., 2007), and lack of developmentally appropriate head holding and side propping (Bhat, Landa, & Galloway, 2011). In later development, vestibular impairments in ASD are reflected by poor static and dynamic balance (Baranek, 1999; Bhat, et al., 2011; Bryson, et al., 2007; Gepner, Mestre, Masson, & de Schonen, 1995; Ghaziuddin & Butler, 1998; Kohen-Raz, Volkmar, & Cohen, 1992; Minshew, et al., 2004; Molloy & Manning-Courtney, 2003; Noterdaeme, Mildenberger, Minow, & Amorosa, 2002; Whyatt & Craig, 2013; Whyatt & Craig, 2012). Thus, signs of vestibular system disturbances are present in infancy and persist into adulthood in ASD.

Visual, somatosensory, and proprioceptive systems also have been implicated during postural control studies of ASD. For example, reduced postural control while standing worsens when visual and/or somatosensory input is obstructed (Gepner, et al., 1995; Minshew, et al., 2004; Molloy & Manning-Courtney, 2003). This suggests individuals with ASD may be over-reliant on visual and somatosensory feedback information for postural stability, or they are less able to use proprioceptive feedback appropriately to ensure balance. In contrast, an earlier study reported improved postural stability relative to controls when visual information was obstructed (Kohen-Raz, et al., 1992). This, in turn, suggests that individuals with ASD may be over-reliant on proprioceptive information and less dependent on other sensory information. This hypothesis is supported by recent findings of over-reliance on proprioceptive information during sensory integration and motor learning tasks (Greenfield, Ropar, Smith, Carey, & Newport, 2015; Izawa et al., 2012b). However, in contrast to both these findings,

researchers recently suggested that motor memory impairments, rather than proprioceptive or sensory feedback deficits, contributed to reductions in accuracy in individuals with ASD when visual stimuli was removed during a precision grip force task (Neely et al., 2016). This suggests that in addition to disrupted integration of sensory and proprioceptive information higher-order processes, like memory, also may play a role in impaired motor control in ASD.

Further evidence of postural instability in individuals with ASD comes from studies assessing postural sway. Anterior-posterior postural sway observed in typically developing individuals is thought to help maintain balance, and decreases in amplitude and area as age increases (Chen, Metcalfe, Jeka, & Clark, 2007; Demura, Kitabayashi, & Uchiyama, 2006). However, children and young adults with ASD have demonstrated increased medial-lateral but reduced anterior-posterior postural sway compared to controls (Chang, Wade, Stoffregen, Hsu, & Pan, 2010; Cheldavi, Shakerian, Boshehri, & Zarghami, 2014; Kohen-Raz, et al., 1992; Memari et al., 2013; Memari, Ghanouni, Shayestehfar, & Ghaheri, 2014). Thus, medial-lateral sway may reflect a developmentally inappropriate strategy to improve balance and/or a compensatory mechanism to counter imbalances in anterior-posterior directions. The latter argument is supported by Nobile and colleagues (2011) who reported increased width of stance during standing. The authors hypothesized that increased stance width was an adaptive strategy used by patients to increase support in the medial-lateral directions as shown by patients with vestibular and cerebellar dysfunction (Baloh, Jacobson, Beykirch, & Honrubia, 1998; Solomon, Jacobs, Lomond, & Henry, 2015). Thus, postural control differences observed in ASD seem to reflect developmentally immature *feedforward* control systems responsible for maintaining posture as well as deficits in *feedback* systems responsible for generating compensatory strategies to improve stability.

Gross Motor Control

Gross motor skills consist of larger movements of the limbs, such as crawling, walking, jumping, and throwing and catching balls. Gross motor behaviors involve the coordination of multiple sensory and motor systems as well as limbs, and are highly dependent on postural control. Gross motor impairments

have been consistently documented in ASD (Jansiewicz et al., 2006; Kanner, 1943, as translated by Frith, 1991; Rinehart et al., 2006b; Vernazza-Martin, et al., 2005). Specifically, gait abnormalities have been demonstrated across the lifespan in individuals with ASD (Esposito & Venuti, 2008; Esposito, Venuti, Maestro, & Muratori, 2009; Hallett et al., 1993; Nobile, et al., 2011; Rinehart, et al., 2006b; Vernazza-Martin, et al., 2005; Vilensky, Damasio, & Maurer, 1981). Signs of gait abnormalities appear to be present within the first two years of life, as evidenced by retrospective video analyses showing asymmetry of gross motor movements during both infancy (e.g., prone lying, sitting, and crawling; Teitelbaum, et al., 2004; Teitelbaum, et al., 1998) and early childhood (Esposito & Venuti, 2008; e.g., walking; Esposito, Venuti, Apicella, & Muratori, 2011; for negative findings see Ozonoff, et al., 2008). However, later in development, gait seems to be less asymmetrical but still abnormal in ASD. Reduced stride length (Ambrosini, Courchesne, & Kaufman, 1998; Hallett, et al., 1993; Nobile, et al., 2011; Vernazza-Martin, et al., 2005; Weiss, 2009) and reduced walking velocity (Ambrosini, et al., 1998; Weiss, 2009) as well as increased step width (Nayate et al., 2012; Nobile, et al., 2011; Shetreat-Klein, et al., 2014), cadence (steps per minute; Calhoun, Longworth, & Chester, 2011) and increased time between steps (Vilensky, et al., 1981; Weiss, 2009) all have been reported in affected individuals. In addition, increased variability of gait kinematics has been documented in several studies (Nayate, et al., 2012; Nobile, et al., 2011; Rinehart et al., 2006a; Rinehart, et al., 2006b). For example, individuals with ASD demonstrate increased variability of stride length (Rinehart, et al., 2006a), walking velocity, and stride times (Rinehart, et al., 2006a). Thus, the uncoordinated and clumsy gait documented in initial descriptions of ASD may be a consequence of abnormal stride characteristics and increased gait variability in affected individuals. Overall, this suggests that disruption of multiple motor control processes, including *feedforward* and *feedback* motor control processes, may disrupt the development of gross motor behaviors in ASD.

Fine Motor Control

Fine motor skills involve the precise manipulation of objects with the fingers and thumb. They are used to perform tasks of daily living, such as using utensils, buttoning clothes, brushing teeth, and

handwriting. Individuals with ASD demonstrate fine motor skill delays (Bryson, et al., 2007; Flanagan, et al., 2012; Ozonoff, et al., 2008) and impairments (Freitag, 2007; Green, et al., 2002; Williams, Goldstein, & Minshew, 2006). Poor dexterity, reduced motor strength and speed, difficulty handling, reaching for, and grasping objects, poor handwriting, and deficits in fine motor planning all have been reported in ASD (Beversdorf et al., 2001; Freitag, 2007; Fuentes, Mostofsky, & Bastian, 2009; Ghaziuddin, 2008; Green, et al., 2002; Jasmin et al., 2009; Minshew, et al., 1997; Mostofsky, Burgess, & Gidley Larson, 2007; Provost, et al., 2007a; Vanvuchelen, Roeyers, & De Weerdt, 2007b; Williams, et al., 2006). In addition, increased left- or mixed-handedness has been reported in ASD (Preslar, Kushner, Marino, & Pearce, 2014; Soper et al., 1986), which supports findings of reduced and abnormal lateralization in affected individuals (D'Cruz, et al., 2009; Escalante-Mead, Minshew, & Sweeney, 2003; Hauck & Dewey, 2001; Lindell & Hudry, 2013). This implicates reduced specialization of the dominant hemisphere and/or atypical brain lateralization as a potential mechanism for fine motor skill impairment in ASD (Lindell & Hudry, 2013). Furthermore, disrupted *feedforward* and *feedback* mechanisms also may contribute to observed fine motor deficits in ASD. For example, the ability to feed oneself with a spoon requires a *forward* model of each motor step (e.g., pick up the utensil, get food on the utensil, move the utensil to one's mouth) as well as proprioceptive, visual, and tactile sensory *feedback* information regarding the progress of each motor behavior. Because hypotonia, reduced manual motor and grasping strength (Hardan, Kilpatrick, Keshavan, & Minshew, 2003; Williams, et al., 2006) and impaired visuo-motor integration (Jasmin, et al., 2009; Provost, et al., 2007b) also may be associated with fine motor impairments, it is unclear whether fine motor impairments can be solely accounted for by deficits in *feedforward* and *feedback* control or whether more diffuse disturbances underlie these motor impairments.

Prehension. Several studies of reaching and grasping, or prehension, have attempted to better identify underlying mechanisms of motor impairments in individuals with ASD. Prehension is an important motor skill that develops rapidly in infancy and is highly involved in the performance of daily

life skills (e.g., feeding, cleaning up toys) and creating learning opportunities through the exploration of the environment (Holstein, 1982). The abilities to reach and grasp are obtained hierarchically during development, with reaching developing first and then grasping, reflecting the successive development of postural and limb control (Davies, 2011; Holstein, 1982). Successful reaching and grasping requires both *feedforward* and *feedback* motor control (Gentilucci et al., 1991; Simoneau et al., 1999). Thus, sensory processes are particularly important during reaching and grasping as visual, proprioceptive, and tactile information regarding the distance, size, and spatial orientation of the body and object are needed to execute accurate and consistent reaching and grasping behaviors.

Glazebrook and colleagues (2006) reported increased temporal and spatial variability of arm reaching movements as well as reduced velocity, reduced peak acceleration, and increased latency to peak velocity of arm reaches in ASD subjects compared to controls. Consistent with these findings, Campione and colleagues (2016) also found increased latency to peak velocity during arm reaches in individuals with ASD. In addition, Mari and colleagues (2003) reported increased movement duration and deceleration time, increased time to maximum grip aperture (i.e., separation between thumb and finger), and reduced peak velocity during a reaching and grasping task in children with ASD. This suggests atypical upper limb movement kinematics in ASD, especially at the beginning of reaching movements, which may reflect impaired *feedforward* control. Individuals with ASD also demonstrate a reduced ability to modulate their reaching and grasping behavior according to changes in task demands. For example, children with ASD failed to modify their velocities to accommodate for the increased difficulty of the task (Fabbri-Destro, Cattaneo, Boria, & Rizzolatti, 2009) as well as their end-grasp positions based upon object orientation (Hughes, 1996) suggesting that forward models guiding the motor plan are abnormal in ASD. Therefore, studies of reaching and grasping in ASD suggest *feedforward* control deficits contribute to impaired fine and gross motor skills in ASD; however, because *feedback* mechanisms were not specifically probed in these studies, their contribution to impairments during prehension is less clear.

Precision Grip Force Control. Few studies of fine motor skills have been able to quantify the impairments in individuals with ASD with a high degree of temporal and spatial precision. However, two recent studies have been able to more precisely characterize manual motor impairments by assessing precision grip force. During this task, participants use their thumb and index finger to press against two opposing precision load cells in order to move a force line, presented on a monitor in front of them, upward towards a target line. Thus, as the load cells are pressed harder, the force line moves further upward. The task may vary according to the amount of force required to reach the target line or the integrity of visual feedback regarding participants' performance (i.e., visual gain).

During initial rapid force contractions, individuals with ASD demonstrated greater target overshoot and elevated rates of force increase compared to controls at the lowest force level only (i.e., 5% of their maximum voluntary contraction (MVC); Mosconi, et al., 2015a), suggesting alterations in *feedforward* control of initial force pulses. With lower force demands, motor control must be more precise and rely almost entirely on internally guided *feedforward* control since the time it takes to complete these smaller movements is faster, and thus does not allow for visual feedback regarding performance. Therefore, impaired rapid force contractions at lower force levels in ASD implicated disrupted *feedforward* mechanisms. Additionally, we found that during the sustained period of force contractions in which individuals attempted to maintain a constant level of force for 15 seconds (sec), increased force variability was observed in individuals with ASD compared to controls, especially at larger force levels (i.e., 45, 65, and 85% MVC). This suggests that when motor demands are increased, affected individuals demonstrate more severe disruptions in their ability to appropriately adjust their motor output based upon sensory input. Thus, findings of increased sustained variability implicated impaired *feedback* control in ASD. Notably, these two findings were not associated with each other in individuals with ASD, suggesting that *feedforward* and *feedback* deficits may be relatively independent and have discrete underlying impairments.

During conditions in which the integrity of visual feedback varied, individuals with ASD similarly demonstrated increased force variability of sustained force contractions, especially at the lowest and highest levels of visual gain (Mosconi, et al., 2015a). In other words, as visual feedback regarding performance was highly degraded or highly amplified, performance for individuals with ASD worsened, indicating a greater sensitivity to changes in visual feedback information during precision gripping. Additionally, individuals with ASD showed reduced complexity of their movements across sustained force contraction tasks, especially when higher levels of visual feedback were provided. This suggests that, compared to controls, patients use a less dynamic control strategy characterized by the use of fewer control processes to precisely and rapidly adjust force output.

In a similar study, Wang and colleagues (2014b) examined precision gripping in two tasks that varied the amplitude and duration of force contractions. They used a novel analysis approach to objectively differentiate initial gripping strategies. The authors found that whereas controls tended to change their motor control strategy based upon force level and force duration, individuals with ASD demonstrated reduced flexibility in the strategies they utilized to produce initial force contractions. Specifically, individuals with ASD consistently used a strategy characterized by rapid increases in force output that overshot the target, followed by relaxation of force. Healthy controls used a similar strategy when target force levels were low or when the duration of the trials was short. However, as the target force level or duration of trials were increased, controls shifted to a strategy in which their rate of force increase was more gradual and efficient, whereas individuals with ASD continued to use their strategy of overshooting the target. These results suggest failures in planning appropriate motor strategies according to changing task demands as well as the use of developmentally less appropriate motor strategies in ASD (van Roon, et al., 2008). Together, results from studies of precision gripping support previous findings of disrupted *feedforward* mechanisms during manual tasks as well as provide novel evidence for disrupted *feedback* mechanisms responsible for effectively using sensory feedback information to dynamically adjust manual motor output during sustained force contractions.

Oculomotor Control

Eye movements are uniquely well-suited for translational studies because of the reduced number of processes that affect them, including inertia that is less impacted by interacting torques, gravitational forces, and interacting joints relative to limb movements. Furthermore, the neural processes that control eye movements are better characterized, and the spatial and temporal dynamics of eye movements are more precisely quantifiable than those of more complex movements (Leigh, 2006). Multiple distinct types of eye movements have been studied in ASD. For example, visual fixation, smooth pursuit eye movements, and saccadic eye movements each appear to be abnormal in ASD (for review see Mosconi, Wang, Schmitt, Tsai, & Sweeney, 2015b).

Visual Fixation. Visual fixation is an active process used to maintain an image on the fovea so that a stationary object may be viewed. Studies of visual fixation in ASD suggest subtle impairments when visual feedback is disrupted (e.g., removal of target; Nowinski, Minshew, Luna, Takarae, & Sweeney, 2005; Shirama, Kanai, Kato, & Kashino, 2016) but relatively intact abilities when visual feedback is not disrupted (Aitkin, Santos, & Kowler, 2013; Nowinski, et al., 2005; Shirama, et al., 2016). These findings indicate that visual fixation systems are relatively spared in ASD, except when individuals attempt to foveate peripheral targets or remembered locations.

Pursuit Eye Movements. Pursuit eye movements track moving targets that have already been foveated, thus relying on visual motor processing and translating sensory information to motor commands (Rosano et al., 2002). Visual pursuit is dependent on both *feedforward* and *feedback* processes. Specifically, during the open-loop phase (i.e., the first 100ms after pursuit onset), *feedforward* control uses internally generated information about target motion and accuracy to guide the movement. In contrast, during the closed-loop phase (i.e., after 100 ms of pursuit), sustained pursuit relies on memory of target velocity, predictions about target motion, and visual information available to make online adjustments via *feedback* control.

Individuals with ASD demonstrate reduced pursuit gain (i.e., eye movement velocity:target velocity) during the open-loop (Takarae, et al., 2004a) and closed-loop phases of smooth pursuit. In addition, increases in the size (Aitkin, et al., 2013; Takarae, et al., 2004b) and number of catch-up saccades (Takarae, et al., 2007) have been observed in affected individuals. Furthermore, Takarae and colleagues (2004a) reported reduced pursuit gain during the closed-loop stage, especially in patients over 16 years old, suggesting atypical maturation of visual pursuit processes in ASD. Also, reductions in the visual gain of smooth pursuit and primary catch-up saccades were found during rightward but not leftward open-loop movements in ASD, suggesting lateralized deficits in *feedforward* control. Thus, visual pursuit abnormalities in ASD indicate both *feedforward* and *feedback* control deficits and dysmaturation, but suggest *feedforward* impairments may be lateralized.

Saccadic Eye Movements. Saccades are rapid ballistic eye movements used to shift gaze. They are commonly assessed using visually-guided saccade (VGS) paradigms in which a peripheral target appears to the left or right of central fixation. Because of the relative simplicity of this task and its ability to precisely quantify spatial and temporal characteristics of saccades, VGS tasks are highly translational across species and useful for identifying specific impairments. Due the ballistic nature of saccadic eye movements, visual feedback is not yet available to make corrective adjustments, and thus VGS studies also provide a useful approach for assessing *feedforward* motor control systems. Saccade accuracy, variability of accuracy, dynamics (e.g., velocity, duration), and, to a lesser degree, latency all appear to be abnormal in ASD (for review see Mosconi, et al., 2015b).

In the first VGS study of individuals with ASD, Rosenhall and colleagues (1988) showed a pattern of saccade hypometria (i.e., undershooting the target) and reduced saccade velocity suggesting disrupted *feedforward* control of eye movements in patients. Later studies replicated findings of hypometria (Luna, et al., 2007b; Takarae, et al., 2004b) and also documented increased variability of saccade accuracy involving both hypo- and hyper-metric movements in patients (Takarae, et al., 2004b). Subsequent studies have supported findings of saccade dysmetria and increased trial-wise variability in

saccade accuracy (Johnson, et al., 2012; Mosconi, et al., 2013; Schmitt, et al., 2014; Stanley-Cary, Rinehart, Tonge, White, & Fielding, 2011), and indicate that these deficits may be more pronounced at larger target amplitudes (Johnson, et al., 2012; Schmitt, et al., 2014). Additionally, several studies have documented that reductions in saccade accuracy and increases in trial-wise variability of saccade accuracy are less severe in patients with a history of language delay compared to patients without a history of language delay (Johnson, et al., 2012; Stanley-Cary, et al., 2011; Takarae, et al., 2004b), suggesting saccade impairments may co-segregate in patient samples based upon specific developmental patterns. More recently, several studies demonstrated that individuals with ASD show reduced rates of saccade learning (Johnson, Rinehart, White, Millist, & Fielding, 2013; Mosconi, et al., 2013) suggesting that *feedback* control mechanisms involved in adjusting forward control models in response to systematic sensory errors are altered in ASD. Overall, findings from saccades studies suggest that individuals with ASD have a reduced ability to update internal representations used for *feedforward* control of rapid eye movements.

Although Rosenhall's (1988) initial study reported reduced velocities of saccades in ASD, the majority of subsequent studies have failed to replicate this finding (Kemner, van der Geest, Verbaten, & van Engeland, 2004; Luna, et al., 2007b; Minshew, et al., 1999; Wilkes, Carson, Patel, Lewis, & White, 2015). In more recent studies, increased saccade duration (Schmitt, et al., 2014; Stanley-Cary, et al., 2011), reduced saccade peak velocity (Schmitt, et al., 2014), and increased time to accelerate saccades to peak velocity (Johnson, et al., 2012; Schmitt, et al., 2014) have been documented in individuals with ASD compared to controls. Several studies of reaching also have documented a profile of increased accuracy variability and atypical movement dynamics, suggesting common deficits across motor effectors (Campione, et al., 2016; Glazebrook, et al., 2006; Glazebrook, Gonzalez, Hansen, & Elliott, 2009). The authors hypothesized that affected individuals may compensate for their impaired *feedforward* control by slowing their reaching at the beginning of their movements in order to receive sensory information

regarding their performance that can be subsequently used for *feedback* control (Glazebrook, et al., 2006; 2009). It is possible that a similar compensatory strategy may be used during saccadic eye movements.

Although the majority of saccade studies have suggested there are no group differences in saccade latencies (Johnson, et al., 2012; Luna, et al., 2007b; Minshew, et al., 1999; Mosconi et al., 2009b; Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011; Takarae, et al., 2004b; for positive finding see Wilkes, et al., 2015), evidence of increased latency variability suggests potential alterations in the processes underlying movement initiation (Schmitt, et al., 2014; Stanley-Cary, et al., 2011). The Gap/Overlap paradigm, which varies the timing between the central fixation cue offset and target cue onset, has been used to examine attentional engagement on the basic motor behavior by manipulating attention-shifting processes. However, several groups argue that observed latency differences during overlap versus gap conditions are not due to attentional processes, and instead other oculomotor processes, including movement preparation and fixation disengagement (Fischer & Breitmeyer, 1987; Klein, Taylor, & Kingstone, 1995; Reuter-Lorenz, Hughes, & Fendrich, 1991). The use of Gap/Overlap paradigms in individuals with ASD has yielded inconsistent findings. Some studies have found shorter latencies during the Overlap, but not Gap condition in individuals with ASD compared to controls (Kawakubo et al., 2007; van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001), whereas others found increased saccade latencies in both trial types compared to controls (Goldberg et al., 2002), and others demonstrating no group differences (Mosconi, et al., 2009b; Schmitt, et al., 2014). Together, latency findings suggest attentional processes appear to be relatively unaffected in the context of motor control in ASD.

Lastly, Luna and colleagues (2007b) studied children 8 – 12 years old; adolescents, 13-17 years old; and adults, 18-33 years old in order to examine saccade disturbances in ASD from a developmental perspective. Their results revealed age-related differences in saccade performance such that reduced saccade accuracy was observed in children, but not adolescents or adults with ASD. This supports previous findings of unimpaired saccade accuracy in adolescents and adults with ASD (Kemner, et al.,

2004; Minshew, et al., 1999). Recently, Schmitt and colleagues (2014) found developmental reductions in saccade error and saccade error variability in both individuals with ASD and controls, but patients continued to show deficits across the lifespan. Thus, in contrast to previous studies, we found that saccade abnormalities do not normalize with age.

Overall, oculomotor studies suggest compromised *feedforward* and *feedback* motor control systems in ASD. *Feedforward* systems have been most prominently implicated, based upon findings from pursuit and saccadic eye movement studies. Thus, internal action representations guiding saccades generated by the *forward* model as well as the ability to precisely update this internal representation appear to be disrupted in ASD.

Motor Control, The Brain, and ASD

The Relationship between Sensorimotor Abnormalities and Core Symptoms of ASD

Despite the high prevalence and early emergence of motor disturbances in ASD, the relationship between motor disturbances and core symptoms of ASD remains poorly understood. Several studies have reported that worse dyspraxia on standardized measures is associated with more severe social-communication impairments and restricted, repetitive behaviors in individuals with ASD (Dowell, Mahone, & Mostofsky, 2009; Dziuk, et al., 2007; Freitag, 2007; Green, et al., 2009; Hilton, et al., 2007; Liu, et al., 2006; Whyatt & Craig, 2012). Additionally, Freitag and colleagues (2007) observed a link between poor coordination of manual movements as well as poor dynamic balance and more severe clinically-rated social abnormalities. Reduced balance and postural stability have been found to be associated with more severe restricted, repetitive behaviors and social-communication deficits as well as behavioral and emotional disturbances (Papadopoulos et al., 2012; Travers, Powell, Klinger, & Klinger, 2013). Other studies have demonstrated that early motor delays and impairments predict the degree of language delay (Gernsbacher, Sauer, Geye, Schweigert, & Goldsmith, 2008; Iverson & Wozniak, 2007) as well as the severity of clinical symptoms in individuals later diagnosed with ASD (Gernsbacher, et al., 2008). Also, a recent study (LeBarton & Iverson, 2016) demonstrated that early motor delay predicted

later language delays in infant siblings of ASD. This suggests that early motor symptoms may be indicative of later phenotypic expression and even an indicator of risk of development of ASD.

Notably, two precision grip force studies found that greater reductions in the accuracy of initial force contractions in individuals with ASD were associated with more severe social-communication abnormalities (Mosconi, et al., 2015a; Wang, et al., 2014b) and restricted, repetitive behaviors (Mosconi, et al., 2015a). Also, reductions in force irregularity were associated with more severe social-communication deficits (Mosconi, et al., 2015a). More recently, this same group demonstrated a relationship between more severe social-communication abnormalities and reduced sustained force accuracy in the absence of visual feedback, suggesting core diagnostic features also may be related to motor memory impairments in ASD (Neely, et al., 2016). Together, these findings indicate that individuals demonstrating more severe clinical features of ASD also demonstrate more impaired *feedforward* and *feedback* motor control deficits. However, it remains unclear whether common mechanisms underlie motor disturbances and core ASD deficits, or whether early emerging sensorimotor impairments may contribute to the dysmaturation of social, language, and cognitive systems in children with ASD.

From a developmental perspective, motor and higher-order skills, like social-communication, language, and cognition, and the brain regions responsible for them are highly inter-related and inter-connected. Infants predominately interact with their environment through physical means, via reaching and grasping, object manipulation, locomotion, and eye gaze. These motor skills are used to scaffold emerging social-communication and language skills during development. Maturation of associated brain regions proceeds in a similar hierarchical process with systems involved in fundamental sensory processing and movement abilities developing more rapidly than those supporting higher-level abilities.

Consistent with the hypothesis that sensorimotor abilities provide a critical foundation for the development of social-communication skills, several studies document a relationship between motor imitation deficits and language development in ASD (Mandelbaum et al., 2006; Rogers, et al., 2003).

Motor imitation plays an important role in the development of nonverbal (e.g., gestures) and verbal language (Whitehurst & Vasta, 1975; Zambrana, Ystrom, Schjolberg, & Pons, 2013). Thus, motor deficits may impair the ability to imitate others appropriately in order to develop language and other social-communication skills. Similarly, other groups have hypothesized that because motor skills are critical for interacting with the world, impaired motor abilities limit an individual's ability to appropriately engage with others and their environment (Bhat, et al., 2011; Iverson & Wozniak, 2007; Nickel, et al., 2013). For instance, Bhat and colleagues (2011) suggested that early motor impairments, such as poor head and arm motor coordination, reduce the infant's ability to respond to and initiate social overtures towards others, and that later motor impairments and delays in walking and motor planning reduce opportunities to directly interact and play with caregivers and peers. Additionally, a recent finding of the relationships between motor memory impairments and cognitive and social functioning in ASD (Neely, et al., 2016) suggests broader clinical implications of motor deficits, specifically indicating that a reduced ability to store and recall information may impact not only motor, but also developmental and cognitive abilities. Therefore, social development may be impeded by early emerging motor limitations in ASD.

In addition, other groups have argued from a more neurobiological perspective and hypothesized that pre- and peri-natal disruptions to motor brain regions, especially the cerebellum, have downstream effects on higher-order brain regions and associated functions (D'Mello & Stoodley, 2015; Rogers et al., 2013; Wang, Kloth, & Badura, 2014a). Wang and colleagues (2014a) proposed a developmental diaschesis model for ASD suggesting that dysfunction in the cerebellum affects the maturation of neocortical structures and circuitry. D'Mello and Stoodley (2015) similarly emphasized that because motor regions develop prior to structures involved in language and cognition, differences in these early developing brain regions likely impact the development of the neocortical brain regions to which they are connected. This is consistent with findings of positive correlations between early disturbance to cerebellar circuitry and ASD symptoms (Beversdorf et al., 2005; Courchesne, et al., 2001; Hashimoto, et

al., 1995; Limperopoulos et al., 2007) and cerebellar damage at birth being the highest non-genetic risk factor (risk ratio = 40) associated with ASD (Limperopoulos, et al., 2007). Because of our poor understanding of the mechanisms underlying motor impairments in ASD, the link between motor and core features in this disorder remains speculative. Thus, a better understanding of motor impairments in ASD is needed to identify disrupted pathways causing these impairments as well as core clinical symptoms.

Brain Circuitry Supporting Motor Control

At the lowest level, motor control involves motor neurons and interneurons of the spinal cord responsible for carrying sensory information from the skin and muscles to the cortex, and then carrying motor commands from the cortex to effectors (e.g., limbs). Brainstem neurons, especially within the reticular formation and vestibular nuclei, project to spinal cord neurons to control postural stability and locomotion. Cells within the pons of the brainstem fire based upon the velocity and duration of desired movements (Fuchs, Kaneko, & Scudder, 1985; Sparks, 2002). Thus, the brainstem is important not only for postural stability and walking, but also for movement dynamics. The cerebellum supports a variety of motor functions, including maintenance of balance and posture, coordination of voluntary movements, and motor learning. It is hypothesized to serve as the *forward* controller of both motor behavior and cognition (Ito, 1984, 2008; Miall & Reckess, 2002).

At a higher level, regions within the cerebral cortex play important roles in motor behavior, including the primary motor cortex (M1), premotor cortex, prefrontal cortex (PFC), supplementary area (SMA), pre-SMA and parietal cortex. M1 and premotor cortex are responsible for motor execution (Hepp-Raymond, 1988; Porter & Lemon, 1993), whereas PFC, SMA, and parietal cortices are responsible for motor planning (Kalaska, Scott, Cisek, & Sergio, 1997; Rizzolatti & Luppino, 2001; Wise, Boussaoud, Johnson, & Caminiti, 1997). Additionally, areas of the parietal and somatosensory cortices are necessary for integrating sensory information from distinct pathways and across modalities (Fogassi & Luppino, 2005). Motor planning also is supported by the basal ganglia, which is comprised of

numerous subcortical grey matter structures (e.g., caudate nucleus, putamen, globus pallidus, substrantia nigra), and its many interconnections with frontal, temporal, and parietal cortices as well as cerebellum. These cortico-striatal pathways also are responsible for the execution and inhibition of motor behaviors, via functionally and anatomically distinct direct and indirect pathways (Alexander, Crutcher, & DeLong, 1990; DeLong & Strick, 1974). Selective pathways involving brainstem, cerebellum, basal ganglia, and neocortical areas are dedicated to supporting precision gripping and saccadic eye movements. Circuits dedicated to supporting *feedforward* and *feedback* motor control processes also appear to be segregated within manual and oculomotor effector systems.

Cerebellar Involvement in Motor Control

The cerebellum has well-established roles in motor control, coordination, and learning (Ito, 1984; Kawato et al., 2003; Thach, Goodkin, & Keating, 1992). In particular, the cerebellum has been suggested to be involved in *feedforward* and *feedback* control of motor behavior (Ito, 2008; Wolpert & Kawato, 1998). The highly invariant cellular architecture of the cerebellum consists of two main inputs to the cerebellar cortex, climbing fibers and mossy fibers, and the sole output of the cortex—Purkinje cells. Mossy fibers receive their inputs from cortical areas via the brainstem, particularly the pontine nuclei, which are then relayed to granular cells and then to parallel fibers, which synapse with Purkinje cells (Eccles, 1967; Geborek, Bengtsson, & Jorntell, 2014; Ramnani, 2006; Vogel, Ji, Millen, & Joyner, 1996). Climbing fibers originating from the inferior olive of the medulla oblongata form the other input to the cerebellar cortex innervating Purkinje cells via the inferior cerebellar peduncle. Signals sent from climbing fibers to the Purkinje cells are involved in long-term depression (LTD), or the process in which the cerebellum modifies *forward* internal models (Wolpert & Kawato, 1998). During LTD, parallel fiber-Purkinje cell synapses are selectively pruned to change the strength of inhibitory output from the Purkinje cells to deep nuclei (Nguyen-Vu et al., 2013). Like somatosensory maps of the cortex, the cerebellum is highly organized according to movement type and the effector being controlled (for review see Manni & Petrosini, 2004). For example, saccadic eye movements are controlled by a specific region known as the

oculomotor vermis, which includes posterior lobules VI-VII and Crus I-II of the ansiform lobule (Alahyane et al., 2008; Panouilleres et al., 2012; Takagi, et al., 1998). Crus I-II, the flocculus, and the paraflocculus are involved in gaze fixation and pursuit eye movements (Baier, Stoeter, & Dieterich, 2009; Hashimoto, et al., 1995; Robinson, Straube, & Fuchs, 1993). In contrast, upper limb movements are controlled by anterior lobules I-V as well as lateral lobules V-VII and medial regions of Crus I-II (Kuper et al., 2012; Maderwald et al., 2012; Stefanescu et al., 2013; Thach, et al., 1992). The medial vermis and intermediate cerebellum are involved in the control of balance and gait (Brooks & Thach, 1981; Sullivan, Rose, & Pfefferbaum, 2010; Vassar & Rose, 2014). Thus, the high degree of functional specialization of the cerebellum suggests that parsing distinct patterns of sensorimotor deficits in ASD may provide important insights into the distinct brain pathways that are compromised in ASD.

Feedforward and Feedback Control Brain Systems

Feedforward and *feedback* motor control processes are mediated by overlapping yet distinct brain systems (Desmurget & Grafton, 2000; Ghez, et al., 1991; Golla et al., 2008; Takagi, et al., 1998; Vaillancourt, Mayka, & Corcos, 2006; Vaillancourt, Thulborn, & Corcos, 2003; Vilis & Hore, 1981). Feedback control systems involve striate and extrastriate cortices that relay visuospatial information regarding target location from to parietal and frontal cortices in order to guide motor commands sent to brainstem nuclei and then the spinal cord (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998). An efference copy of this motor command is sent to the cerebellum to compare the predicted motor behavior to the actual motor behavior (Wolpert et al., 1998). When the action repeatedly deviates from the expected outcome, the cerebellum's internal action representation can be refined to reduce error in subsequent motor actions via *feedforward* control (Bruno & Simons, 2002; Herzfeld & Shadmehr, 2014; Izawa, et al., 2012b).

Feedback systems also control for error but only after receiving sensory information regarding the initial motor output and subsequently creating new motor commands to make appropriate adjustments (Desmurget & Grafton, 2000; Slifkin, Vaillancourt, & Newell, 2000; Sosnoff & Newell, 2005). During

feedback control, some movement error can be corrected online by the cerebellum via input into the brainstem and within the posterior cerebellar lobules. Specifically, visual information is encoded in striate cortices, transferred to parietal cortices, and then sent to posterior cerebellum (Chen-Harris, et al., 2008; Kawato, et al., 1987; Stein, 1986) in order to transform the sensory information into new motor commands, which are then relayed to primary motor cortex (Vaillancourt, et al., 2003). Online correction of movement error typically occurs during the latter part of the movement due to the inherent time delay in the system (Robinson, et al., 1993). The cerebellum in particular is essential for both the precision and consistency of motor behaviors. Further, recent evidence suggests that cerebellar lobular organization extends to *feedforward* and *feedback* control. For instance, anterior lobules I-V are thought to be responsible for *feedforward* control, whereas more posterior regions, including lobules VI-IX, may play a more prominent role in *feedback control* (Neely, Coombes, Planetta, & Vaillancourt, 2013a). Thus, it may be possible to isolate disrupted circuits based upon profiles of motor disturbances in ASD.

Brain Systems Supporting Precision Grip Force Control

Fronto-parietal networks project to the cerebellar cortex and deep nuclei to support manual motor force generation. Cerebellar sub-regions specifically dedicated to modulating different grip force parameters (e.g., the rate of force increase, the amplitude of force increase) have been postulated. For example, activity levels of superior and medial cerebellar regions scale with force amplitude during precision gripping, whereas activity in inferior and lateral cerebellar regions is associated with the rate at which grip force is increased (Spraker et al., 2012). In addition, cortical and subcortical regions involved in grip force are specialized for rapid versus sustained force contractions. During rapid force contractions, which rely predominantly on *feedforward* control, M1 and anterior cerebellum as well as left-lateralized SMA, superior parietal lobe, fusiform gyrus, and visual area V3 are more strongly activated compared to sustained force. In contrast, cortical motor regions and the posterior cerebellum as well as right-lateralized inferior parietal lobe, ventral premotor cortex, and dorsolateral prefrontal cortex are more strongly involved in supporting sustained precision gripping guided by visual feedback

processes (Neely, et al., 2013a). This suggests that cortico-cerebellar loops responsible for precision gripping are highly specialized based upon the movement type and level of *feedforward* and *feedback* control that is involved.

Brain Systems Supporting Saccadic Eye Movement Control

The cortical-ponto-cerebellar circuits responsible for saccadic eye movements have been well-characterized due to the highly translational nature of eye movements. The initiation of saccades relies on the tonic inhibition of pontine burst cells and the simultaneous release of omnipause cells as well as excitatory signals from the superior colliculus (Leigh, 2006; Sparks, 2002). The firing rates of pontine burst neurons help control saccade dynamics including peak velocity, duration, acceleration, and deceleration (Fuchs, et al., 1985). Firing rates also control the amplitude and accuracy of movements via their interaction with cerebellar output (Luschei & Fuchs, 1972; Van Gisbergen, Robinson, & Gielen, 1981; Yoshida, Iwamoto, Chimoto, & Shimazu, 1999). Saccade accuracy and the consistency of saccade accuracy are primarily dependent on *feedforward* and *feedback* mechanisms under the control of the cerebellum (Barash et al., 1999; Ritchie, 1976; Sato & Noda, 1992). Lastly, fronto-striatal circuits help mediate saccade latency and prefrontal regions help facilitate saccade planning and execution (for review see Leigh, 2006).

Brain Systems Supporting Motor Control in ASD

Post-mortem Studies

In post-mortem studies, 35-95% fewer cerebellar Purkinje cells have been reported in the brains of individuals with ASD compared to control brains (Arin, 1991; Bailey, et al., 1998b; Bauman & Kemper, 1985b; Ritvo et al., 1986a; Skefos et al., 2014; Wegiel et al., 2014b; Whitney, et al., 2008b) and remaining Purkinje cells appear to be reduced in size by approximately 24% (Fatemi et al., 2012). Kemper and Bauman's group have documented reduced Purkinje cell number and size in vermal lobules in ASD, but to a lesser degree than lateral regions (Arin, 1991; Bauman & Kemper, 1985b). In addition, reduced deep cerebellar nuclei (Bauman, 1991) and fastigial nuclei cell numbers (Bauman, 1991; Rodier,

2002) have been documented in post-mortem studies of individuals with ASD. These findings are important in light of evidence suggesting lateral cerebellar hemispheres are not only involved in motor coordination and planning, but also higher-order cognitive behaviors, whereas the vermis is particularly important for balance, gait, coordination of eye movements, and even emotional processing, all of which are impaired in ASD (Schmahmann, 2004; Stoodley & Schmahmann, 2009). This suggests cognitive and social impairments in ASD also may stem from cerebellar abnormalities.

Importantly, post-mortem findings also implicate brainstem regions. Rodier and colleagues (1996) reported shortened brainstem projections and absent superior olivary climbing fibers in their ASD sample. Additionally, post-mortem studies have documented malformation of the inferior olive in ASD (Bailey, et al., 1998b; Bauman & Kemper, 1985b; for negative findings see Blatt, 2012). The brainstem is of particular importance because of its projections to the cerebellum and involvement in motor initiation, dynamics, and even accuracy (Luschei & Fuchs, 1972; Van Gisbergen, et al., 1981; Yoshida, et al., 1999).

A few post-mortem studies also implicate cortical and sub-cortical brain regions involved in motor control. For example, Casanova and colleagues (2002) documented increased density of neurons within the prefrontal and visual association cortices of brain samples from individuals with ASD and narrower and more dense minicolumns (vertical column through cortical layer of brain comprised of ~100 neurons) in the primary sensory, motor, and visual areas as well as the dorsolateral prefrontal areas of the frontal cortex (Casanova et al., 2006). These results suggest that neuronal density may be abnormal in ASD and may contribute to findings of aberrant neural circuitry (Casanova & Trippe, 2009). However, others studies have found no group differences (Bailey, 1993; Coleman & Blass, 1985), suggesting variability in neuronal density across the ASD sample.

Brain Imaging Studies

Hypoplasia of vermal lobules VI-VII has been repeatedly reported in MRI studies of ASD (Courchesne, et al., 1988; Hashimoto, et al., 1995; Kaufmann et al., 2003b; Schaefer et al., 1996; Webb et

al., 2009). Yet, several groups have reported typical vermis size (Hardan, Minshew, Harenski, & Keshavan, 2001; Hazlett, et al., 2005; Herbert et al., 2003; Holttum, Minshew, Sanders, & Phillips, 1992; Kleiman, Neff, & Rosman, 1992; Manes et al., 1999; Piven, Saliba, Bailey, & Arndt, 1997b). Inconsistent findings may be due to smaller sample sizes, differences in approaches for matching control groups, methodological differences in the collection and analysis of imaging data, and heterogeneity within this population. Interestingly, Courchesne and colleagues (1988) reported hypoplasia of vermal lobules VI-VII in 77% of their participants with ASD, with no evidence of hyperplasia in the remaining patients. Yet, in their later study, the authors documented hypoplasia of vermal lobules VI-VII in 86% of ASD patients, and hyperplasia in 12% of ASD patients (Courchesne, et al., 1994). These results suggest that previous negative findings of size differences may be a result of variability in the nature of cerebellar defects across patients. The authors' findings indicate a heterogeneous presentation of vermal lobules VI-VII size in ASD, with reduced size being the most consistent feature.

In addition, reduced size of vermal lobules VIII-X (Hashimoto, et al., 1993; Rojas et al., 2006; Schaefer, et al., 1996), pons (Ciesielski, Harris, Hart, & Pabst, 1997; Gaffney, et al., 1988; Hashimoto, et al., 1993; Hashimoto, et al., 1995) and midbrain (Hashimoto, et al., 1993; Hashimoto, et al., 1995) as well as reduced cerebellar white and grey matter volumes (Courchesne, et al., 2001; Hallahan et al., 2009; McAlonan et al., 2005) have been reported in ASD. Importantly, reduced integrity of cerebellar and cerebro-cerebellar tracts have been implicated in diffusion tensor imaging studies, suggesting that in addition to cerebellar abnormalities, connections from the cerebellum to cortical and subcortical brain regions also are disrupted, which may contribute to deficits integrating sensory information and controlling outgoing movement commands (Catani et al., 2008; Shukla, et al., 2010; Travers, et al., 2013).

Anatomical and post-mortem studies each implicate the cerebellum in ASD, but differences across these two types of study are notable. Whereas the majority of neuroimaging studies suggest more medial vermal abnormalities, post-mortem studies more consistently identified Purkinje cell loss within lateral hemispheres. One factor that may account for these differences is that participants in post-mortem

and *in vivo* imaging studies may differ on important clinical characteristics. For example, brain tissue used for post-mortem studies often has been acquired from more severe cases of ASD who had a history of seizure disorder. In contrast, neuroimaging studies typically have excluded individuals with seizure histories and often have included only individuals without intellectual disability. Thus, differences in regional findings from post-mortem and neuroimaging studies may arise from differences in sample characteristics.

Cortical and sub-cortical motor areas also have been implicated in brain imaging studies of ASD. For example, enlargement of the caudate nucleus has been repeatedly documented in ASD (Haznedar et al., 2006; Hollander, et al., 2005; Rojas, et al., 2006; Sears, et al., 1999; but see Hardan et al., 2003 for discrepant results) and has been found to be associated with repetitive motor behaviors (Hazlett, et al., 2005; Hollander, et al., 2005; Rojas, et al., 2006; Sears, et al., 1999). In addition, several studies have found that individuals with ASD have reduced size of frontal (Carper & Courchesne, 2005; Courchesne, Press, & Yeung-Courchesne, 1993) and parietal cortices (Courchesne, et al., 1993) as well as the thalamus (Tsatsanis et al., 2003) compared to controls. Thus, individuals with ASD demonstrate abnormal volumes of cortical and sub-cortical brain regions involved in *feedforward* and *feedback* motor control.

Functional imaging studies of individuals with ASD have demonstrated differences in activity of cortical, sub-cortical, and posterior fossa brain regions involved in motor control. In a functional MRI (fMRI) VGS task, ASD patients demonstrated reduced activation in regions typically involved in saccadic movements including frontal, supplementary, and parietal eye fields as well as cerebellar hemispheres (Takarae, et al., 2007). Yet, ASD patients demonstrated increased activation in regions typically associated with higher-order cognitive functions, including dorsolateral prefrontal cortex, caudate, thalamus, and dendate nucleus of the cerebellum—the primary output to the association cortex. These findings suggest that individuals with ASD may compensate for compromised motor systems by recruiting regions typically dedicated to higher cognitive processes during basic motor functions. Similar patterns of reduced activation of motor networks and increased activation of cognitive networks have

been documented in fMRI studies of manual motor control in ASD (Mostofsky et al., 2009; Muller, Pierce, Ambrose, Allen, & Courchesne, 2001).

These findings are consistent with the "crowding effect" (Teuber, 1974) hypothesis of ASD (Allen, Muller, & Courchesne, 2004), which posits that brain regions that are relatively less compromised take over the functions of regions that are more compromised. More specifically, because lower-level structures, like the brainstem and cerebellum, are impaired in ASD (i.e., as a result of abnormal Purkinje cell development), higher-order structures must be recruited to help perform basic sensorimotor functions (Allen, et al., 2004). However, because higher-level brain systems are being recruited to carry out lower-level functions, they are no longer able to available to control the execution of higher-level skills for which they are dedicated in healthy individuals (e.g., executive and social-communication functioning). Longitudinal fMRI studies across development are needed to test this hypothesis and clarify the maturational processes involved in abnormal brain developments in ASD.

Motor Impairments as Biological Intermediate Phenotypes

Few biomarkers of ASD exist, and even fewer, if any, meet Gould and Gottesman's (2006) definition of intermediate phenotypes. The brain mechanisms subserving precision gripping and saccadic eye movements have been well-characterized and are implicated in ASD, and thus their study in family members to determine their utility as biological intermediate phenotypes associated with ASD is warranted. By better characterizing saccadic eye movement and precision gripping deficits in individuals with ASD, we may gain a better understanding of the pathophysiological mechanisms underlying sensorimotor disturbances in this disorder.

As Gould and Gottesman (2006) identified, an effective intermediate phenotype is one that is quantifiable, measurable, and reflective of biological processes. Precision gripping and saccade impairments match each of these criteria. In addition, intermediate phenotypes should be heritable, co-segregate within families of affected individuals, and be present in unaffected relatives. Previous findings of saccadic eye movements suggest eye movement impairments may be familial in ASD. Mosconi and

colleagues (2010) reported that in a sample of unaffected first-degree relatives of individuals with ASD (e.g., parents, siblings), family members demonstrated a profile of *feedforward* and *feedback* eye movement deficits similar to those shown by individuals with ASD. Specifically, unaffected first-degree relatives demonstrated reduced saccade accuracy and increased variability of saccade accuracy (especially at larger target amplitudes) as well as reduced rightward open-loop and bilateral closed-loop pursuit gain (Mosconi, et al., 2010). Importantly, Mosconi and colleagues (2010) indicated that the severity of impairments in *feedforward* and *feedback* motor control were not associated with each other among family members, suggesting that different forms of motor deficits may co-segregate in different families.

Family studies may be a useful approach for determining intermediate phenotypes associated with ASD. Family studies have demonstrated that parents of individuals with ASD show a pattern of personality characteristics, social-communication skills, and language and speech profiles similar to those of individuals with ASD, suggesting that core symptoms of the disorder may manifest in sub-clinical forms in unaffected relatives. These sub-clinical features of ASD are collectively referred to as the "broad autism phenotype", or BAP (Murphy et al., 2000; Pickles et al., 2000; Piven, 2001; Piven, Palmer, Jacobi, Childress, & Arndt, 1997a; Piven et al., 1994). Importantly from these studies, it also was found that parents of multiple children with ASD demonstrate more BAP features compared to parents of only one child with ASD. And, in families with multiple children with ASD, both parents more frequently demonstrate BAP features than families with one child with ASD (Piven & Palmer, 1999), suggesting differential expression of BAP features across families with putative differences in the genetic processes involved in their child/ren's ASD. These findings highlight the importance of studying parents of individuals with ASD as they often share characteristic features of the disorder, albeit more subtly, and thus can provide critical insight into potential pathways and mechanisms of transmission in ASD. Still, the complex brain systems that support personality, social and pragmatic communication development and thus are implicated by family studies of the BAP remain unclear. In contrast, prior studies of sensorimotor alterations in unaffected relatives used relatively simple and translational paradigms that

provided important insight into possible pathophysiological processes, including dysfunctions of cortical-cerebellar and cortico-striatal brain systems. The extent to which different types of motor behaviors are affected in parents of individuals with ASD has not been examined. Additionally, previous motor studies of family members of individuals with ASD have been limited because they primarily assessed female family members and they did not include probands with ASD (Mosconi, et al., 2010), and thus familiality could not be determined.

The proposed study aims to assess family trios (individual with ASD, biological mother, biological father) performing tasks of saccadic eye movements and precision gripping. This is the first known project to examine the interrelationship of sensorimotor dysfunctions across family trios and across different motor effector systems. Although underlying mechanisms supporting oculomotor and manual motor behaviors are overlapping, they also are largely distinct. By studying family trios, we will be able to precisely quantify *feedforward* and *feedback* control of ocular and manual motor abilities in ASD and determine whether motor impairments are present across effectors and control mechanisms, suggesting more generalized motor disturbance and dysfunction of motor processes, or whether motor impairments are more prominent in one effector and/or control mechanism, suggesting more isolated impairments. To the extent that distinct biological intermediate phenotypes co-segregate in different families, this type of study design may be leveraged to identify distinct pathophysiological mechanisms and help resolve heterogeneity in ASD.

AIMS AND HYPOTHESES

Motor impairments are common among individuals with ASD, and they are among the earliest emerging symptoms in affected infants. While motor impairments are supported by brain systems known to be disrupted in ASD, the motor control processes and brain mechanisms underlying these deficits remain unclear. Our previous family study suggests that eye movement deficits in unaffected relatives of individuals with ASD may be familial, but the extent to which they are related among family members has not been tested. Based on these findings, we aim to test the central hypotheses that saccadic eye

movements and precision grip force are impaired in ASD, and these impairments are familial. These hypotheses will be tested through the following Specific Aims:

Aim 1: Characterize eye movement and precision grip force deficits in ASD.

Hypothesis 1: Based upon previous findings, we hypothesized that saccades will be less accurate and more variable in their accuracy in individuals with ASD compared to healthy controls implicating *feedforward* control systems.

Hypothesis 2: Based upon previous findings, we hypothesized that individuals with ASD will demonstrate reduced accuracy in their initial grip force pulses consistent with deficits in *feedforward* motor control. We also predicted that individuals with ASD will show increased variability in their sustained precision gripping suggesting that *feedback* motor control is disrupted.

Hypothesis 3: We determined the extent to which *feedforward* and *feedback* control deficits are associated with one another in individuals with ASD. Based on our prior findings suggesting that *feedforward* and *feedback* impairments are independent in patients, we predicted that *feedforward* and *feedback* deficits will not be associated with one another in individuals with ASD.

Aim 2: Characterize the familiality of eye movement and precision grip force deficits in ASD.

Hypothesis 1: Based upon previous findings, we hypothesized that unaffected biological parents of individuals with ASD will demonstrate saccade and grip force deficits similar to those observed in individuals with ASD.

Hypothesis 2: We predicted that saccade and force deficits will correlate among individuals with ASD (probands) and their parents, indicating that they are familial. We further examined the extent to which deficits co-vary in mother-proband versus father-proband dyads.

Hypothesis 3: Based on findings that *feedforward* motor control impairments were not associated with *feedback* control motor impairments in family members or individuals with ASD, we hypothesized that these deficits will be independent from one another in parents of individuals with ASD.

Aim 3: Characterize the relationships between sensorimotor abnormalities and clinical and sub-clinical features of ASD.

Hypothesis 1: We determined the extent to which saccade and precision force deficits are related to core social-communication and behavioral features of the disorder. The relationship between sensorimotor abnormalities and sub-clinical autism phenotypic features also were examined in unaffected parents.

CHAPTER THREE
Methodology

PARTICIPANTS

Forty family trios (individual with ASD, biological mother, biological father) and 88 healthy controls (38 matched to individuals with ASD, 50 matched to parents) completed assessments of sensorimotor and cognitive functioning. An additional fourteen individuals with ASD completed testing, but only had one biological parent that completed testing thus a total of 106 parents of individuals with ASD were included in the study (Table 1). No participants had a previous head injury resulting in loss of consciousness, took any medications known to affect sensorimotor function including stimulants, anticonvulsants, or antipsychotics (Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008), consumed caffeine within 24 hours of testing, used nicotine within one hour prior to testing, or had corrected far visual acuity of less than 20/40. Adult participants provided written consent and minors provided assent in addition to written consent from their legal guardian. This study was approved by the Institutional Review Board of the UT Southwestern Medical Center. All participants received compensation for their time.

Participants who were 6 years or older completed the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999; ASD = 48, Parent = 105, Control = 83) to assess intellectual abilities. Participants under the age of 6 years old or those under 8 years old suspected of having cognitive delays completed the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV; Wechsler, 2012; ASD = 2, Control = 3) or the Differential Ability Scales, Second Edition (DAS-II; Elliot, 2006; ASD = 3). One individual with ASD was unable to complete the WASI due to anxiety, which prohibited him from responding to questions. One mother of an individual with ASD and two adult male controls were not able to complete intelligence testing due to limited English proficiency. One adult male control did not complete IQ testing because he had recently completed the WASI as part of a separate evaluation. Individuals with a nonverbal-scale IQ score $\leq$ 70 were not included in this sample.

Participants with ASD

Fifty-four participants with ASD, henceforth referred to as probands, between the ages of 5-22 years old were recruited through local outpatient clinics, advertisements posted within the community, and community events. Probands scoring ≥ 15 on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003a) were asked to participate in the study. A diagnosis of ASD as defined by the DSM 5 (APA, 2013) was confirmed using the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003b), the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012b) and by expert clinical opinion. Probands were excluded if they had a known genetic disorder associated with ASD (e.g., Fragile-X syndrome, tuberous sclerosis), or they had a medical history of non-febrile seizures. Individuals with ASD who only had one biological parent available for participation at the time of recruitment were excluded from the study. Forty probands had mother-father dyads who completed testing, and 14 had only one parent complete testing. Four participants with ASD had taken medication within 48 hours of testing. Of these 4 individuals, 3 were taking antidepressant medications, including Zoloft, Viibryd, or Lexapro. Two of these probands also were taking the anti-hypertensive Intuniv. One additional proband was taking the anti-hypertensive Tenex.

Biological Parents of Individuals with ASD

One-hundred six biological parents (henceforth referred to as "ASD parents", "ASD fathers", or "ASD mothers") completed all testing procedures (Table 1). Parents were included if they had a child with a diagnosis of ASD, were medically healthy, had no known major psychiatric disorder (e.g., bipolar disorder), and were under the age of 55 years. The upper age limit was chosen in order to minimize variable effects of age-related declines in motor performance. Parents also completed the SCQ, and those who scored ≥ 8 (n = 12) met with a clinician to review answers and determine the need for diagnostic assessment for ASD. Two of these twelve parents completed the ADOS to determine whether they met criteria for ASD, but neither of these two parents met criteria for ASD. With regard to medication use, three fathers and three mothers of individuals with ASD had taken medication within 48 hours of testing. Three fathers had taken an anti-hypertensive, including either Lisinoprol or Propranolol. One father also

had taken a stimulant, Adderall. Two mothers had taken an antidepressant, including either Effexor or Wellbutrin. The mother taking Effexor also took an anxiolytic, Ambien, and an additional mother had taken an anti-hypertensive, Lisinoprol.

Healthy Controls Matched Separately to Probands and Biological Parents

Healthy controls were recruited from the community through flyers and online advertisements. Thirty-eight controls were matched to the proband group on age, handedness, and nonverbal IQ (Table 1; henceforth known as "ASD Controls"). Fifty controls (22 male, 28 female) were matched to the parent group of their same sex on age, handedness and IQ (henceforth known as "Parent Controls", "Father Controls" and "Mother Controls"). All controls completed the SCQ as well as a brief screener to determine eligibility based upon their medical and psychiatric history. Healthy controls were excluded if they reported a personal history of psychiatric illness, had a first-degree relative with a major psychiatric illness (e.g., schizophrenia), had a first- or second-degree relative with ASD, or were suspected of having ASD based on a failed SCQ (score $\geq$ 8) and meeting classification criteria on the ADOS-2. One father control had taken an anti-hypertensive, Lisinoprol, 48 hours prior to testing.

PROCEDURES

Testing Environment

Manual Motor Testing (Precision Gripping Tasks)

For manual motor testing, participants were tested in a darkened black room and seated 53 cm from a 27-inch monitor with a resolution of 1920 × 1080 and a 120 Hz refresh rate. They sat with their elbow at 90 degree (deg) and their forearm resting in a relaxed position on a custom-made arm brace (Figure 1A). The arm brace was clamped to a table in order to keep the participant's arms stable throughout testing. Participants' hands were pronated and laid flat with the

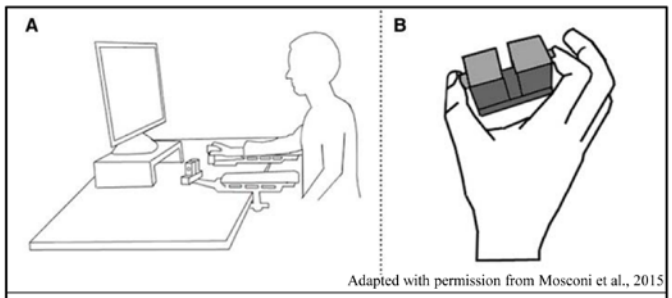

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Figure 1. Manual Motor Testing Set-Up. (A) Schematic of the experimental set-up for both precision grip force tasks. (B) Schematic of participant pressing on opposing load seeing with their index finger and thumb.

digits comfortably extended. They used their thumb and index fingers to press against two opposing ELFF-B4 precision load cells 1.27 cm in diameter (Measurement Specialties; Hampton, VA) secured to a custom grip device (Figure 1B). Analog signals from the load cells were amplified through a Coulbourn (V72-25; Allentown, PA) resistive bridge strain amplifier. A 16-bit A/D converter was used to sample the force output at 120 Hz. Data were converted to Newtons (N) of force using a calibration factor derived from known weights before the study. The system could detect forces down to 0.0016 N. Stimuli were presented using Presentation Software (NeuroBehavioral Systems; Albany, CA).

Ocular Motor Testing (Visually-Guided Saccade Tasks)

During eye movement testing, participants were seated in a darkened black room and positioned in a chin-rest to minimize head movement (Figure 2A). They were seated 61 cm from a 40-inch anti-glare LCD screen monitor with a resolution of 1920 x 1080 and a 60 Hz refresh rate. Visual stimuli included white dots presented against a black background (Figure 2B). Stimuli subtended 0.5 deg of visual angle and were presented on a horizontal plane at eye level using Presentation Software (NeuroBehavioral Systems; Albany, CA). A Dell Precision PWS490 computer (Intel Xeon CPU, 2.00 GB of RAM) with a processing speed of 2.33 GHz controlled the timing of the events while a second Dell Precision PWS390 computer (Intel Core2 CPU, 1.00GB of RAM) with a processing speed of 1.86 GHz registered eye movement data and recorded response time via an Ethernet connection.

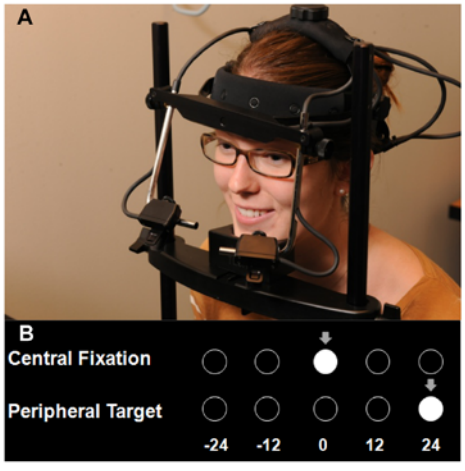


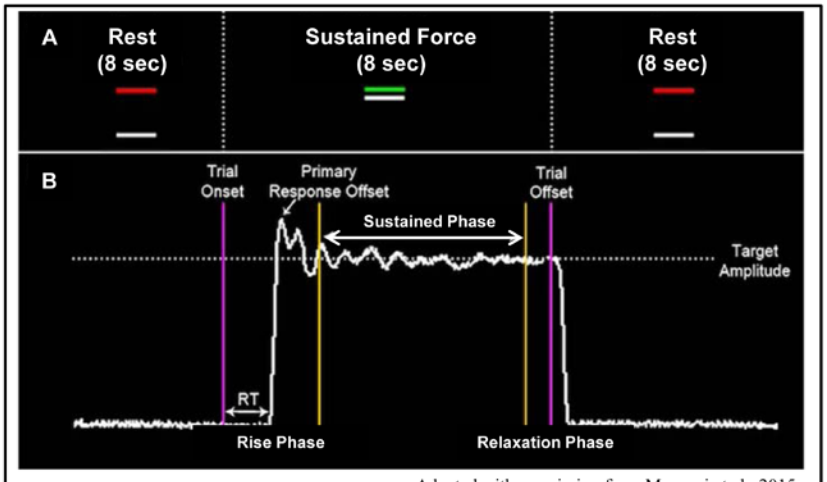
Figure 2. Oculomotor Testing Set-Up. (A) Eye movement testing set-up (B) Schematic representation of visually-guided saccade (VGS) task.

Eye movement data were recorded using a camera-based eye tracking system, Eyelink II (Figure 2A; SR Research Ltd., Canada), which has a 500 Hz temporal resolution and a gaze-position error of < 0.5 deg. The system used infrared, binocular video-based tracking technology to

compute the pupil center and pupil size of both eyes. An infrared head mounting tracking system tracked the head motion. Although the system compensates for head movements, the participant's head was stabilized using a chin rest. Data was digitized at 1000 Hz with a 16-bit A/D converter.

Testing Paradigms

Precision Gripping Tasks. Participants completed two precision gripping tasks. Prior to testing, each participant's MVC was calculated separately for each hand using the average of the maximum force output during three trials in which participants pressed as hard as they could on the load cells. Three trials within a range of 15 N were collected and averaged to estimate MVC (Vaillancourt, et al., 2003). During precision grip force testing, participants viewed two horizontal bars: a static red/green target bar and a white force bar that moved upward with increased force and downward with decreased force. The target bar was red during rest and turned green to cue the participant to begin pressing at the beginning of each trial (Figure 3A). Participants received two instructions: 1) press the load cells as quickly as possible when the red target bar turns green to move the force bar to the height of the target bar; and 2) keep pressing so that the force bar stays as steady as possible at the level of the green target bar.



Adapted with permission from Mosconi et al., 2015

Figure 3. Precision Force Task. (A)Stimulus presentation showing target (red/green) and force (white) lines. During rest, target line is red. During each trial, target line turns green to cue the participant to begin pressing. (B) Sample force trace from 8-sec trial.

During testing, participants completed two precision gripping tasks that differed in the durations of the trials and rest periods as well as the number of trials that were administered. During the *2-sec* precision force task, two blocks of five 2-sec trials were presented for each hand at each force level (15%, 45%, and 85% of each participant's MVC). Each force trial was 2-sec in duration and was followed by 2-

sec of rest. A longer 15-sec rest period was provided after each block of trials. During the *8-sec* precision force task, participants completed two blocks of three 8-sec trials for each hand at each force level (15%, 45%, and 85% of each participant's MVC). Trials were followed by 8 sec of rest, and each force block was separated by 15-sec rest blocks. The same hand was never tested on consecutive blocks for either test. The administration order of different force levels was randomized across blocks, and the order of the two experiments (*2-* and *8-sec*) was randomly assigned to each participant. Prior to each precision gripping task, participants successfully completed two practice trials at 30% of their MVC with each hand to demonstrate that they understood task instructions.

Seven individuals with ASD and their mother-father dyads were unable to complete the *2-sec task* and *8-sec* task due to technical issues or time constraints. Eight probands were unable to complete the *2-sec task* and seven probands were unable to complete the *8-sec task* due to non-compliance (e.g., did not follow instructions, refusal to participate). An additional four parents did not complete the *8-sec* task due to time constraints, of which three also did not complete the *2-sec* task for the same reason. All ASD controls completed the 2-*sec* task; however, three ASD controls were unable to complete the *8-sec* task due to technical issues or time constraints and two due to non-compliance. Ten parent controls did not complete the *2-sec* or *8-sec* task due to technical issues or time constraints. Additionally, one father control did not complete testing due to non-compliance.

Visually-Guided Saccade Tasks. Participants completed two visually-guided saccade tasks, each consisting of 30 trials. One task consisted of only *12-deg* targets and the other task consisted of only *24-deg* targets. Targets appeared unpredictability, but with equal probability, to the left or right of center fixation. Trials began with a central target appearing for 1.5 to 2.5 sec (varied randomly in 200 msec intervals), followed by a peripheral target, which was presented for 1.5 seconds. Participants were instructed to look towards the peripheral target as soon as it appeared and return their fixation to center at the end of each trial.

Twenty-one probands and 8 ASD controls were unable to complete any ocular motor testing due to non-compliance and/or excessive movement. An additional five probands did not complete the *12-deg* task and an additional nine did not complete the *24-deg* task due to time constraints. Four ASD controls also did not complete the *24-deg* task due to time constraints. Four probands and five ASD controls did not complete the *24-deg* task due to non-compliance and/or excessive movement. Nine mother-father dyads and three parent controls did not complete any ocular motor testing due to time constraints. An additional two mothers were unable to complete either task due to time constraints. One ASD mother and one ASD father (of different family trios) did not complete the *12-deg* task due to excessive movement. An additional three mothers were unable to complete the *24-deg* task due to time constraints and two mothers due to excessive movement. One mother control and one father control did not complete the *12-deg* task due to excessive movement, and one mother control did not complete the *12-deg* task due to non-compliance.

Data Analysis

Precision Gripping Tasks. Each force trace was low-pass filtered via a double-pass second-order Butterworth filter with a cutoff of 15 Hz. In order to examine initial pulse characteristics, the first, second, and third derivatives of force data were calculated in MATLAB (MathWorks; Natick, MA). Then, these derivative profiles were smoothed using a low-pass filter with a cutoff of 6-Hz to reduce noise introduced from the differentiation procedure. Precision grip force trials were excluded from analyses if the onset of force was <100 msec. For each participant, only conditions with more than two valid trials were included in the final analyses. We defined the onset of grip force as the time point at which the rate of force increase first exceeds 5% of the peak rate of force increase and remains above this level for at least 100 ms (Grafton & Tunik, 2011). This marks the beginning of the participant's initial force pulse response (i.e., the primary pulse) as well as the rise phase (Figure 3B) The offset of the primary pulse was marked at the first zero-crossing in the trace of the first, second, or third derivative, depending on which occurs first.

The reaction time, accuracy, peak rates of force increase, and duration of participants' initial force contractions were examined for *2-sec* and *8-sec* trials. To determine the accuracy of the initial force contraction, which is hypothesized to be controlled primarily by *feedforward* processes, we calculated the proportion of the force level at the offset of the initial force contraction relative to the target force level. Accuracies greater than 100 correspond to force overshoots, whereas accuracies less than 100 correspond to undershoots.

In addition to the rise phase analyses that provided information regarding the ability to rapidly initiate a rapid motor response, we also examined the sustained phase of *8-sec* force contractions in order to assess steady-state force variability over an extended period (Figure 3B). Sustained force output was assessed using the force time series excluding the first and last seconds of force generation for each trial in order to minimize the influence of rise and relaxation phases (Mosconi, et al., 2015a; Vaillancourt, et al., 2003; Wang, et al., 2014b). Trials in which participants did not sustain contractions for >5 sec or those in which force level returns to zero for >1 sec will not be included in the analyses as suggested previously (Robichaud, Pfann, Vaillancourt, Comella, & Corcos, 2005). In order to examine sustained force control guided by *feedback* control processes, mean force, accuracy of sustained force (i.e., mean force / target force), the standard deviation of the detrended time series, and the coefficient of force variation were calculated (Jiang et al., 2014). The CoV was calculated by dividing the standard deviation of the detrended time series by the mean force output. CoV was used to examine sustained force variability while controlling for possible differences in mean force output between groups.

Visually-Guided Saccade Task. Digital finite impulse response filters with non-linear transition bands were applied with a gradual transition band (from pass to no pass) between 20 and 65 Hz for velocity and position data, and between 30 and 65 Hz for acceleration data. Data from each trial was visually-inspected offline and scored blind to knowledge of participant characteristics. Trials were assessed to determine the presence of confounding measurements (e.g., excessive noise in the signal, large head movements, or task non-compliance). If the scorer judged any of these factors to be present,

the trial was omitted from analyses. Visually-guided saccade trials were calibrated independently using fixation data of central and peripheral target locations. Stable center fixation was marked prior to trial onset, and peripheral fixation was marked after the participant has acquired the peripheral target. If signal drift or head movement occurs during the performance of the task, trials were recalibrated using within-trial data from fixation of targets of interest as we have done previously (for example see Schmitt, et al., 2014; Takarae, et al., 2004b). Saccade onset and offset were marked when eye velocity rose above and below 30 deg per sec, respectively. Trials in which blinks occurred between 100 msec prior to stimulus presentation and the end of the primary saccade were not included.

The latency, accuracy, and dynamics of each saccade were measured. Latencies will be calculated based on the difference between peripheral target onset and saccade initiation. Saccades with latencies less than 70 msec were considered anticipatory and were not included in analyses. Accuracy of the primary saccade was calculated by using the absolute value of the spatial error in degrees of visual angle relative to the peripheral target position. As previously done, we used the absolute value of spatial error between primary saccade amplitude and target location because both hypometric (target undershoot) and hypermetric (target overshoot) saccades have been observed in participants with ASD (Schmitt, et al., 2014). In addition, we calculated saccade gain, or the ratio of primary saccade amplitude over target amplitude in order to determine the accuracy of saccades. In order to assess the variability of saccade accuracy over trials, we also calculated the standard deviation of the absolute value of saccade error and gain for each subject.

With regard to saccade dynamics, we measured the peak velocity and duration of each saccade. In addition, we measured the peak acceleration, peak deceleration, the time from saccade onset to peak saccade velocity (duration of saccade acceleration) and the time from peak saccade velocity to the end of the saccade (duration of saccade deceleration) as we have done previously (Schmitt, et al., 2014). Lastly, we examined the variability of saccade latency, velocity, duration, acceleration, deceleration, and the

durations of saccade acceleration and deceleration by calculating their standard deviation across trials for each subject.

Clinical Measures

The ADOS-2 and ADI-R were used to establish a diagnosis of ASD in probands and to examine the relationship between sensorimotor impairments and clinical features of ASD.

ADOS-2. The ADOS-2 is a semi-structured, standardized interaction with a trained examiner in which individuals' social, play, and communication skills are assessed (Lord, et al., 2012b). The examiner conducts standardized "presses" with the goal of eliciting social-communication behaviors. One of five Modules is conducted with the individual based upon their level of expressive language or age. Module 1 is used for individuals with no language or only single words; Module 2 is used for individuals who demonstrate phrase speech but are not yet verbally fluent; Module 3 is used for children and adolescents who are verbally fluent; Module 4 is for older adolescents and adults who are verbally fluent, and; the Toddler Module is for children between 12-30 months of age. One proband completed Module 1, 6 completed Module 2, 40 completed Module 3, and seven completed Module 4. Algorithm scores from the social-affective and restricted, repetitive behavior scores as well as the algorithm total score will be used for the current analyses in order to examine the relationships between sensorimotor performance and the severity of diagnostic features of ASD.

Studies of the psychometric properties of the ADOS-2 have demonstrated moderate to high reliability and validity (Hus, Gotham, & Lord, 2014). With regards to reliability, the social affect domain has high internal consistency (Cronbach's $\alpha > .85$ across Modules 1- 4) and the restricted, repetitive domain shows moderate internal consistency (Cronbach's $\alpha > .47$ across Modules 1- 4). Similarly, test-retest reliability is moderate to high across domains and total scores (.68 - .92). Inter-rater reliability for item coding is > 71% and weighted kappa > .60 across all Modules. Agreement in diagnostic classification is high and ranges from 92 – 98%. In terms of validity, items were selected for the algorithm based upon exploratory and confirmatory factor analyses examining the independent

contribution of each item to diagnostic classification. Items were correlated with each other < .70. Sensitivity and specificity for differentiating ASD from typical development or other developmental disabilities were estimated at 60-95% and 75-100%, respectively.

ADI-R. The ADI-R is a semi-structured interview (Rutter, et al., 2003b) comprised of 93 questions regarding both current and early development of communication, social interaction, and behavioral aspects of ASD. Three algorithms are derived to separately rate language/communication, reciprocal social interaction, and restricted, repetitive, and stereotyped behaviors and interests. A fourth algorithm score is computed based upon children's developmental history (e.g., age of first words, age at which first symptoms were present). The behavior and developmental algorithm scores will be examined in relation to sensorimotor performance in probands. For all ADOS-2 and ADI-R ratings, higher scores reflect greater abnormality.

The ADI-R is considered to be the most reliable and valid measure of developmental history in individuals with ASD (Rutter, et al., 2003b). With regards to reliability, test-retest and inter-rater reliabilities across all items exceed mean kappas of 0.73, and inter-class coefficients are greater than .90. Higher mean kappa and inter-class correlations values are found for algorithm items (0.75 and 0.93, respectively). Internal consistency of algorithm items is high (Cronbach's α 0.69 - 0.95). Test-retest reliability also is high. Exact agreement is over 83% on items rated by multiple examiners. Concurrent validity also is high (mean kappa =0.74). Lastly, sensitivity and specificity for differentiating ASD from typical development and other developmental disabilities are high (1.0 and 0.97, respectively; Lord, Rutter, & Le Couteur, 1994; Rutter, et al., 2003b).

Broad Autism Phenotype Questionnaire (BAP-Q). Parents of individuals with ASD completed the BAP-Q (Hurley, Losh, Parlier, Reznick, & Piven, 2007) in order to determine the relationship between sensorimotor impairments and sub-clinical features of ASD. The BAP-Q is a 36-item self- and informant (e.g., spouse)-report questionnaire for adults examining sub-clinical characteristics of ASD (referred to as the BAP) among three primary subscales: aloof personality, rigid personality, and

pragmatic language. These three domains were chosen to parallel social deficits, stereotyped, repetitive behaviors, and social language deficits that are defining features in ASD. Higher scores on the BAP-Q reflect greater abnormality. Both self- and informant-report scores will be used for analyses.

Initial findings (Hurley, et al., 2007) showed that the BAP-Q demonstrates high internal consistency (Cronbach's $\alpha > .85$ for all subscales, .95 for all items) and inter-item reliability (Cronbach's $\alpha > .90$). More recent research has confirmed the psychometric properties of the three BAP-Q subscales (Ingersoll, Hopwood, Wainer, & Brent Donnellan, 2011; Sasson et al., 2013). Cut-off scores for each subscale as well as the total score were established to predict the presence or absence of corresponding traits. Sensitivity and specificity for differentiating parents with a child with ASD from parents without a child with ASD were both >70% for all subscales and both >80% for total BAP-Q scores. Additionally, the BAP-Q is able to differentiate parents with individuals with ASD who demonstrate subclinical ASD features from those parents with individuals with ASD who do not demonstrate such features and from controls. Although sensitivity and specificity are similar for males and females, increased sensitivity was found for males within the aloof subscale and for females within the pragmatic language subscale. Similarly, increased specificity also was found for females within the aloof subscale. Self- and informant-reports were correlated (r's >.31). Informant scores tend to be higher than self-report scores; however, these differences were not significant. Although the original report (Hurley et al., 2007) could not determine gender effects on self-report compared to informant-report due to small sample sizes, Sasson and colleagues (2014) recently found that self- and informant-reports were moderately to strongly correlated, except when the self-reporting parent was positive for the trait being rated. However, this finding was only significant when fathers were trait positive. For example, fathers who were rated as aloof by their spouse did not rate themselves as aloof. The authors concluded that the BAP-Q is a valid and reliable measure of subclinical features of ASD and that self- and informant-reports are highly correlated, but fathers may under-estimate their traits when trait-positive and reporting on themselves.

STATISTICAL ANALYSES

Analyses of Sensorimotor Abilities in Probands and ASD Parents

For precision grip force data, we will use a series of 2 x 3 x 2 analyses of variance (ANOVA) models to examine the effects of diagnostic group (ASD versus controls), force level (15% versus 45% versus 85% of MVC) and hand (dominant versus non-dominant) on our dependent variables. We also will examine interaction effects of group x force level, group x hand, and group x force level x hand. For parents, in order to probe for paternal and maternal influences on probands' sensorimotor abilities, we will use a series of 2 x 2 x 3 x 2 ANOVA models to examine the effects of diagnostic group (parent versus control), sex (male versus female), force level (15% versus 45% versus 85% of MVC) and hand (dominant versus non-dominant) on our dependent variables. We also will examine interaction effects of group x sex, group x force level, group x hand, group x sex x force level, group x sex x hand, group x force level x hand, and group x sex x force level x hand. Due to the disproportionate rate of affected males compared to females, we did not have sufficient power to analyze sex differences among individuals with ASD on our sensorimotor tests. Separate analyses will be conducted for the *2*- and *8-sec* tests. Follow-up t-tests using Bonferroni corrections will be used to probe significant main and interaction effects.

To analyze data from the VGS test, we used a series of 2 x 2 x 2 ANOVA models including the between-subject factor diagnostic group (ASD versus control) and within subject factors target location (12-deg versus 24-deg) and direction (left versus right). Interaction terms included group x location, group x direction, and group x location x direction. Similar to precision grip force analyses, we added sex into our ANOVA model for analysis of parent data using a series of 2 x 2 x 2 x 2 ANOVA models to examine the effects of diagnostic group (parent versus control), sex (male versus female), target location (12-deg versus 24-deg) and direction (left versus right) on our dependent variables. Interaction terms included group x sex, group x location, group x direction, group x sex x location, group x sex x direction,

group x location x direction, and group x sex x location x direction. We performed follow-up t-tests using Bonferroni corrections to probe significant interaction effects. Alpha levels were set to 0.05.

Analyses of the Relationships between Sensorimotor Abilities, ASD Symptoms, and Demographic Characteristics

Assessing the inter-relationships between hand and eye movement impairments will help determine whether similar deficits are seen across motor systems. Thus, we used Pearson correlation coefficients to determine the inter-relationships of saccade and force measures for all participants. In addition, to determine the relationships between age and cognitive abilities with hand and eye movement functioning, we examined Pearson correlation coefficients between force/saccade measures found to be different between groups and age and IQ. Finally, we determined the relationship between hand and eye impairments and clinical (probands) and sub-clinical features of ASD (parents). For probands, we used algorithm total and domain scores from the ADOS-2 and ADI-R. For parents, we used BAP-Q total and sub-domain scores to assess sub-clinical symptoms. In order to directly compare the strength of correlations between groups (ASD vs. controls; ASD Parents vs. parent controls), we converted Pearson's r-values to Z values using a Fisher's transformation. Due to the large number of correlations that will be performed, we used a more conservative alpha level of 0.01.

Familiality Analyses

In the absence of monozygotic twin pairs or second-degree relatives, strong claims to traditional genetic heritability is problematic (Kendler & Neale, 2009). Thus, we used the more conservative term “familiality” to refer to the degree to which sensorimotor measures are predicted by family membership. To estimate the familiality of sensorimotor deficits, we assessed family trio pedigrees using the Sequential Oligogenic Linkage Analysis Routines (SOLAR; Southwest Foundation for Biomedical Research; Almasy & Blangero, 1998) software version 6.0 as has been done previously (Ethridge et al., 2015; Hamm et al., 2014). This analysis approach determines the contribution of family membership to a specific phenotype (i.e., force and saccade impairments) by performing a variance component analysis of

the family data. In SOLAR, the total variance in the phenotype is decomposed into components that are due to family membership, random environmental effects (e.g., common environmental factors, measurement error, non-additive genetic factors), and any measured covariates. The relative contribution of family membership to the phenotype can then be estimated by the familiality, or h^2 statistic. h^2 represents the proportion of phenotypic variance accounted for by family membership. A maximum likelihood model is used to test the statistical significance of h^2 against the null hypothesis ($h^2 = 0$), such that a model in which performance is explained by family membership is compared relative to a model in which performance is not explained by family membership. When the h^2 value is closer to 0, this indicates that the phenotypic variance is not accounted for by family membership, and thus the probability of the phenotype being familial is low. In contrast, when the h^2 value is closer to 1, this indicates that the phenotypic variance is accounted for by family membership, and thus the probability of the phenotype being familial is high. Thus, force and saccade measures with stronger covariance between genetically related individuals relative to individuals who are not genetically related will have higher familiality estimates (Glahn et al., 2007).

In the current analyses, force and saccade factors that are determined to be significantly different in the group analyses (proband versus control) were used as single dependent variables in the SOLAR models. In addition, a pedigree of family membership was entered into SOLAR analyses in order to establish family relatedness. In the first model, we did not use any covariates to estimate familiality. Any demographic and cognitive factors found to be associated with our dependent variables (e.g., age, sex, IQ), were used as covariates in additional models. In order to compare maternal versus paternal effects on phenotypic variance, similar analyses were conducted, with the exception of setting phenotypic information (force and saccade measure) unknown for fathers and mothers, respectively.

CHAPTER FOUR
Results

PRECISION GRIP FORCE TASKS

Probands versus Proband Controls

Thirty-nine individuals with ASD and 38 matched controls completed the *2-sec* precision force grip task. Forty individuals with ASD and 33 matched controls completed the *8-sec* precision grip task. For both tasks, performance was similar across hands for most force variables (F's > 3.270, p's > .075), and no hand x group interactions were observed for force performance (F's > 3.555, p's > .064). Sustained accuracy (i.e., mean force / target force) was significantly reduced in the left versus the right hand ($F = 20.655$, $p < .001$); however, because no group interactions were found, we collapsed performance across hands for final analyses. Because individuals with ASD had lower MVCs compared to controls ($F = 8.768$, $p = .004$), all reported variables controlled for group differences in force production (Tables 2-3). Comparisons that did not control for group differences in force production can be found in Appendix A, Supplementary Tables 1-2.

2-sec task

The reaction time between onset of the target signal and onset of force production (i.e., latency of force production) increased with increasing target force levels ($F = 4.035$, $p = .048$), but was similar across groups ($F = 1.127$, $p = .292$). The accuracy of the initial force contractions (i.e., end of initial force contraction / target force x 100) varied as a function of force level ($F = 15.951$, $p < .001$), such that participants tended to overshoot their target at lower force levels (15%) but undershoot at higher force levels (85%). The accuracy of initial force contractions was reduced in individuals with ASD compared to controls ($F = 4.004$, $p = .049$). This was particularly true at the lowest force levels (Figure 4A; target x group interaction: $F = 5.177$, $p = .026$), such that affected individuals exceeded their target level at 15% MVC, but demonstrated relatively accurate performance at 45 and 85% MVC. The peak rate of force increase was greater at higher compared to lower force levels ($F = 111.412$, $p < .001$). However,

individuals with ASD and controls demonstrated similar peak rates of force increase after controlling for group differences in maximum force (F = .526, p = .470). The duration of the initial force contraction also scaled with increasing force levels (F = 136.847, p < .001), and we did not find group differences (F = 1.877, p = .175).

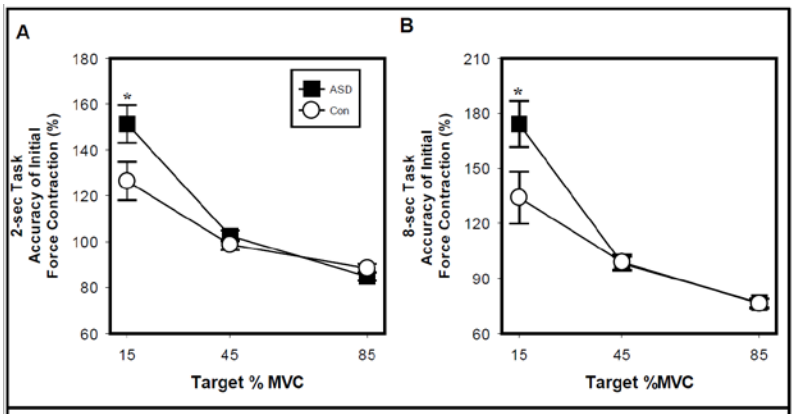


Figure 4A-B. Accuracy initial force contractions for individuals with ASD and controls. Individuals with ASD demonstrated overshooting of the target at the lowest force level for both the *2-sec* (A) and *8-sec* (B) precision force tasks.

8-sec task

The latency of the onset of force production increased with increasing force level (F = 13.280, p = .001); however, no group differences or interactions were significant (F's < 3.218, p's > .077). The accuracy of the initial force contraction varied as a function of target force level. Participants overshot force targets at the lowest force level and undershot at higher force levels (F = 64.678, p < 0.001). We also found a significant target x group interaction effect, such that individuals with ASD overshot targets more than controls at the lowest force level (Figure 4B; F = 6.077, p = .016), but not at 45 or 85% MVC (F=; p=). Group differences across force levels did not reach significance (F = 3.717, p = .079). Peak rates of force increase during the initial force contraction scaled with force level (F = 57.893, p < .001). Individuals with ASD demonstrated higher peak rates of force increase across all force levels compared to controls (Figure 5A; F = 4.430, p =.039). In addition,

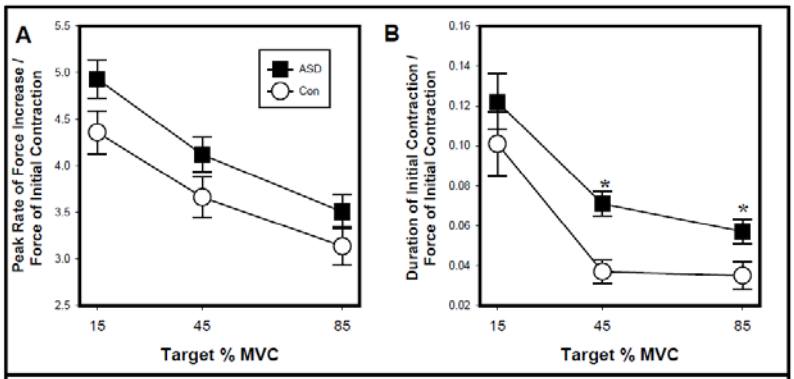


Figure 5A-B. Force dynamics for individuals with ASD and matched controls. During the *8-sec* task, individuals with ASD demonstrated increased peak rates of increase (A) and reduced duration (B) of their initial force contractions compared controls.

the duration of initial force contractions increased with increasing force levels ($F = 39.011$, $p < .001$) and individuals with ASD had significantly longer initial force pulse durations compared to controls (Figure 5B; $F = 5.843$, $p = .018$).

The accuracy of sustained force contractions (i.e., mean force / target force x 100) was reduced at higher force levels (Figure 6A; $F = 50.508$, $p < 001$). We also observed group differences in sustained accuracy that varied by target force level (Figure 6A; target x group interaction: $F = 5.762$, $p = .019$), such that individuals with ASD demonstrated excess force compared to controls at the lowest (15% MVC) force level, similar levels of force as controls at the medium force level (45% MVC), and reduced force compared to controls at the highest force level (85% MVC). The coefficient of variation (COV; detrended standard deviation / mean force) was examined to compare levels of sustained force variability between groups while controlling for group differences in mean force. Participants demonstrated more variable force production at higher target force levels ($F = 228.000$, $p < .001$). Individuals with ASD demonstrated greater sustained force variability compared to controls across force levels (Figure 6B; $F = 5.835$, $p = .018$).

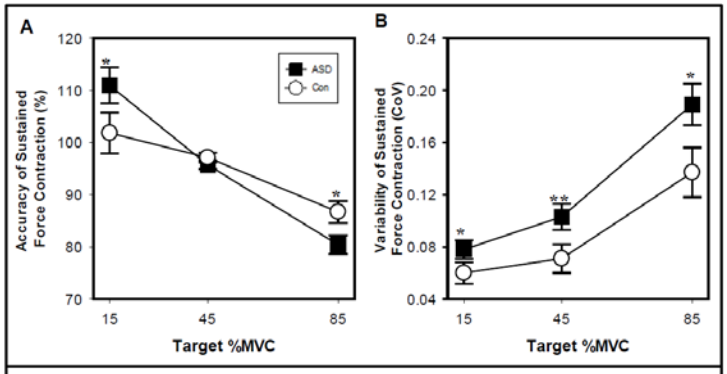


Figure 6A-B. Accuracy and variability of sustained force contractions for individuals with ASD and matched controls. Individuals with ASD demonstrated worse accuracy at lowest and highest target force levels compared to controls (A). Additionally, individuals with ASD demonstrated increased variability in sustained performance across target force levels compared to controls (B).

Parents versus Parent Controls

Eighty-nine parents of individuals with ASD (47 mothers; 42 fathers) and 39 age and sex-matched controls (22 mothers; 17 fathers) completed the *2-sec* task. Eighty-eight parents of individuals with ASD (47 mothers; 41 fathers) and 40 matched controls (23 mothers; 17 fathers) completed the *8-sec* precision force grip task. For both tasks, performance was similar across hands for most force variables (F's > 3.191, p's > .077), and no hand x group interactions were observed for force performance (F's > 1.581, p's > .211). During the *8-sec task*, peak rates of force increase ($F = 4.598$, $p = .034$) and

acceleration (F = 4.664, p = .033) were significantly reduced in the left versus the right hand. However, because no group interactions were found, performance was collapsed across hands for the remainder of the analyses. During both tasks, males had higher MVCs than females (F's > 39.618, p's < .001). Parents of individuals with ASD had similar MVCs compared to controls (F's < 3.057, p's > .083), and sex x group interaction effects were not significantly different (F's < .625, p's > .431). However, due to sex differences in maximum force, we controlled for the amount of each individual's force production when analyzing force output (Tables 4-5).

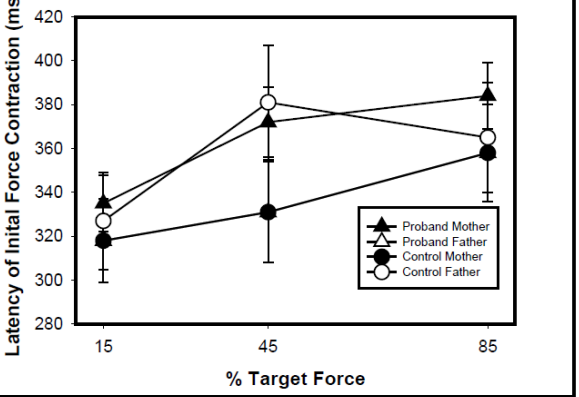


Figure 7. Latency of initial force contractions for parents of individuals with ASD and controls. Proband mothers demonstrated longer latencies compared to control mothers, especially at larger force levels. Proband fathers demonstrated similar latencies to control fathers, except at 45% MVC, where control fathers demonstrated longer latencies.

2-sec task

Force production latency was greater at higher target force levels (F = 49.774, p < .001), and although no group differences were observed for the latency to the onset of force production (F = .001, p = .980), a force x sex x group interaction emerged (Figure 7; F = 4.892, p = .029). Specifically, mothers of individuals with ASD began their initial force contraction later than female controls, especially at larger force levels. Fathers of individuals with ASD demonstrated similar latencies compared to male controls, with the exception at 45% MVC in which ASD fathers were faster to initiate their force contraction than control males. Accuracy of initial force contractions went down with increasing target force levels (F = 105.514, p < .001). However, no significant group or interaction effects were found (Figure 8A; F's > 2.800, p's > .097). Peak rate of force increase of the initial force contraction scaled with force level (F = 200.278, p < .001) and males demonstrated greater peak rate of force increase compared to females (F = 4.288, p = .040). No group or interaction effects were found (F's < 1.378, p's > .243). Similarly, the duration of initial force contractions increased with increasing force levels (F =

264.464, p < .001) and males demonstrated reduced durations compared to females (F = 24.961, p < .001), which became more severe at higher force levels (target force level x sex interaction; F = 14.839, p < .001). Groups had similar durations of their initial force contractions (F = .102, p = .750).

8-sec task

Group differences in force production latency were not significantly different (F = .057, p = .812), but the target x sex x group interaction was significant (F = 4.065, p = .046). Mothers of individuals with ASD were slower than fathers of individuals with ASD, especially at lower (15%) and higher (85%) force levels, whereas no differences in the latency to the onset of force production were seen between female and male controls. The accuracy of the initial force contraction varied as a function of target force level (F =115.106, p < .001), such that participants overshot targets at lower force levels (15%) and undershot targets at higher force levels (85%). Males demonstrated greater accuracy than females (F = 6.381, p = .013), especially at lower force levels (target x sex interaction; F = 4.584, p = .034). However, no group main or interaction effects were found (Figure 8B; F's < 2.499, p > .116). All participants scaled their peak rate of force increase with force level (F = 222.721, p < .001), but no other main or interaction effects were significant (F's < 3.062, p's > .083). The duration of the initial force contraction also scaled with force level (F = 19.821, p < .001). In addition, we found that males demonstrated shorter durations than females (F = 8.040, p = .005) and parents of individuals with ASD had significantly shorter durations than controls (F = 4.636, p = .033). Reductions in durations were more severe at lower force levels (target x group interaction: F = 8.396, p = .004).

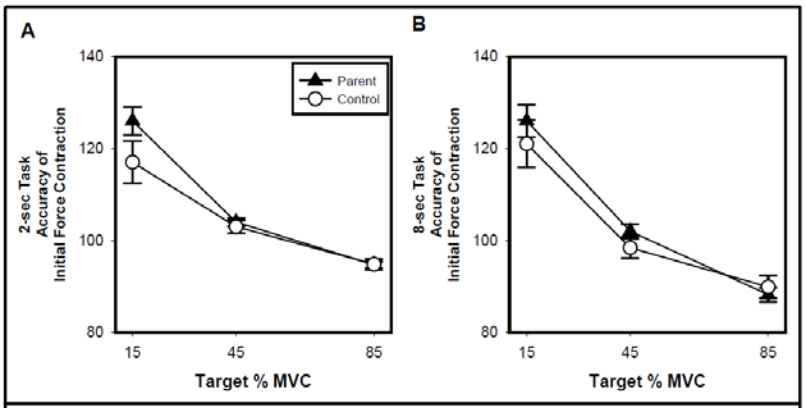


Figure 8A-B. Accuracy of initial force contractions for parents of individuals with ASD and controls. Overall groups demonstrated similar accuracies of their initial force contractions during the *2-sec* task (A) and *8-sec* task (B).

During sustained force, accuracy of sustained contractions decreased with increased target force level (F = 157.833, p < .001). Additionally, parents of individuals with ASD demonstrated reduced accuracy of their sustained contractions compared to controls (Figure 9A; F = 4.972, p = .028). The variability of sustained force contractions increased as a function of target force level (F = 199.083, p < .001). Parents of individuals with ASD showed greater sustained force variability compared to controls (Figure 9B; F = 4.193, p = .043).

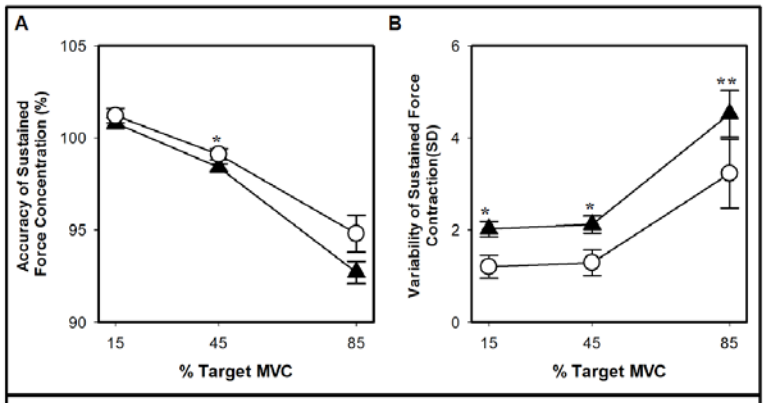


Figure 9A-B. Accuracy and variability of sustained force contractions for parents of individuals with ASD and controls. Parents of individuals with ASD demonstrated reduced accuracy (A) and increased variability (B) of their sustained force contractions compared to controls, which was was especially true at larger target force levels.

Familiality

Familiaity analyses were conducted with variables found to be significantly different between groups. For the *2-sec* precision grip task, no variables were found to be familial (h^2's < .001, p's > .500). Because gender differences emerged in the parent analyses, we also determined whether there were gender differences in familiaity by examining mother-proband and father-proband dyads in additional to family trios. No significant findings were observed (h^2's < .001, p's > .500).

For the *8-sec* precision grip task, initial force contraction variables were not found to be familial (h^2's < .001, p's > .500). However, in terms of the sustained force contraction, increased variability of the sustained force contraction was familial (Table 6; h^2 = .326, p = .030). Due to a force x group interaction in which probands were found to have more severe elevations in force variability at 85% MVC, we also examined the familiaity of sustained variability at 85% MVC. Variability of sustained force at 85% MVC was familial (h^2 = .328, p = .023). Gender differences that emerged in parent-control contrasts were further examined to compare mother-proband versus father-proband dyads; however, no variables were found to be significantly familial in these dyads.

VISUALLY-GUIDED SACCADE TASK

Probands versus Proband Controls

Twenty-seven individuals with ASD completed the *12-deg* task, 24 completed the *24-deg* task and 21 individuals completed both tasks. Thirty matched controls completed the *12-deg* task, 26 completed the *24-deg* task and 25 completed both tasks. Because performance was similar across directions for all saccade variables, and no direction x group interactions were observed (F's < 2.492, p's > .123), we averaged saccade performance across directions for all analyses. Because the absolute value of saccade amplitude was reduced in individuals with ASD compared to controls (F = 4.563, p = .039), we controlled for differences when comparing saccade dynamics by examining the ratio of dynamic variables over amplitude (Table 7). Group comparisons in which differences in saccade amplitude were not controlled for can be found in Appendix A, Supplementary Table 3.

Saccade latency was greater at larger target amplitudes (F = 16.574, p < .001), but latencies did not differ between groups (F = .926, p = .342). The variability of saccade latency did not differ across amplitudes (F = 1.051, p = .312) or groups (F = .723, p = .400). The absolute value of saccade error (i.e., absolute saccade error) increased with increasing target amplitude for all participants (F = 51.219, p < .001). Additionally, individuals with ASD demonstrated increased absolute saccade error compared to controls (F = 7.268, p = .010), especially at larger target amplitudes (Figure 10A; target x group interaction: F = 6.379, p = .016). Saccade gain (i.e., saccade amplitude / target amplitude) decreased with increases in target amplitude (F = 7.396, p = .010), but groups showed similar gain levels (F = 2.449, p = .126). Variability of saccade error (F = 58.867, p <

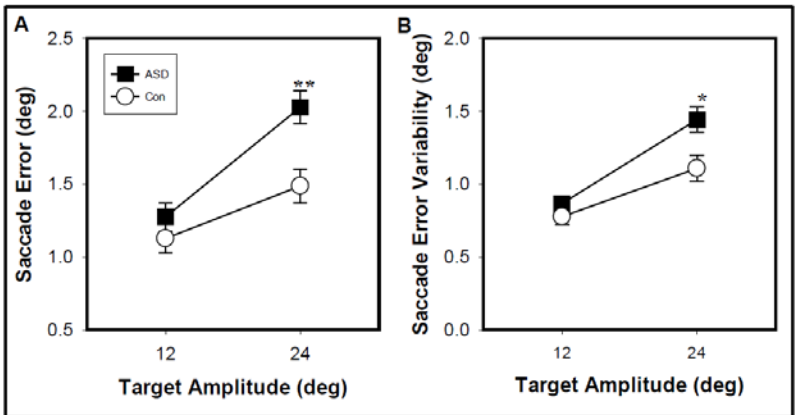


Figure 10A-B. Saccade error and variability of saccade error for individuals with ASD and controls. Individuals with ASD demonstrated increased saccade error, especially at larger target amplitudes (A). Additionally, individuals with ASD demonstrated increased trial-wise variability in their saccade error, particularly at larger target amplitudes (B).

.001) and saccade gain (F = 13.044, p = .001) increased as target amplitude increased. Individuals with ASD demonstrated increased trial-wise variability of saccade error (F = 6.161, p = .017) and saccade gain (F = 6.103, p = .018) compared to controls. Additionally, trial-wise error variability increases in ASD were more severe at larger amplitudes (Figure 10B; F = 4.238, p = .046).

Both saccade velocity (F = 396.535, p < .001) and saccade duration (F = 640.829, p < .001) scaled with increasing target amplitude. Individuals with ASD demonstrated increased peak saccade velocities (Figure 11A; F = 8.825, p = .005) and reduced saccades durations (Figure 11B; F = 5.453, p = .025). Participants' trial-to-trial variability of saccade velocity (F = 15.063, p < .001) and saccade duration (F = 156.772, p < .001) increased with increasing target amplitude; however, group differences and interactions with group were not different for velocity variability or duration variability (F's < 1.593, p's > .214). In addition, rates of saccade acceleration were higher at larger target amplitudes for all participants (F = 320.237, p < .001), and individuals with ASD demonstrated increased rates of acceleration compared to controls (Figure 11C; F = 7.217, p = .011). Rates of saccade deceleration also scaled with increasing target amplitude (F = 498.720, p < .001), and were increased in individuals with ASD relative to controls (Figure 11D; F = 6.212, p = .017). The trial-wise variability of saccade acceleration (F = 301.237, p < .001) and deceleration (F = 5.205, p = .028) increased as target amplitudes increased; however, no group differences or group interaction effects were found (F's < 2.565, p's > .117).

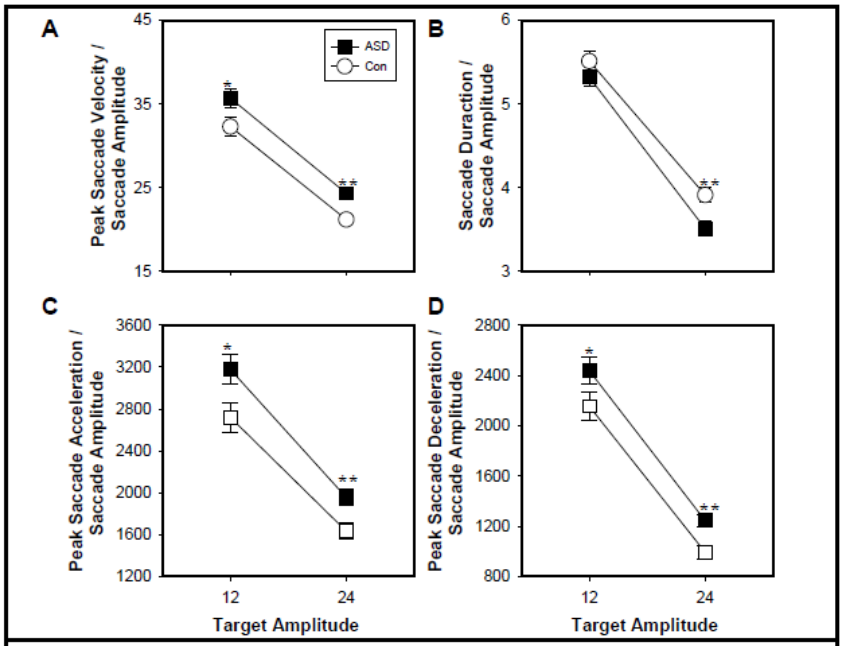


Figure 11A-D. Saccade dynamics for individuals with ASD and controls. Individuals with ASD demonstrated increased saccade peak velocity (A), acceleration (C),and deceleration (D) as well as reduced saccade durations compared to controls (B).

The durations of acceleration (i.e., time from saccade onset to peak saccade velocity; $F = 655.590$, $p < .001$) and deceleration (i.e., time from peak velocity to end of primary saccade; $F = 339.389$, $p < .001$) scaled with target amplitude. Individuals with ASD and controls had similar durations of their acceleration phases ($F = 2.745$, $p = .106$). Group differences for the duration of the deceleration phase approached significance ($F = 3.950$, $p = .054$), and the target x group interaction was significant ($F = 12.807$, $p = .001$). Individuals with ASD and controls demonstrated similar durations of their deceleration phases at smaller amplitudes, but probands showed reduced duration during their deceleration phases at larger target amplitudes compared to controls. The ratio of time spent in the acceleration phase compared to the deceleration phase was greater for smaller target amplitudes ($F = 81.627$, $p < .001$), and this was particularly true for the patient group (Figure 12; target x group interaction: $F = 8.745$, $p = .005$). Individuals with ASD spent less time than controls in the acceleration phase at smaller amplitudes, but increased amount of time compared to controls in the acceleration phase at larger amplitudes.

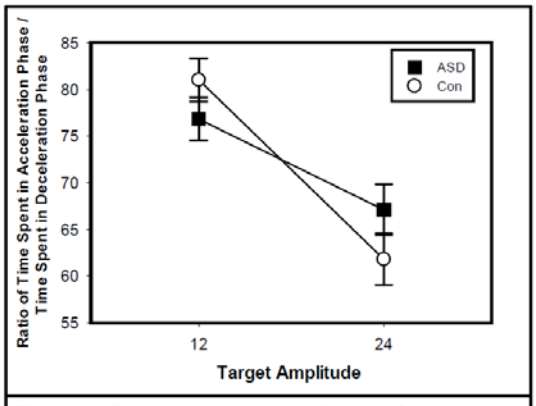


Figure 12. Ratio of time spent in the saccade acceleration phase versus time spent in the saccade deceleration phase in individuals with ASD and controls. Individuals with ASD spent a reduced amount of time in the acceleration phase compared to controls at smaller saccade amplitudes. But at larger saccade amplitudes, individuals with ASD spent a greater amount of time in the deceleration phase relative to controls.

Parents vs. Parent Controls

Eighty-four parents of individuals with ASD completed the *12-deg* task and 79 completed the *24-deg* task; 79 parents (38 mothers; 41 fathers) completed both tasks. Forty-four matched controls completed the *12-deg* task and 47 completed the *24-deg* task; 44 parent controls (26 mother controls; 18 father controls) completed both tasks. Performance was similar across directions for all saccade variables, and no direction x group interactions were observed for saccades (F's < 2.226, $p > .139$); thus, performance was averaged across directions for all analyses. However, because the absolute value of saccade amplitude (i.e., absolute saccade amplitude) demonstrated sex differences with males showing

reduced saccade amplitudes compared to females (F = 5.582, p = .020), saccade dynamics were analyzed relative to absolute saccade amplitude (Table 8).

Saccade latency increased at larger target amplitudes (F = 9407.241, p < .001), and this was particularly true for parents of individuals with ASD (target x group interaction: F = 5.502, p = .021), and especially mothers of individuals with ASD (target x sex x group interaction: F = 4.469, p = .037). Trial-wise saccade latency did not differ across targets (F = .139, p = .710). However, we found a target x sex x group interaction (F = 9.100, p = .003). Mothers of individuals with ASD and control fathers had greater latency variability at larger compared to smaller target amplitudes. In contrast, fathers of individuals with ASD and control mothers had reduced latency variability at larger compared to smaller target amplitudes.

Saccade error increased with increasing target amplitude (F = 115.412, p < .001) and males demonstrated greater saccade error than females (F = 5.553, p = .020). Additionally, we found a sex x group interaction (Figure 13; F = 5.144, p = .025), such that mothers of individuals with ASD demonstrated greater saccade error than female controls, whereas fathers of individuals with ASD and father controls demonstrated similar levels of saccade error. With regard to saccade gain, we did not observe differences across target amplitudes (F = 3.367, p = .067). However, we found that males showed reduced saccade gain compared to females (F = 7.484, p = .007). Furthermore, when comparing groups, fathers of individuals with ASD and father controls demonstrated similar performance, but mothers of individuals with ASD had reduced saccade gain compared to mother controls (sex x group interaction; F = 8.234, p = .005). Trial-to-trial variability of saccade error increased as a function of target amplitude (F = 1077.252, p < .001) and was greater among

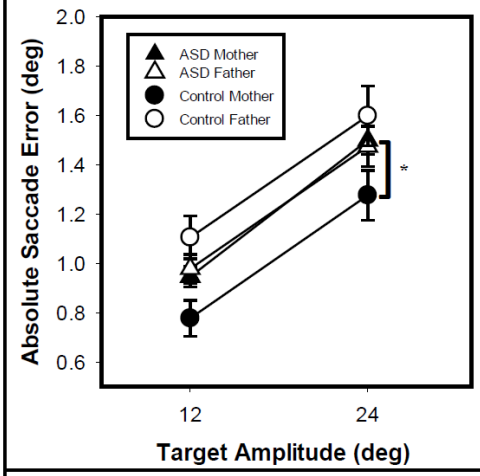


Figure 13. Saccade error for parents of individuals with ASD and controls. Mothers of individuals with ASD demonstrated increased error compared to mother controls, but fathers of individuals with ASD demonstrated a similar degree of saccade error compared to control fathers.

males than females (F = 5.791, p = .018); however, group main and interaction effects were not significant (F's < 2.027, p's > .157). Similarly, trial-to-trial variability of saccade gain increased with increasing target amplitude (F = 1126.343, p < .001), especially among males (target x sex interaction: 6.312, p = .013), but neither group main effects nor group interactions were significant (F's < .284, p's > .595).

In terms of saccade dynamics, peak saccade velocity (F = 1508.327, p < .001) and saccade duration scaled (F = 395.871, p < .001) with increasing target amplitudes. No sex differences were observed (F's < 1.944, p's > .166), but parents of individuals with ASD demonstrated increased saccade velocity (Figure 14A; F = 4.578, p = .034) and reduced duration compared to controls (Figure 14B; F = 7.796, p = .006). Variability of peak saccade velocity did not differ between sexes or groups (F's < 2.416, p's > .123); however, parents of individuals with ASD demonstrated reduced variability of saccade duration compared to controls (F = 3.974, p = .049). In addition, peak rates of saccade acceleration (F = 1180.827, p < .001) and deceleration (F = 1072.486, p < .001) scaled with target amplitude. However, no group or sex differences emerged for either variable (Figures 14C-D; F's < 3.068, p's > .082). Times spent during the acceleration (F = 470.916, p < .001) and deceleration (F = 356.318, p < .001) phases of saccades scaled with target amplitude. Parents of probands demonstrated reduced duration of their acceleration (F = 4.067, p = .046) and deceleration phases (F = 7.875, p = .006) compared to controls. The ratio of time spent in the

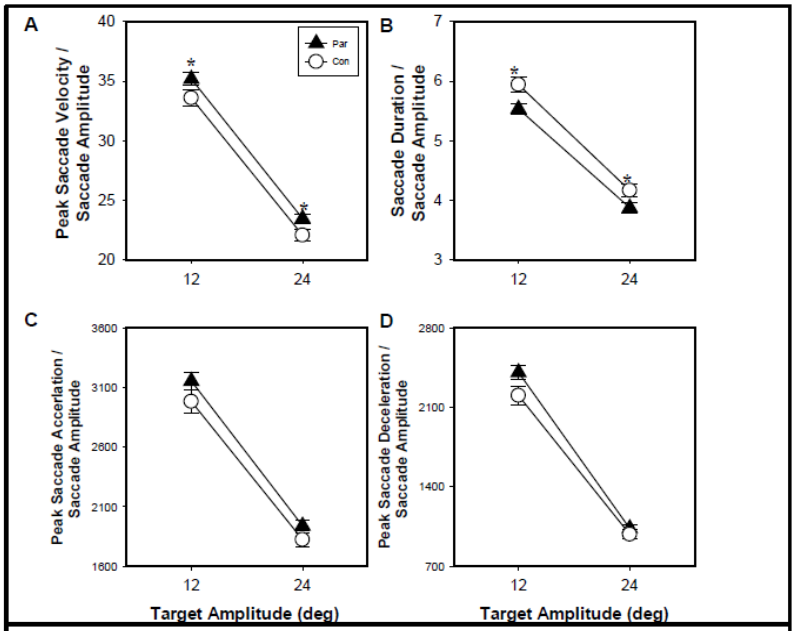


Figure 14A-D. Saccade dynamics for parent of individuals with ASD and controls. Parents of individuals with ASD demonstrated increased peak saccade velocity (A) and reduced duration (B). There were no group differences in peak saccade acceleration (C) and deceleration (D).

acceleration phase compared to deceleration phase differed depending on target amplitude ($F = 105.541$, $p < .001$), with more time spent in the acceleration phase at smaller target amplitudes compared to larger amplitudes. No other group differences emerged as significantly different for the trial-wise variability of the saccade dynamic variables (F's < 2.416, p's $> .123$).

Familiality of Saccade Impairments

Saccade accuracy and variability of accuracy were not familial (h^2's $< .035$, p's $> .453$). However, because gender differences emerged in parent versus control contrasts, we also examined whether familiality was dependent on gender for accuracy measures. Yet, no significant findings of familiality were demonstrated for mother-proband or father-proband dyads (h^2's $< .049$, p's $> .444$). In contrast, several saccade dynamic variables were found to be familial (Table 6). Specifically, peak saccade velocity ($h^2 = .778$, $p = .001$), peak saccade acceleration ($h^2 = .874$ $p < .001$) and peak saccade deceleration ($h^2 = .796$, $p = .009$) were inter-correlated among probands and their parents. The familiality of saccade duration was not significant ($h^2 = .141$, $p = .337$). Given the significant target amplitude x group interactions seen for saccade velocity and deceleration, we also examined the familiality of these variables for 24 deg targets. Again, peak saccade velocity ($h^2 = .592$, $p = .012$) and peak saccade deceleration ($h^2 = .472$, $p = .035$) had significant estimates of familiality.

FAMILY TRIOS

When examining only full family trios, 40 families were included and matched on age and NVIQ to healthy controls (Table 9). The 80 parents also were age- and IQ-matched to healthy controls. Thirty family trios completed the 2-sec precision grip task, and 31 family trios completed the 8-sec precision grip task, including one family that included two probands. Twenty-six families completed both the 2-sec and *8-sec task*s. Seventeen family trios completed the visually-guided saccade task, with 12 overlapping families of the *8-sec task* and 11 overlapping with the *2-sec task*. Five of the family trios that completed the visually-guided saccade task did not complete any manual motor tasking. Ten family trios completed all three tasks. Individuals with ASD and their parents who were included in family trio analyses will be

referred to as FT individuals with ASD and FT parents, respectively. Because FT individuals with ASD had lower MVCs compared to controls ($F = 5.964$, $p = .018$) and males had higher MVCs compared to females ($F = 35.359$, $p < .001$), we examined force performance relative to overall strength. Only variables found to be significantly different in our larger group analyses were analyzed.

Precision Gripping Tasks

2-sec task

When examining the accuracy of initial force contractions, neither group differences ($F = 3.851$, $p = .054$) nor target x group interaction reached significance ($F = 3.971$, $p = .051$). FT parents were not different from controls for the latency of force production ($F < .001$, $p = .989$), but a force x sex x group interaction emerged ($F = 5.937$, $p = .017$), such that FT mothers of individuals with ASD were slower than female controls, especially at larger force levels, but FT fathers of individuals with ASD were faster than male controls.

8-sec task

Accuracy of the initial force contraction was reduced in FT individuals with ASD compared to controls at the lowest force level (target x group interaction: $F = 4.574$, $p = .037$), such that FT individuals with ASD overshot the target. Additionally, FT probands demonstrated increased peak rates of force increase compared to controls ($F = 4.135$, $p = .047$). Force durations were not different between FT probands and controls ($F = 2.693$, $p = .106$). The accuracy of force contractions during the sustained phase did not differ between FT probands and controls across force levels ($F = .014$, $p = .908$), but FT individuals with ASD demonstrated greater undershooting than controls at higher force levels (target x group interaction: $F = 5.657$, $p = .021$). FT individuals with ASD also showed greater levels of force variability compared to controls across force target levels ($F = 6.266$, $p = .015$).

FT parents and controls did not differ in their force reaction times ($F = .640$, $p = .426$); however, the force x sex x group interaction was significant ($F = 7.804$, $p = .006$), such that FT mothers of individuals with ASD were slower than female controls, especially at larger force levels, but FT fathers of

individuals with ASD were faster than male controls. The duration of initial force contractions were similar for FT parents and controls ($F = .611$, $p = .436$). During the sustained portion of force contractions, FT parents demonstrated reduced accuracy ($F = 4.121$, $p = .045$) and increased force variability compared to controls ($F = 7.229$, $p = .008$), especially at larger target force levels ($F = 5.662$, $p = .019$).

Visually-Guided Saccade Task

FT individuals with ASD demonstrated increased absolute saccade error compared to controls ($F = 8.847$, $p = .005$), especially at larger target amplitudes (target x group interaction: $F = 4.367$, $p = .044$). FT individuals with ASD also demonstrated increased trial-wise variability of saccade error ($F = 7.327$, $p = .010$) and saccade gain ($F = 7.790$, $p = .008$). Saccade velocity was increased in FT individuals with ASD compared to controls ($F = 6.417$, $p = .016$). Similarly, saccade duration was reduced in FT individuals with ASD compared to controls ($F = 9.326$, $p = .004$), especially at larger target amplitudes (target x group interaction: $F = 8.515$, $p = .006$). Group differences in the durations of acceleration and deceleration phases were not significant (F's < 3.187, p's $> .083$). Yet, the ratio of time spent in the acceleration versus deceleration phase differed between groups at smaller but not larger target amplitudes (target x group interaction: $F = 10.163$, $p = .003$). In addition, peak rates of saccade acceleration and deceleration were greater in FT probands compared to controls (F's > 4.528, p's $< .040$).

For comparisons between FT parents and controls, a target x sex x group interaction was found for saccade latency ($F = 4.590$, $p = .035$), and saccade latency variability ($F = 4.865$, $p = .030$). With regard to absolute saccade error, the sex x group interaction was significant ($F = 5.009$, $p = .028$). FT mothers and control mother showed similar levels of saccade error; however, FT fathers and controls differed from each other, such that control fathers demonstrated greater saccade error than FT fathers. A sex x group interaction also was found for saccade gain ($F = 10.534$, $p = .002$), such that FT mothers of individuals with ASD demonstrated reduced saccade gain compared to control mothers, whereas FT fathers of individuals with ASD demonstrated increased saccade gain compared to control fathers.

Saccade velocity ($F = 3.200$, $p = .078$) and saccade duration ($F = 3.940$, $p = .051$) did not differ between FT parents and controls. Also group differences in the time spent accelerating and decelerating saccades were no longer significant (F's < 2.354, $p >$'s $.129$).

Familiality of Grip and Saccade Deficits in Family Trios

No measures of initial force contractions for the *2-sec* or *8-sec* tasks were found to be familial. However, familiality estimates for variability of sustained force at the largest force level (85%) approached significance ($h^2 = .388$, $p = .051$). With regard to familiality of saccade variables, saccade accuracy and saccade accuracy variability were not found to be familial. However, absolute peak saccade velocity ($h^2 = .870$, $p = .002$) and peak deceleration ($h^2 = .910$, $p = .009$) were each found to be inter-correlated among family members. Since a target x force interaction was found for saccade velocity, we also examined the familiality of peak saccade velocity at 24 deg, and results indicated that velocity deficits at 24 deg were familial ($h^2 = .638$, $p = .025$).

MOTOR AND CLINICAL/DEMOGRAPHIC ASSOCIATIONS

All correlational analyses conducted included only variables found to be significantly different during proband-control comparisons. If main and interaction effects both were observed to be significantly different, then we chose to analyze the variable(s) from the interaction effects that were significantly different between groups (e.g., absolute saccade error at *24 deg* versus absolute saccade error across target amplitudes). Reported results will focus on correlational analyses conducted with the larger sample of individuals with ASD and their parents; however, consistencies or differences with the smaller family trio sample are indicated. Due to the high number of correlational analyses conducted, we chose to use a more conservative alpha level ($p < .01$). Correlation matrices can be found for each group in Tables 10-13.

The Relationship between Precision Grip Force and Saccade Performance

For individuals with ASD, initial overshooting of the target at 15% MVC during the *2-sec* precision grip task was related to the following measures during the *8-sec* task: overshooting of initial

force contractions at 15% MVC ($r = .707$, $p < .001$), overshooting of sustained force contractions at 15% MVC ($r = .440$, $p = .007$), undershooting of sustained force contractions at 85% MVC ($r = -.527$, $p = .001$), and increased sustained variability ($r = .775$, $p < .001$). In addition, overshooting of initial force contractions at 15% MVC on the *2-sec* task was significantly related to increased saccade error at *24 deg* ($r = .598$, $p = .007$). The relationship between initial force overshooting at 15% MVC and saccade variability at 24 deg approached significance ($r = .543$, $p = .016$). Additionally, peak rates of force increase at 85% MVC were related to dynamic aspects of initial force contractions during the *8-sec* task, including peak rates of force increase ($r = .730$, $p < .001$) and of force acceleration ($r = .679$, $p < .001$).

For healthy controls, accuracy of the initial force contraction at 15% MVC during the *2-sec* task was not related to any variables from the *8-sec* task (accuracy of initial force contraction: $r = .107$, $p = .567$; sustained accuracy at 15% MVC: $r = -.200$, $p = .272$; sustained accuracy at 85%: $r = .100$, $p = .586$; sustained variability: .015, $p = .933$). Additionally, controls did not demonstrate significant relationships between accuracy of their initial force contraction and accuracy of their saccades ($r = .245$, $p = .298$). However, peak rates of increase during the *2-sec* task was related to peak rates of force increase ($r = .853$, $p < .001$) as well as peak acceleration ($r = .844$, $p < .001$) during the *8-sec* task.

The relationship between initial overshooting during the *2-sec* task and initial overshooting during the *8-sec* task was significantly stronger for probands compared to controls ($z = 3.16$, $p = .002$). Similarly, the relationships between initial overshooting and sustained accuracy ($z = 2.75$, $p = .006$) and sustained variability ($z = 4.00$, $p < .001$) also were stronger for individuals with ASD compared to controls. Although the relationship between initial force contraction accuracy and saccade accuracy was significant for probands but did not reach significance for controls, the strength of this relationship did not differ between groups ($z = 1.26$, $p = .208$). Additionally, individuals with ASD and controls showed a similar degree of association between precision grip dynamics across the *2-sec* and *8-sec* tasks ($|z|$'s < 1.38, p's > .168).

During the *8-sec task*, the accuracy of the initial force contraction was related to the accuracy ($r = .588$, $p < .001$) and variability of sustained force ($r = .562$, $p < .001$) in individuals with ASD. Accuracy during sustained contractions at 85% MVC was related to peak rates of force increase ($r = .440$, $p = .004$), peak rates of acceleration ($r = .400$, $p = .001$), and variability of the sustained force contraction ($r = -.721$, $p < .001$). This suggests that increased sustained variability is related to reduced accuracy at higher force levels and overshooting at lower force levels. There were no significant relationships between *8-sec* precision grip variables and saccade variables.

For controls, the accuracy of the initial force contraction was related to the accuracy ($r = .707$, $p < .001$), but not variability of sustained force ($r = .124$, $p = .505$) during the *8-sec* task. Accuracy during sustained contractions at 85% MVC was not related to precision grip dynamics (peak rates of force increase: $r = -.100$, $p = .585$; peak rates of acceleration: $r = -.099$, $p = .592$). Variability of the sustained force contraction was negatively related to the accuracy of the sustained movements at 85% MVC ($r = -.721$, $p < .001$). There were no significant relationships between 8-sec precision grip variables and saccade variables.

Compared to controls, individuals with ASD demonstrated a stronger relationship between accuracy of initial force contractions and variability of sustained force contractions ($z = 2.05$, $p = .040$). Additionally, the relationship between precision grip dynamics and accuracy of sustained contractions was stronger and more positive in probands compared to controls (peak rates of increase: $z = 2.30$, $p = .021$; peak rates of acceleration: $z = 2.10$, $p = .036$). Individuals with ASD and controls demonstrated similar relationships between initial accuracy and sustained accuracy ($z = -0.83$, $p = .407$) as well as between sustained accuracy and sustained variability ($z = .001$, $p < .001$).

Individuals with ASD demonstrated a strong relationship between saccade error and saccade error variability ($r = .863$, $p = .001$). Saccade error was not related to any saccade dynamic variables (peak velocity: $r = -.016$, $p = .942$; duration: $r = -.222$, $p = .296$; acceleration: $r = .138$, $p = .519$). Saccade error variability also was not related to any saccade dynamic variables for individuals with ASD (peak velocity:

r = .040, p = .852; duration: r =-.194, p =.364; acceleration: r = .290, p = .169). However, saccade dynamic variables were related to each other (velocity and duration: r = -.776, p < .001; velocity and acceleration: r = .698, p < .001; duration and acceleration: r = -.666, p < .001).

For controls, we found a strong relationship between saccade error and saccade error variability (r = .876, p < .001). However, neither saccade error (velocity: r = -.110, p = .643; duration: r = -.183, p =.440; acceleration: r = .143, p = .557) nor saccade error variability (velocity: r = .151, p = .524; duration: r = -.419, p =.066; acceleration: r = .266, p = .257) were related to any saccade dynamic variables. Peak saccade velocity and duration were related to each other (r = -.752, p < .001); however, the relationship between peak saccade velocity and peak saccade acceleration did not reach significance (r = .519, p = .019). Additionally, saccade duration and peak saccade acceleration also were not related (r = -.241, p = .306).

Individuals with ASD and controls demonstrated similar strengths of relationships between saccade accuracy and saccade variability (z = -0.15, p = .881). Groups also demonstrated similar strength of relationships between peak saccade velocity and saccade duration (z = -0.17, p = .865) and peak saccade acceleration (z = 0.83, p =.407). While individuals with ASD demonstrated a significant relationship between saccade duration and peak saccade acceleration whereas controls did not, the magnitude of this relationship did not differ between groups (z = -1.60, p = .110).

Parents of Individuals with ASD

For parents of individuals with ASD, the accuracy of the initial force contraction was related to peak rates of force increase during the *2-sec* task (r = .280, p = .007). Additionally, the accuracy of the initial force contraction at 15% MVC during the *2-sec* task was related to the following measures of force during the *8-sec* task: accuracy of initial force contraction (r = .401, p < .001) and peak rate of force increase (r = .354, p = .001). Also, accuracy of the initial force contractions during the *2-sec* task demonstrated a significant relationship with peak saccade velocity (r = .340, p = .004) and a trend-level association with saccade error (r = -.251, p = .037). Accuracy of the initial force contraction during the *8-*

sec task was related to accuracy of the sustained force contraction at 15% MVC ($r = .334$, $p = .001$) and variability of the sustained force contraction ($r = .437$, $p < .001$). However, during the *8-sec* task, accuracy of the initial force contraction at 15% MVC was not related to the accuracy of the sustained force contraction at 85% MVC ($r = .087$, $p = .418$). Additionally, parents did not show a relationship between sustained accuracy at 15% MVC and sustained variability ($r = .094$, $p = .380$); however, reduced accuracy of sustained contractions at 85% MVC was related to increased variability of sustained contractions ($r = -.438$, $p < .001$). Initial and sustained force variables during the *8-sec* task were not related to any saccade variables. Saccade error was strongly related to variability of saccade error ($r = .567$, $p < .001$) and peak saccade velocity ($r = -.385$, $p < .001$). Saccade error was not associated with saccade duration ($r = .077$, $p = .496$) or peak saccade acceleration ($r = -.211$, $p = .060$). Saccade dynamics variables were strongly related to each other (velocity and duration: $r = -.730$, $p < .001$; velocity and acceleration: $r = .670$, $p < .001$; duration and acceleration: $r = -.474$, $p < .001$).

For parent controls, the accuracy of the initial force contraction was not related to peak rates of force increase during the *2-sec* task ($r = -.047$, $p = .771$). However, the accuracy of the initial force contraction at 15% MVC during the *2-sec* task was related to the accuracy of the initial force contraction at 15% MVC during the *8-sec* task ($r = .676$, $p < .001$). The relationships between initial force accuracy at 15% and saccade error ($r = .118$, $p = .475$) and peak saccade velocity ($r = -.064$, $p = .697$) were not significant. During the *8-sec* task, accuracy of the initial force contraction at 15% MVC was not related to peak rates of force increase ($r = .209$, $p = .173$), accuracy of the sustained force contraction at 15% MVC ($r = .339$, $p = .025$), accuracy of the sustained force contraction at 85% MVC ($r = .198$, $p = .203$), or variability of the sustained force contraction ($r = .030$, $p = .846$). Controls also did not show a relationship between sustained accuracy at 15% MVC and sustained variability ($r = -.024$, $p = .876$); however, reduced accuracy of sustained contractions at 85% MVC was related to increased variability of sustained contractions ($r = -.556$, $p < .001$). No force measures from the *8-sec* task were related to saccade variables. Saccade error was strongly related to variability of saccade error ($r = .532$, $p < .001$), but not to

saccade dynamics (velocity: r = -.157, p = .291; duration: r = .147, p = .324; acceleration: r = .034, p = .882). However, saccade dynamics variables were related to each other (velocity and duration: r = -.724, p < .001; velocity and acceleration: r = .684, p < .001; duration and acceleration: r = -.520, p < .001).

The strengths of these relationships were similar between parents and parent controls with two exceptions. The relationship between accuracy of the initial force contraction and variability of the sustained force contraction during the *8-sec* was stronger in parents of individuals with ASD compared to controls (z = 2.30, p = .021). Additionally, the relationship between initial force accuracy during the *2-sec* task and peak saccade velocity was significantly stronger and more positive in parents compared to controls (z = 1.99, p = .047). Further, because certain precision grip and saccade variables demonstrated sex-specific results for parents of individuals with ASD we examined whether parents demonstrated different relationships among these variables. However, strengths in relationships between these variables did not differ significantly between fathers and mothers of individuals with ASD.

The Relationships between Sensorimotor Behavior and Age

In the *2-sec task*, individuals with ASD showed a significant relationship between increased age and decreased accuracy of initial force contractions at 15% MVC (r = -.515, p < .001) suggesting that individuals with ASD overshoot less as they get older. During the *8-sec task*, individuals with ASD did not demonstrate a significant relationship between age and accuracy of initial force contractions (r = -.199, p = .213). However, age-related improvements were demonstrated for accuracy of sustained force contractions (r = .565, p < .001) and variability of sustained force contractions (r = -.597, p < .001). During both tasks, peak rates of force increase also were associated with age in probands (2-sec: r = .472, p = .001; 8-sec: r = .565, p < .001). However, no saccade variables were associated with age in individuals with ASD.

Healthy controls did not demonstrate a relationship between age and accuracy of initial force contractions at 15% MVC during the *2-sec* (r = -.229, p = .200) or *8-sec* task (r = -.363, p = .045). Although, a significant relationship was found between age and sustained force variability (r = -.515, p =

.003), the relationship between age and accuracy of sustained force did not reach significance ($r = .376$, $p = .034$). Similar to probands, peak rates of force increase increased with age (2-sec: $r = .687$, $p < .001$; 8-sec: $r = .457$, $p = .009$). Controls demonstrated age-related reductions in saccade latency ($R = -.557$, $p = .004$), but no other saccade variables showed developmental improvements. The strengths in relationships between age and motor variables did not differ between groups.

Parents of Individuals with ASD

No sensorimotor variables demonstrated age-related associations for parents of individuals with ASD or matched controls.

The Relationships between Sensorimotor Performance and Cognitive Ability

Individuals with ASD

No precision gripping or saccade variables were associated with IQ for individuals with ASD or matched controls.

Parents of Individuals with ASD

Neither precision grip nor saccade performance was related to IQ among parents of individuals with ASD. However, controls demonstrated improved accuracy of their sustained contractions during the *8-sec* task with increasing Verbal IQ scores ($r = .428$, $p = .008$). The strength of this relationship was greater for controls compared to parents of individuals with ASD ($z = -2.34$, $p = .019$). Additionally, higher Nonverbal IQ (NVIQ) was related to reduced sustained precision gripping variability in controls ($r = -.425$, $p = .009$); however, the strength of this relationship did not differ between groups ($z = 1.43$, $p = .153$). Controls also were observed to have a significant negative relationship between saccade error and NVIQ ($r = -.472$, $p = .004$), such that reductions in error were associated with increases in NVIQ. Control parents demonstrated a stronger relationship between saccade error and NVIQ than proband parents ($z = 2.37$, $p = .018$).

Relationships between Sensorimotor Performance and Clinical and Sub-Clinical Features of ASD

For individuals with ASD, increased force overshoot was related to more severe restricted, repetitive behaviors as rated on the ADOS (Table 14; $r = .497$, $p < .001$). When examining the accuracy of the initial force contraction at 15% MVC, this relationship was no longer significant ($r = .369$, $p = .021$). The relationship between initial force overshooting and repetitive behaviors was not significant for the smaller sample of individuals with ASD who were included in family trio analyses ($r= .367$, $p = .054$). No other precision grip variables were associated with clinical symptoms of ASD. Further, saccade variables were not found to be associated with any clinical features in individuals with ASD.

Parents of Individuals with ASD

For parents of individuals with ASD, reduced accuracy of initial force contractions during the *8-sec* task was associated higher BAP-Q self-rated aloof subdomain scores ($r = -.339$, $p = .002$) and total scores ($r = -.312$, $p = .005$). No gender differences emerged when comparing strength of relationships between mothers and fathers. Reduced saccade peak velocity and acceleration were related to more severe spouse-rated pragmatic language (velocity: $r = -.373$, $p = .001$; acceleration: $r = -.332$, $p = .004$) and overall sub-clinical symptoms (velocity: $r = -.321$, $p = .006$; acceleration: $r = -.349$, $p = .003$) in parents of individuals with ASD. No gender differences emerged when comparing the strengths of relationships between mothers and fathers.

CHAPTER FIVE
Discussion

OVERVIEW

Our results show three key findings regarding sensorimotor functioning in individuals with ASD and their biological parents. First, individuals with ASD demonstrated deficits during tests of rapid manual and eye movement behaviors, and during a test of sustained manual motor control. These findings suggest that *feedforward* processes involved in rapid behaviors are impaired in ASD, and that visual *feedback* processes involved in correcting motor error also are impaired in ASD. Further, our findings showing that these deficits are correlated in ASD, but not in controls, suggest that ocular and manual motor as well as *feedforward* and *feedback* motor control processes are less differentiated in individuals with ASD, and thus may have more diffuse underlying impairments. Second, parents of individuals with ASD showed a profile of saccade and precision grip force deficits that was similar to the one shown by individuals with ASD indicating that *feedforward* and *feedback* impairments also are present in unaffected biological parents. Our findings that abnormalities of sustained precision gripping and saccade dynamics were inter-correlated among parents and individuals with ASD suggest that sensorimotor deficits in ASD are familial. Third, rapid grip force deficits were related to restricted, repetitive behaviors in ASD suggesting that deficits in rapid motor behaviors may represent broader clinical impairments and/or shared pathogenic mechanisms with core diagnostic features.

SENSORIMOTOR IMPAIRMENTS IN INDIVIDUALS WITH ASD

Saccadic Eye Movements in ASD

Confirming our hypothesis and consistent with previous findings (Johnson, et al., 2012; Luna, Doll, Hegedus, Minshew, & Sweeney, 2007a; Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011; Stanton, Peloso, Brown, & Rodier, 2007; Takarae, et al., 2004b), we found that individuals with ASD show reduced accuracy and increased trial-to-trial accuracy variability of their saccadic eye movements, implicating disrupted *feedforward* mechanisms. Previous studies have indicated that

saccades are less accurate in individuals with ASD, and specifically are hypometric (i.e., they consistently undershoot their targets; Johnson, et al., 2012; Luna, et al., 2007a; Rosenhall, et al., 1988; Takarae, et al., 2004b). Here, we demonstrated similar saccade gains across groups. However, when the absolute values of saccade errors were compared, individuals with ASD showed greater saccade error suggesting that they under- and over-shoot targets and are less precise in their movements than controls. This is consistent with our finding that individuals with ASD show increased trial-to-trial variability of their saccade error compared to controls. Therefore, while individuals with ASD do not appear to consistently over- or under-shoot targets when making saccades, they show a reduced ability to consistently adjust their movements to precisely reach their target. Importantly, we also demonstrated that saccade dysmetria (i.e., the repeated failure of saccadic eye movements from landing on the target) was more pronounced at larger target amplitudes suggesting that as demands on the ocular motor system are increased, the severity of saccade deficits increases in ASD, as found in previous studies (Johnson, et al., 2012; Schmitt, et al., 2014). These findings implicate predominantly impaired *feedforward* motor control processes responsible for controlling the accuracy of movements when visual feedback information is not yet available. This also is consistent with findings from our pursuit study documenting reduced smooth pursuit accuracy in patients during the open-loop phase when visual feedback is not yet available and thus relies on internal representations to guide the movement (Takarae, et al., 2004a).

Also consistent with prior studies, we found that individuals with ASD demonstrated abnormal dynamic components of their saccadic eye movements (Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011). Specifically, we found that individuals with ASD showed increased peak saccade velocity, reduced saccade duration, and increased rates of acceleration and deceleration. Our findings of speeded saccades in the current sample are consistent with a study that reported faster arm movements for individuals with ASD (Mari, et al., 2003), though prior studies of saccade dynamics have reported similar velocities and durations of eye movements in individuals with ASD and controls (Johnson, et al., 2012; Luna, et al., 2007a; Takarae, et al., 2004b). One reason that our findings differ

from prior studies may be that we examined saccade dynamics relative to the amplitude of movements. Saccade velocity and duration are tightly (and inversely) coupled and scale with saccade amplitude according to a well-defined main sequence (Bahill, Clark, & Stark, 1975; Leigh, 2006). Saccade peak velocity increases in a stereotyped, non-linear fashion as the amplitude of the saccade increases. Saccade duration follows a similar non-linear trajectory with increasing saccade amplitude. Thus, our findings of increased saccade velocity and reduced saccade duration relative to saccade amplitude in ASD suggest that dynamic components of the movement are not modulated appropriately to match the highly uniform main sequence, suggesting disruption in saccade generation processes. Further, altered saccade dynamics may contribute to observed difficulties with consistently completing movements of a desired trajectory. Increases in peak saccade acceleration relative to controls also demonstrates abnormalities in the rate at which velocity is increased in ASD possibly leading to a reduced time in which the saccade can be terminated to precisely land on or close to the target. In addition, findings of increased peak deceleration suggest that saccades are ended more abruptly in ASD owing perhaps to failures to appropriately plan the movement using predictive mechanisms.

We found that individuals with ASD spent a greater proportion of time accelerating small saccades (e.g., 12 deg) compared to controls, which may contribute to reduced control of the movement trajectory and final position. These findings are consistent with our prior study documenting a protracted acceleration phase of saccadic eye movements in ASD (Schmitt, et al., 2014). Further, this unique profile of movement deficit may impact other motor behaviors as other studies also have shown increased durations of acceleration phases of limb and finger movements (Campione, et al., 2016; Glazebrook, et al., 2006). We also found that individuals with ASD show a greater proportion of time decelerating their saccades compared to controls when making larger eye movements (i.e., 24 deg). These results suggest that individuals with ASD may be slower to terminate larger movements that reach higher velocities. Increased time spent in the deceleration phase may reflect systematic online adjustments to the velocity and duration of eye movements in order to improve accuracy (Robinson, et al., 1993). Still, individuals

with ASD demonstrated increased error at these large amplitudes compared to controls, suggesting that dynamic adjustments were unrelated to saccade accuracy and/or not sufficient to improve saccade accuracy.

A recent study using a saccade adaptation paradigm assessed changes in saccade velocity profiles based upon induced changes to saccade target amplitude (Johnson, et al., 2013). Under this paradigm, it would be hypothesized that during adaptation trials (when the target is displaced from its original location), individuals prolong the latter part of their eye movement when visual feedback is available to make appropriate adjustments to land closer to the target. Indeed, controls in this study increased the amount of time they spent in the deceleration phase during adaptation trials, which was paired with more rapid adaptation to the new target location. In contrast, individuals with ASD demonstrated a protracted acceleration phase during both baseline and adaptation trials and delayed saccade adaptation (Johnson, et al., 2013). This suggests that individuals with ASD did not alter their saccade dynamics systematically between baseline and adaptation trials to improve accuracy, and thus differences in saccade dynamics found in this and the current study may represent fundamental disruptions in predictive models used for saccade generation in ASD.

Notably, our results showing abnormal saccade dynamics in ASD differ from several previous reports. Whereas we found increased saccade velocity and reduced saccade duration in ASD, previous studies have reported the opposite—reduced saccade velocity and increased saccade duration (Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011). However, two of these prior studies (Rosenhall, et al., 1988; Stanley-Cary, et al., 2011) did not correct for differences in saccade amplitude when examining saccade dynamics as we did in the current study, suggesting that comparisons of saccade dynamics between individuals with ASD and controls may differ depending on whether or not they are analyzed relative to differences in the amplitudes of the movements. Yet, Schmitt and colleagues (2014) documented reduced velocities and increased durations of saccades in ASD after correcting for saccade amplitude. Our prior study also did not find increases in peak saccade accelerations or decelerations in

ASD. Differences between our studies may reflect variability across or within individuals with ASD or important methodological differences between the two studies. Prior studies have documented increased intra-individual variability of movement dynamics in individuals with ASD, especially during walking (Nayate, et al., 2012; Nobile, et al., 2011; Rinehart, et al., 2006a; Rinehart, et al., 2006b); however, the current study did not observe increased variability of saccade dynamics in ASD. Also, our prior study (Schmitt, et al., 2014) used electro-oculography (EOG) to measure saccades. EOG affords greater resolution for characterizing eye movement accuracy at larger visual angles, but it is a less precise method of saccade detection compared to the camera-based infrared system used in the present study. Analyses of first and second derivatives of saccadic eye movements collected using EOG may be particularly susceptible to error in the detection of the beginning and end of the eye movements. Direct comparisons of saccade dynamics in ASD using EOG and infrared systems are needed to determine if inconsistencies among the results of our two studies reflect systematic differences in these two approaches or variation within the ASD population.

Moreover, prior reports of movement dynamics across different behaviors in ASD also have yielded inconsistent findings, with some documenting no differences, others documenting speeded movements, and other documenting slowed movements in ASD (Ambrosini, et al., 1998; Cook, et al., 2013; Focaroli, Taffoni, Parsons, Keller, & Iverson, 2016; Forti et al., 2011; Glazebrook, et al., 2006; Johnson, et al., 2012; Johnson, et al., 2013; Luna, et al., 2007a; Mari, et al., 2003; Papadopoulos, et al., 2012; Rinehart, et al., 2006a; Takarae, et al., 2004b; Weiss, Moran, Parker, & Foley, 2013). Because these studies examined movement dynamics over a variety of effectors and paradigms, their results suggest that movement dynamics may be altered in ASD but the nature of these deficits may vary across different behaviors and movement effectors. Systematic comparisons of movement dynamics across different effectors and movement types are needed to understand the nature and underlying mechanisms of sensorimotor deficits in ASD.

Precision Grip Force in ASD

Dynamic gripping (2-sec task)

Also, consistent with our hypothesis and previous findings, individuals with ASD demonstrated abnormal precision gripping during rapid force contractions (Mosconi, et al., 2015a; Wang, et al., 2014b). Specifically, individuals with ASD showed reduced accuracy of their initial force contractions at the lowest force level (15% MVC) characterized by excess force that overshot the target. These results suggest an impaired ability to predictively control low levels of force or complete gripping tasks that require high levels of precision (e.g., grasping a delicate object). In addition, because the durations of rapid contractions are reduced at low compared to high levels of force, it is possible that these deficits reflect a reduced ability to predictively control grip force levels in the absence of visual feedback processes that are not available to modulate force output until 200-300 ms after force initiation (Kawato, 1999; Miall, 1998). Thus, our results implicate disrupted *feedforward* control of initial motor output in individuals with ASD when visual feedback processes cannot be used to adjust motor output.

We also found that individuals with ASD demonstrated increased peak rates of force increase and durations of their initial force contractions compared to controls, which may reduce one's ability to dynamically and appropriately adjust motor output in ASD. This suggests disruption of internal *feedforward* models that determine the appropriate rate of force needed given the motor demand. These results are consistent with our prior studies of precision grip in ASD (Mosconi, et al., 2015a; Wang, et al., 2014b) as well as are our current findings of atypical saccade dynamics. Yet, Wang and colleagues (2014b) reported *reduced* peak rates of force increase in ASD relative to controls, although this finding did not reach significance. Inconsistent findings may reflect a younger-aged proband sample used in our prior study (Wang, et al., 2014b). Overall, our profile of abnormal rapid force changes and saccade dynamics suggests that *feedforward* control mechanisms responsible for controlling ocular and manual motor movements are disrupted in ASD and compromised in similar ways.

The present study documented disrupted precision grip dynamics in the *8-sec* but not the *2-sec* task. Wang and colleagues (2014b) also reported this dissociation, suggesting that movement dynamics

may be controlled differently based upon the context of the motor task (i.e., rapid versus sustained force contraction). Further, this suggests that mechanisms underlying precision gripping may be differentially impacted in ASD based upon motor demands, including the amplitude and duration of force required. Our results suggest that individuals with ASD use a more speeded response when the task demand was to sustain a constant level of force over a longer period of time. This is a relatively inefficient strategy as faster increases in force are more difficult to control and harder to decelerate to hit the target. This suggests failures of predictive motor plans to appropriately refine internal representations based upon the context of the motor task in ASD. These findings support previous studies that documented that individuals with ASD failed to modulate the velocities of their arm and hand movements based upon the size (Fabbri-Destro, Cattaneo, Boria, & Rizzolatti, 2009) and orientation of the object (Hughes, 1996) during prehension tasks. Another possible explanation is that precision grip dynamics during more repetitive tasks may be relatively spared in ASD, such that it may be easier for individuals with ASD to modulate their force dynamics during a repeated motor action. Additional studies should be aimed at determining the extent to which certain motor processes and effectors are spared during repetitive versus continuous motor tasks.

Sustained precision gripping

Supporting our hypothesis, we revealed less accurate and more variable sustained precision grip force contractions, replicating our previous studies (Mosconi, et al., 2015a; Wang, et al., 2014b). Specifically, during continuous steady-state contractions, individuals with ASD demonstrated reduced accuracy of their mean force output compared to controls at the lowest (15%) and highest (85%) force levels, such that they showed excess mean levels of force at lower target force levels, and reduced mean levels of force at higher target force levels. These findings that individuals with ASD produce excess force at low force levels during a sustained contraction are similar to our findings during rapid force contractions when individuals with ASD overshot the target at the lowest force level. This suggests that patients have a reduced ability to precisely modulate their force output when low levels of force and/or a

greater degree of precision are required, even when visual feedback processes are available and may be used to support ongoing motor behavior.

We also found that individuals with ASD demonstrate increased variability of their sustained force output as we documented previously (Mosconi, et al., 2015a; Wang, et al., 2014b). In contrast to initial force contractions, sustained force contractions are supported by slower visual feedback processes. During sustained contractions, the ability to utilize visual input to update internal models in order to make corrective motor adjustments during behavior is necessary to ensure the accuracy and steadiness of sustained movements (Gepner & Mestre, 2002). Our findings of increased force variability suggest that affected individuals may be over- or under-correcting for errors in their precision grip output based upon visual feedback, similar to the elevated levels of trial-to-trial variability of saccadic accuracy documented here. Still, despite evidence of motor adjustments, individuals with ASD demonstrate overall reductions in accuracy of their sustained force. Our findings of reduced accuracy of *feedback* controlled motor behaviors are consistent with our previous pursuit eye movement studies documenting reduced pursuit accuracy during the closed-loop phase when visual feedback is available (Takarae, et al., 2004a). Further, we found that elevated force variability in ASD becomes more severe at higher force levels, suggesting that as motor demands increase, individuals with ASD demonstrate more severe impairments in their ability to maintain an accurate and constant level of precision force. Therefore, increased force variability in ASD appears to reflect, at least in part, disturbances in motor control and execution systems as opposed to deficits in processing sensory feedback.

Motor Control Mechanisms of Rapid and Sustained Motor Impairments in ASD

Our findings of disruptions in saccadic eye movements and precision gripping in ASD implicate *feedforward* control systems involved in guiding rapid motor behaviors and *feedback* systems involved in controlling sustained motor behaviors. *Feedforward* motor control is completed prior to sensory feedback becoming available, and thus relies on internal action representations that are needed to generate predictive motor commands that will estimate the distance, speed, and direction that the body must move

based upon its current state. *Feedforward* control relies both on: 1) inverse models to calculate the motor command based upon the current motor state position versus the desired motor outcome, and 2) forward models that use a copy of this motor command, called the efference copy, to predict the sensory consequences of the motor action (Kawato, 1999; Miall, 1998). If the predicted sensory consequences, guided by the forward model, and actual sensory consequences are mismatched, the initial motor command will be re-calibrated via *feedforward* control to ensure accuracy of subsequent motor actions as part of motor learning. In contrast, *feedback* motor control relies on incoming sensory information to make corrective adjustments to ongoing movements (Todorov & Jordan, 2002; Wolpert & Kawato, 1998). Although *feedback* control is highly accurate since it updates the system with actual sensory information, it comes at the expense of an inherent time delay. Sensory information first must be detected, and then it must be relayed to motor command centers to generate and execute appropriate adjustments. Both *feedback* and *feedforward* control mechanisms are necessary to guide and ensure the accuracy of ongoing movements. However, rapid movements often are completed too quickly to rely on *feedback* control for accuracy, and thus rely predominantly on *feedforward* control. Yet, the accuracy of subsequent ballistic movements may incorporate sensory feedback regarding accuracy to update forward models. In contrast, slower and/or sustained movements use a combination of *feedforward* and *feedback* control processes to ensure motor accuracy.

Our findings of saccadic and rapid grip force impairments in ASD implicate disrupted *feedforward* control. Internal models used by feedforward controllers determine the necessary movement velocity, duration, acceleration, and deceleration needed to achieve the desired motor state based upon the current motor state. Thus, observations of impaired accuracy as well as altered dynamics during rapid ocular and manual motor behavior suggest that internal models responsible for guiding *feedforward* control processes are disrupted across multiple motor effectors in ASD. Because the current study demonstrated *feedforward* deficits in relatively isolated contraction of distinct muscle group (i.e., extraocular muscles for saccades, first dorsal interosseous muscle for precision grip), our findings suggest

that prior studies documenting atypical rapid upper limb movements in ASD reflect disrupted *feedforward* mechanisms in addition to possible difficulties in coordinating the timing and force level of different muscle groups (Davis, Bockbrader, Murphy, Hetrick, & O'Donnell, 2006; Glazebrook, et al., 2006; Glazebrook, et al., 2009; Gowen & Miall, 2005).

Although rapid eye and hands movements are predominantly under *feedforward* control, *feedback* mechanisms also are involved in determining and adjusting for movement error. For instance, increased trial-wise variability of saccade accuracy may reflect disrupted *feedforward* and/or *feedback* mechanisms. Failure of *feedforward* processes to make an accurate and consistent predictive motor plan could lead to variable performance across trials. Additionally, failure of *feedback* processes to effectively integrate visual feedback information regarding trial performance in subsequent forward models for future performance also may lead to increased variability of saccade error. This could occur in a number of ways, including over-correction for prior errors and/or reduced precision when making reactive adjustments based on prior movements. Thus, individuals with ASD may attempt to adjust for saccade error, but these attempts are insufficient because they under- and/or over-correct for the error. Similarly, during precision gripping, excess force at the lowest target force also suggests that individuals with ASD have a reduced ability to refine *feedforward* internal models via visual feedback information regarding prior inaccurate performance. Together, impairments in controlling rapid motor responses as well as correcting rapid motor responses reflect developmentally immature *feedforward* control systems responsible for generating an appropriate motor command as well as deficits in *feedback* systems responsible for updating forward models and generating compensatory strategies to improve accuracy.

Deficits in *feedback* control also may contribute to abnormalities of the deceleration phase of eye movements in ASD as this phase of the movement may be modulated based upon visual feedback regarding performance (Robinson, et al., 1993). Saccade duration may be extended or shortened during the deceleration phase so that movements are terminated closer to the target location (Fuchs, Robinson, & Straube, 1993; Ohtsuka & Noda, 1992; Pelisson & Prablanc, 1988; Robinson, et al., 1993). Our finding

that saccade durations were reduced in ASD, particularly during the deceleration phases, suggests that individuals with ASD terminated their saccades early and this may have contributed to their reduced accuracy. Similarly, we found shortened durations of initial force contractions during precision gripping. Thus, saccade and gripping durations were reduced in ASD, suggesting that individuals with ASD do not systematically adjust the durations of their movements via *feedback* control to improve behavioral accuracy.

Our findings of reduced accuracy and increased variability during sustained precision gripping implicate disrupted *feedback* mechanisms responsible for updating internal models online. During sustained motor behaviors, sensory feedback allows individuals to compare their ongoing motor performance to the desired motor performance and subsequently correct for any motor errors. We previously reported that individuals with ASD show an increased reliance on slower and developmentally less appropriate visual *feedback* mechanisms during continuous motor behavior when compared to controls (Mosconi, et al., 2015a), suggesting that they may utilize inefficient strategies that fail to integrate faster *feedforward* and *feedback* processes to correct for movement error. Thus, individuals with ASD have difficulty making rapid corrections to their motor output, which, because of the time delay in making these corrections, results in increased drift of their force level from the target force. Further, as individuals with ASD spend more time away from the target force, they need to make larger adjustments to correct for this error and they therefore may show increased force variability. Our results are consistent with previous studies documenting difficulties incorporating visual input into movement planning (Dowd, McGinley, Taffe, & Rinehart, 2012; Glazebrook, et al., 2009) and impaired visual *feedback* processing during motor tasks in ASD (Haswell, et al., 2009; Izawa, Criscimagna-Hemminger, & Shadmehr, 2012a; Marko et al., 2015) and suggest that visual *feedback* processes involved in controlling simple motor behaviors are compromised in ASD. Additionally, our pursuit study also implicated impaired *feedback* mechanisms responsible for ensuring the accuracy of smooth pursuit (Takarae, et al., 2004a), and several recent studies demonstrating reduced rates of saccade learning in ASD (Johnson, et al., 2013; Mosconi, et

al., 2013) also implicated *feedback* control mechanisms involved in adjusting forward control models in response to systematic visual errors in ASD.

Importantly, we reported the novel findings that accuracy during rapid ocular motor and manual motor responses are related in individuals with ASD, and that *feedforward* and *feedback* control processes are associated in affected individuals, but not in controls. Thus, patients who demonstrated greater error on rapid precision gripping also demonstrated greater error during saccadic eye movements and during sustained grip force. These findings suggest that *feedforward* systems abnormalities lack specificity for effectors in ASD, and that *feedforward* and *feedback* control processes are less differentiated in patients. In contrast, controls did not demonstrate significant relationships between rapid grip accuracy, saccade accuracy, and sustained grip variability, indicating that *feedforward* processes supporting distinct motor behaviors (e.g., eye versus hand) may operate independently in non-patient populations as do *feedforward* and *feedback* control processes. Differentiation in the control systems involved in eye and hand movements are evident at both central and peripheral levels and involve different brain mechanisms, muscle groups, and time scales (Leigh, 2006). Thus, contrary to our hypothesis and previous findings (Mosconi, et al., 2015a), we provide evidence of less differentiation at the level of effectors and control processes in ASD and suggest that motor abnormalities in patients may reflect more diffuse impairments that impact multiple central and peripheral processes, rather than distinct pathways of disruption. However, Mosconi and colleagues (2015a) used different force variables to measure sustained force accuracy (e.g., mean force versus mean force/target force) and variability (i.e., detrended standard deviation of force versus detrended standard deviation of force/target force), which may account for study differences. Future studies should be conducted to determine the extent to which *feedforward* and *feedback* processes are overlapping or distinct across different behaviors and effectors.

Brain Mechanisms Underlying Ocular and Manual Motor Abnormalities in ASD

The brain mechanisms underlying ocular and manual motor control have been well-documented in human and non-human primate studies and are controlled by overlapping, yet distinct processes.

Notably, the cerebellum demonstrates regional specialization for different effectors. For example, anterior regions, including lobules I-V, and more lateral and posterior regions, including lobules V-VI and Crus I/II, control limb movements (Vaillancourt, et al., 2006). In comparison, saccadic eye movements are controlled by the oculomotor vermis, which includes posterior cerebellar lobules VI-VII and Crus I/II as well as their outputs to the caudal fastigial nuclei (Alahyane, et al., 2008; Takagi, Abe, Hasegawa, Yoshizawa, & Usui, 1993). Furthermore, regional specialization of the cerebellum extends to *feedforward* and *feedback* control processes. For instance, anterior lobules I-V of the cerebellum are thought to be responsible for *feedforward* control, whereas more posterior regions, including lobules VI-IX, may play a more prominent role in *feedback* control (Neely, et al., 2013a).

Within the context of *feedforward* control, the cerebellum is responsible for receiving efference copies of the motor command from cortical regions and providing predictive motor commands to the primary motor cortex in order to modulate the timing and amplitude of initial muscle contractions (Vilis & Hore, 1980). The cerebellum is believed to house internal action representations, which can be refined to adjust future motor actions (Bruno & Simons, 2002; Herzfeld et al., 2014; Izawa, et al., 2012a). The cerebellum also is responsible for transforming visual input into corrective motor commands in order to reduce the variability of motor output via *feedback* control (Vaillancourt, et al., 2006; Vaillancourt, et al., 2003). Thus, the eye and hand movement deficits characterized in this study implicate widespread involvement of cerebellum in ASD. Further, because our findings demonstrate relationships between ocular and manual motor deficits as well as between *feedforward* and *feedback* deficits in ASD, reduced degree of regional specialization of the cerebellum is implicated for individuals with ASD.

Patients with cerebellar lesions show a similar profile of *feedforward* and *feedback* motor control abnormalities as that presented here (Babin-Ratte, Sirigu, Gilles, & Wing, 1999; Brandauer et al., 2008; Fellows, Ernst, Schwarz, Topper, & Noth, 2001; Nowak, Hermsdorfer, Rost, Timmann, & Topka, 2004; Rost, Nowak, Timmann, & Hermsdorfer, 2005; Serrien & Wiesendanger, 1999). Additionally, a similar pattern of saccade dysmetria and abnormal saccade dynamics has been documented in cerebellar-based

ataxias (Federighi et al., 2011; Kirkham, Guitton, Katsarkas, Kline, & Andermann, 1979). Importantly, cerebellar pathology has been consistently implicated in ASD histological, MR anatomical, and functional neuroimaging findings (for review see Mosconi, et al., 2015b). Specifically, reduced number and size of Purkinje cells (Arin, 1991; Bailey et al., 1998a; Bauman & Kemper, 1985a; Bauman & Kemper, 1995; Fatemi et al., 2002; Ritvo et al., 1986b; Skefos, et al., 2014; Wegiel et al., 2014a; Whitney, Kemper, Bauman, Rosene, & Blatt, 2008a) as well as hypoplasia of posterior cerebellar vermal lobules VI-VII (Courchesne, et al., 1988; Hashimoto, et al., 1995; Kaufmann et al., 2003a; Schaefer, et al., 1996; Webb, et al., 2009) have been repeatedly documented in individuals with ASD. Purkinje cells are the sole output from the cerebellum to the deep nuclei, and they receive input from the cortex via the brainstem after it is relayed to the cerebellar granular layers and parallel fibers (Eccles, Sasaki, & Strata, 1967; Geborek, et al., 2014; Ramnani, 2006; Vogel, et al., 1996). Further, Purkinje cells are involved in the modification of internal models used in *feedforward* control via LTD (Wolpert & Kawato, 1998). Thus, our findings of impaired control of the eyes and hand in ASD may reflect functional consequence of fewer and smaller-sized Purkinje cells and/or indirectly via their connections to cortical and subcortical areas involved in motor control (Wassef, Angaut, Arsenio Nunes, Bourrat, & Constantino, 1992). In addition, posterior lobules have known involvement in saccadic eye movements and precision gripping, suggesting hypoplasia in this region also may contribute to the motor impairments we found in this study. Together, our findings of ocular and manual control abnormalities are consistent with cerebellar pathology reported in ASD, and implicate reduced functional specialization of the cerebellum, suggesting diffuse abnormalities at the structural and functional level.

It is unlikely that the cerebellum alone contributes to our observed ocular and manual motor findings. First, the cerebellum has widespread connections with premotor, prefrontal, and parietal cortices through polysynapic circuits via thalamus and basal ganglia as well as with the brainstem via climbing fibers and mossy fibers (input) or Purkinje cells (output; Balsters et al., 2010; Bostan, Dum, & Strick, 2013; Palesi et al., 2015; Stoodley & Schmahmann, 2010). Thus, abnormalities may arise within

the cortical-ponto-cerebellar circuitry itself and/or the regions to which it projects or is innervated by. Several groups have identified atypical cerebellar and cortical-cerebellar circuitry in ASD, including reduced functional connectivity within cortical motor networks (Barnea-Goraly et al., 2004; Mostofsky, et al., 2009) and reduced white matter integrity within the cerebellar peduncles (Hanaie et al., 2013; Shukla, et al., 2010). Further, visual cortices involved in receiving and relaying visuospatial information regarding the target prior to motor execution and processing sensory feedback, parietal cortices responsible for motor planning as well as integrating sensory information, motor cortices responsible for generating and executing motor commands (Fogassi & Luppino, 2005; Gaymard, et al., 1998; Hepp-Raymond, 1988; Kalaska, et al., 1997; Leigh, 2006; Porter & Lemon, 1993; Rizzolatti & Luppino, 2001; Sweeney et al., 1996; Vaillancourt, et al., 2006; Wise, et al., 1997), and subcortical regions, including the thalamus (Sweeney, et al., 1996) and basal ganglia, involved in movement planning, execution, and modulation (Crawford, Henderson, & Kennard, 1989; Hikosaka & Wurtz, 1986) each have been implicated in ASD (Mostofsky, et al., 2009; Sears, et al., 1999; Stanfield et al., 2008a; Wolff, Hazlett, Lightbody, Reiss, & Piven, 2013). Thus, abnormalities within these regions may contribute to deficits integrating sensory information and controlling outgoing movement commands. Notably, a similar profile of inaccurate and variable motor behaviors has been observed in patients with focal lesions of the premotor, primary motor, and parietal cortices (Eidenmuller, Randerath, Goldenberg, Li, & Hermsdorfer, 2014), and Parkinson's patients, who have known damage to the basal ganglia, demonstrate increased force variability during precision gripping as we found here with our patients with ASD (Neely et al., 2013b). Lastly, the pons within the brainstem is involved in generating motor commands as well as determining movement dynamics and accuracy via their interactions with the Purkinje cells within the cerebellar vermal lobules VI-VII that they innervate (Fuchs, et al., 1985; Gaymard, et al., 1998; Luschei & Fuchs, 1972; Van Gisbergen, et al., 1981; Yoshida, et al., 1999). Histological and anatomical studies have consistently implicated the pons in ASD (Bailey, et al., 1998a; Gaffney, et al., 1988; Hashimoto, et

al., 1993; Hashimoto et al., 1991; Hashimoto, et al., 1995; Jou, Frazier, Keshavan, Minshew, & Hardan, 2013).

Our prior functional MRI study of saccadic eye movements demonstrated diffuse impairment of both motor and non-motor regions (Takarae, et al., 2007). Specifically, individuals with ASD demonstrate reduced activation of frontal and supplementary eye fields, posterior parietal cortex, and cerebellar hemispheres compared to controls. The patient group also demonstrated increased activation in the dorsolateral prefrontal cortex, a region typically involved in top-down motor control and other cognitive functions (Sweeney, et al., 1996). This suggests that regions highly specialized for motor control are disrupted and thus may recruit regions associated with higher-order behaviors to compensate for impaired motor functioning. Overall, this implicates a disrupted neural motor circuitry in ASD, which is consistent with our findings are widespread impairments. However, future studies are needed to compare brain activation during ocular and manual motor tasks involving *feedforward* and *feedback* processes in order to determine the extent to which neural processes are disrupted across multiple behaviors and effectors in ASD.

It also is possible that peripheral mechanisms contribute to the motor deficits we observed in this study. Evidence of hypotonia (Lisi & Cohn, 2011) and our finding of reduced MVC in individuals with ASD compared to controls may suggest peripheral involvement. However, low muscle tone and muscle weakness may result from peripheral and/or central mechanisms (Martin, et al., 2005). For instance, reduced modulation of motor neuron pool (i.e., collection of motor neurons that innervate a single muscle) from central mechanisms may contribute to our observed findings in individuals with ASD. Yet, because we adjusted for group differences in MVC, it suggests that precision grip abnormalities in ASD are at least in part due to central deficits and not due to muscle weakness alone. Because few studies have examined peripheral motor disturbances in ASD, it is difficult to determine the extent to which peripheral impairments contribute to our currents findings. Future studies using electromyography should be aimed at isolating the contribution of peripheral abnormalities to motor deficits.

FAMILIALITY OF MOTOR CONTROL ABNORMALITIES IN ASD

Saccadic Eye Movement and Precision Gripping Abnormalities in Parents of Individuals with ASD

Results from saccade and precision grip force tasks indicate that parents of individuals with ASD demonstrate a profile of motor control abnormalities similar to individuals with ASD. Specifically, parents of individuals with ASD demonstrated increased peak saccade velocity, reduced saccade durations and reduced saccade accuracy compared to controls, similar to individuals with ASD in the present study and others (Johnson, et al., 2012; Luna, et al., 2007a; Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011; Stanton, et al., 2007; Takarae, et al., 2004b). In addition, we present three novel findings. First, peak saccade velocity, peak saccade acceleration, and peak saccade deceleration were increased in parents of individuals with ASD relative to controls, and these saccade deficits were correlated with the impairments of their offspring, suggesting that these abnormalities may be familial. Second, we documented abnormal sustained precision gripping as well as subtle impairments to rapid force contractions in parents of individuals with ASD. Third, greater variability of sustained contractions inter-correlated among individuals with ASD and their parents, suggesting that reduced ability to modulate consistent levels of force may be familial.

Here, we replicate and extend findings from our previous family study of oculomotor control in unaffected biological parents and siblings of individuals with ASD (Mosconi, et al., 2010). Consistent with our prior study, we documented increased saccade error in parents. While this prior study did not investigate saccade dynamics, we found that parents of individuals with ASD show abnormal saccade velocities, acceleration, and deceleration. Thus, cerebellar-mediated processes that are involved in modulating the timing and amplitude of rapid motor responses are implicated in parents of individuals with ASD and may represent pathophysiological processes in ASD. These deficits also showed high level of familiality, suggesting that cerebellar-dependent *feedforward* control processes involved in regulating the timing and accuracy of saccades may reflect shared pathogenic mechanisms involved in the development of sensorimotor impairments and other symptoms of ASD.

Results from the precision grip study suggest that parents of individuals with ASD show subtly impaired rapid precision gripping as demonstrated by shortened durations of their initial force contractions. However, accuracy and peak rates of increase were similar across groups, suggesting that the *feedforward* motor control processes responsible for rapid precision gripping are more subtly affected in parents compared to the *feedforward* processes responsible for rapid eye movements. One factor that may account for these differences is that we found only modest correlations between rapid eye and hand movements in our parent sample (r-values between .251 - .340) compared to the strong correlations we found in the ASD sample (r-values between .543-.598). Thus, *feedforward* processes controlling saccades and precision gripping may demonstrate more differentiation in parents of individuals with ASD compared to individuals with ASD, and thus rapid eye and hand movements may exhibit different levels of dysfunction in parents.

Parents of individuals with ASD demonstrated reduced accuracy and increased variability of their sustained force contractions suggesting impairments to *feedback* motor control processes. Variability of sustained force contractions increased at larger target force levels, suggesting greater demands on the manual motor system worsened motor performance in parents of individuals with ASD. These results expand upon findings reported by Mosconi and colleagues (2010) documenting *feedback* deficits in relatives of individuals with ASD during smooth pursuit eye movements. This suggests that in contrast to *feedforward* motor control deficits, *feedback* deficits may be present across motor effectors in parents of individuals with ASD. Future studies are warranted to determine the extent to which *feedback* processes are disrupted across multiple motor behaviors in unaffected parents.

Further, increased sustained force variability inter-correlated among individuals with ASD and their parents, indicating that these deficits may be familial. It also suggests that parents and probands may share pathogenic processes underlying abnormalities in sustained manual motor control. Specifically, because sustained contractions rely on visual feedback, our results implicate cerebellar-dependent *feedback* mechanisms in both individuals with ASD and their parents of individuals with ASD.

Also, as we found in probands, manual motor *feedforward* and *feedback* deficits were related to each other in parents, but not in controls. This suggests that the processes underlying *feedforward* and *feedback* deficits are less differentiated in parents of individual with ASD compared to controls. Thus, cortico-cerebellar circuitry appears to be less specialized for distinct motor control processes in parents of individuals with ASD suggesting more diffuse impairments that may be familial.

Notably, reductions in saccade accuracy in parents were restricted to mothers of individuals with ASD suggesting that they may reflect sex-specific endophenotypes or pathogenic processes. This finding is consistent with studies demonstrating sex-specific expression of the broad autism phenotype characteristics (Klusek, Losh, & Martin, 2014; Piven, et al., 1997a) and risk variants (Kistner-Griffin et al., 2011; Lamb et al., 2005) in parents of individuals with ASD. However, Mosconi and colleagues (2010) demonstrated increased saccade error in first-degree relatives of individuals with ASD across genders. Our prior study examined a predominantly female sample (57%) compared to our current sample (48%), which may have biased a group level effect over a sex x group effect. Further, examination of raw values of saccade error across sexes and groups in the current study revealed that control males demonstrated more saccade error than the other three parent study groups (though not statistically greater). Notably though, fathers and mothers of individuals with ASD demonstrated similar levels of saccade error in the current study. Given the small size of the control male sample, further study of sex differences in saccade performance amongst family members is warranted.

Additionally, Mosconi and colleagues (2010) reported increased trial-wise variability of saccade accuracy in unaffected relatives compared to controls, which was not found in the current study. One explanation for this inconsistency is that our prior study included both parents and siblings of individuals with ASD. Because we previously reported that saccade dysmetria improves with age (Luna, et al., 2007a; Schmitt, et al., 2014), it is possible that the younger-aged family sample in our prior study identified deficits that no longer are present in adult relatives of individuals with ASD. Similarly, this may account for observations of increased trial-to-trial variability of saccade accuracy in individuals with

ASD in the present study as well as in prior studies (Rosenhall, et al., 1988; Schmitt, et al., 2014; Stanley-Cary, et al., 2011; Takarae, et al., 2004b). Thus, alterations in the maturation of cerebellar-cortical brain networks responsible for controlling the consistency of eye movements may be relatively resolved by adolescence or adulthood in relatives of individuals with ASD.

Our finding of relatively spared rapid manual motor behavior in parents of individuals with ASD may be accounted for by critical differences in how we assessed *feedforward* control of eye and hand movements in the current study. Here, we examined reflexive visually-guided saccades that are ballistic in nature and occur rapidly, typically in < 80 ms. In contrast, precision gripping is under greater volitional control, occurs on a longer time scale, and in addition to manual motor processes, engages ocular motor processes responsible for fixating the retina on the force target. Thus, although we chose a rapid manual motor task that would closely match our reflexive saccade task, the precision gripping task does not isolate manual motor processes entirely. Therefore, our results may indicate relatively intact processes and/or the contribution of compensatory mechanisms from other processes involved to improve performance. We suggest the latter hypothesis based upon several findings. First, one mechanism whereby accuracy can be improved is by online corrections to the duration of the movement, such that reductions and extensions of duration can be used to shorten or prolong motor actions, respectively. Thus, current findings of reductions in the duration of rapid force increases in parents of individuals with ASD may be used to compensate for a tendency to overshoot initial force contractions, allowing the force contraction to end closer to the target than initially programmed. This would imply that parents of individuals with ASD are using *feedback* mechanisms to correct for error in their initial *feedforward* models. Second, the significant relationship between initial force contraction accuracy and dynamics, a result not demonstrated in controls or probands, suggests that modulations of precision grip durations are directly related to precision grip accuracy in parents of individuals with ASD. Thus, *feedforward* processes involved in rapid manual motor responses may be impaired in parents of individuals with ASD, but they are able to use compensatory strategies to help reduce these impairments. However, similar

compensatory strategies may not be used effectively to mitigate deficits in saccades because they are completed on a shorter time scale and more reflexive than rapid than grip force contractions.

We also demonstrated that parents of individuals with ASD demonstrated an association between their manual motor *feedforward* and *feedback* deficits. This is inconsistent with findings from Mosconi and colleagues (2010) who reported that *feedforward* saccade deficits were not related to *feedback* pursuit deficits in unaffected relatives. One possible explanation is that the relationship between *feedforward* and *feedback* mechanisms varies for different motor effectors (i.e., eye versus hand). Also, differences between our results and those reported previously (Mosconi, et al., 2010) may reflect differences in age of the family member samples. Developmentally, *feedforward* and *feedback* control processes mature along different time scales, such that *feedback* control is predominantly used to guide movements during childhood, whereas *feedforward* strategies gradually become more prominent in adolescence and adulthood (van Roon, et al., 2008). Thus, a greater level of distinction in Mosconi and colleagues' younger-aged sample may represent differences in the point of maturation at which *feedforward* and *feedback* control processes were examined. In light of these discrepancies, it will be important for future studies to determine the extent to which *feedforward* and *feedback* processes overlap or are differentiated in family members across development.

Ocular and Manual Motor Abnormalities as Intermediate Phenotypes in ASD

Here, we used a novel approach to examine motor abnormalities in individuals with ASD and their unaffected biological parents by studying family trios, which revealed that saccade dynamics and the variability of sustained force contractions inter-correlate among family members in ASD. Thus, these motor abnormalities with stronger covariance between genetically-related individuals implicate familiality of these deficits as well as shared physiological mechanisms. These findings confirm our hypothesis and are consistent with results from studies examining motor abnormalities in schizophrenia and related psychiatric disorders, which also have documented that ocular and manual motor deficits inter-correlate among affected probands and unaffected relatives (Clementz, Grove, Iacono, & Sweeney,

1992; Hong, Hou, Yen, Liou, & Tsai, 2006; Husted, Lim, Chow, Greenwood, & Bassett, 2009; Kathmann, Hochrein, Uwer, & Bondy, 2003; Lencer et al., 1999). In the schizophrenia literature, eye movement impairments have been implicated as an intermediate phenotype and leveraged to help parse the heterogeneity of the complex psychiatric disorder (Gottesman & Gould, 2003; Lencer et al., 2004; Ross, 2000; Sweeney et al., 1993). Based upon our findings, we suggest that saccade and precision gripping abnormalities are potential targets as intermediate phenotypes in ASD. However, the extent to which sensorimotor abnormalities can help parse heterogeneity in ASD remains undetermined as we observed associations between eye and hand impairments as well as *feedforward* and *feedback* deficits among individuals with ASD and parents of individuals with ASD.

Our findings that ocular and manual motor deficits inter-correlate among family members indicate that underlying cerebellar abnormalities may be familial. Given cerebellar regions have been consistently implicated in ASD from structural MRI and post-mortem studies (Fatemi, et al., 2002; Hashimoto, et al., 1995; Stanfield, et al., 2008a), our findings suggest that parents of individuals with ASD also may show a similar profile of cerebellar abnormalities. In fact, Peterson and colleagues (2006) documented volumetric cerebellar abnormalities in parents of individuals with ASD relative to controls. Specifically, they found reduced volume of anterior cerebellar regions and increased volume of posterior cerebellar regions as well as increased volume of the primary motor and somatosensory cortices in parents of individuals with ASD compared to controls (Peterson, et al., 2006). Notably, a previous study examining cerebellar activation in healthy monozygotic versus dizygotic twins revealed that 65% of the variance in cerebellar activation was accounted for by genetics (Blokland et al., 2014), and areas of particularly high genetic association were within lobules VI-II and Crus I. This suggests that cerebellar functioning, especially in regions that are known to be involved in eye and hand movements (Kuper, et al., 2012; Maderwald, et al., 2012; Neely, et al., 2013a; Stefanescu, et al., 2013; Thach, et al., 1992; Vaillancourt, et al., 2003), is heritable. Together, this suggests that functional deficits of regions known to be associated with *feedforward* and *feedback* motor control processes are heritable and are implicated

as familial mechanisms in ASD. Future studies should be aimed at using our present family trio design to determine the extent to which cerebellar abnormalities in ASD inter-correlate among family members.

However, because our SOLAR analyses can only offer conservative estimates regarding familiality, and not heritability (Kendler & Neale, 2009), it remains unknown whether specific genetic pathways contribute to our findings. Our results may be leveraged to provide insight into complex genetic mechanisms and pathways of transmission in ASD. Fundamental to the concept of intermediate phenotypes is the assumption that variation in the intermediate phenotype will depend on fewer genes that aggregate together among families who present with the intermediate phenotype (Gottesman & Gould, 2003). This would suggest that of the known >1000 genes implicated in ASD, those that underlie the specific motor deficits found in this study are fewer in number and more likely present in families who demonstrate motor impairments compared to families who do not demonstrate motor impairments. Thus, our results implicating the familiality of certain ocular and manual motor traits may allow for improved gene detection within more genetically homogenous samples.

It is important to consider hypothesized genetic mechanisms of ASD, including pleiotropy, epitasis, and cumulative and epigenetic effects, in the context of our current findings. For example, pleiotropy is defined as the effect of a single gene/variant on multiple related or unrelated phenotypes (He & Zhang, 2006; Sivakumaran et al., 2011). In this model, a single gene/variant could have causal pathways leading to restricted, repetitive behaviors as well as to motor impairments. In schizophrenia, pleiotropic phenotypes, including cardiovascular disease, have been found to be a risk indicator (Gejman et al., 2010). Thus, in the context of our findings, specific motor impairments, like abnormal saccade dynamics and sustained precision grip variability, may be risk factors for the development of ASD that are present in parents carrying risk genes and in their affected offspring.

Furthermore, epistasis is the interaction between genes, which has been implicated in ASD (Bradford et al., 2001; Folstein & Rosen-Sheidley, 2001; Jones & Szatmari, 2002), and specifically suggests that multiple ASD risk genes could interact with each other to have downstream causal effects.

Relatedly, cumulative genetic effects (Plomin & Kosslyn, 2001; Plomin, Owen, & McGuffin, 1994) also have been implicated in ASD (Klei et al., 2012; O'Roak, et al., 2012), such that a single gene or variant is neither necessary nor sufficient for the overall presentation of ASD. Instead, the majority of ASD cases may be the product of the number and severity of genetic hits as well as their interactions with each other and other environmental factors. Pickles and colleagues (1995) hypothesized that at least three genetic loci are needed to have causal effects in ASD via these epistatic interactions, but as many as 10 genetic loci are involved in a single individual. Here, this could help account for subtle differences observed in motor abnormalities found in individuals with ASD and their parents. For instance, probands and parents may share genetic liability for specific motor deficits, but only probands have enough genetic loading to lead to the disorder. Lastly, epigenetic effects, or changes in gene expression without co-occurring changes in gene sequence, have been indicated for ASD (Badcock & Crespi, 2006; Jiang, et al., 2004; Skuse, 2000; Tordjman et al., 2014), and also could account for differences in phenotypic expression of motor abnormalities between probands and parents. Parents and probands may share similar genetic architecture, but external factors (e.g., *in utero* environment) may influence which genes are turned on or off, thus may have different downstream effects on motor functioning.

CLINICAL AND SUB-CLINICAL ASSOCIATIONS WITH MOTOR DEFICITS

We reported novel finding of a relationship between initial force inaccuracy and restricted, repetitive behaviors in ASD suggesting common pathways underlying motor and core deficits. As previously noted, accuracy of rapid force contractions is dependent on cerebellar-mediated feedforward control. Notably, the cerebellum also is involved in non-motor behavior, including social and cognitive skills (Stoodley & Schmahmann, 2009). And, reduced cognitive flexibility, a manifestation of restricted, repetitive behaviors in ASD, has been observed in mice with 95% Purkinje cell loss (Dickson, Cairns, Goldowitz, & Mittleman, 2016). In addition, the striatum has been implicated in restricted, repetitive behaviors in ASD (Durand et al., 2007; Estes et al., 2011; Hollander, et al., 2005; Peca et al., 2011; Welch et al., 2007) (Hazlett, et al., 2005; Hollander, et al., 2005; Rojas, et al., 2006; Sears, et al., 1999) as well as

in feedforward and feedback processes during precision grip force (Prodoehl, Corcos, & Vaillancourt, 2009). Thus, the relationship between motor abnormalities and core features of restricted, repetitive behaviors may reflect shared cerebellar and/or striatal anomalies in individuals with ASD. Based upon this finding, future studies should be aimed at determining the extent to which saccade and precision gripping abnormalities can discriminate between neurodevelopmental disorders, which may help in the development of biologically-based measures used to diagnosis complex disorders.

Additionally, this relationship may represent broader clinical implications, such that impaired motor functioning may be related to more generalized abnormalities in cognitive and behavioral functioning. In fact, several groups have hypothesized that dsyfunction of the cerebellum, which develops prior to cortical and subcortical regions that support language and cognitive functioning, affects the maturation of the neocortical structures to which they are connected (D'Mello & Stoodley, 2015; Rogers et al., 2013; Wang, Kloth, & Badura, 2014a). Also, others have hypothesized that early motor deficits limit an infant's ability to engage with others and their environment, thus limiting his/her development of critical social-communication and cognitive skills. Yet, we did not find any significant relationships between motor abnormalities and cognitive or social-communication functioning in ASD. It should be noted that the present study used individuals with ASD who were of average intelligence, and possible associations between intellectual ability and motor deficits should be examined over a broader range of cognitive ability. Also, because our previous studies demonstrated a relationship increased precision gripping abnormalities and more severe social-communication deficits, (Mosconi et al., 2015a; Wang et al., 2014b), but we did not here, future studies also are needed to clarify the relationship between motor abnormalities and social-communication features of ASD.

As we previously reported (Schmitt, et al., 2014), individuals with ASD demonstrated age-related improvements in several motor variables, and the strengths of these relationships did not differ with controls. This suggests that the severity of motor deficits remain stable over time, and it also suggests that motor deficits emerge early in development and persist throughout the lifespan. This is consistent

with studies documenting that the cerebellum undergoes rapid growth between the last trimester and early postnatal period (Arsenio Nunes & Sotelo, 1985; Holland et al., 2014), and further refinement of motor circuitry occurs within the first postnatal months (Ashwell & Zhang, 1992). Thus, dysmaturation of cerebellum and associated motor circuits that occur prenatally or early postnatally may have cascading effects on the development of motor, cognitive, and social skills. In the context of our findings, early dysmaturation and impairments of *feedback* control processes, which are used predominantly in infancy and early childhood to guide motor behaviors, may lead to the dysmaturation and impairments of the regionally- and functionally-related *feedforward* control processes, that gradually become more prominent in adolescence (van Roon, Caeyenberghs, Swinnen, & Smits-Engelsman, 2008). Because *feedforward* and *feedback* mechanisms are involved in the majority of motor behaviors, it is possible that the dysmaturation of these processes impact more complex motor actions and behaviors, like walking and performing daily tasks of living (e.g., feeding, brushing teeth). Future studies are warranted to determine the extent to which *feedforward* and *feedback* deficits relate to other motor and adaptive behavior impairments observed in ASD. Notably, perinatal cerebellar injury is associated with a 36-fold increased risk of developing ASD, which is the greater known non-genetic risk factor in ASD (Limperopoulos, et al., 2007). Thus, early emergence of motor deficits likely represents early development of abnormalities within neural networks associated with motor functioning, and therefore may be leveraged for early identification of ASD risk.

In parents, we also documented novel findings of an association between motor deficits and subclinical features of ASD. Parents who had higher self-rated broad autism phenotype characteristics demonstrated more severe reductions in the accuracy of their initial force contractions. Consistent with previous findings in individuals with ASD (Wang, et al., 2014b), these findings suggest that there may be common mechanisms underlying social and motor deficits in parents of individuals with ASD. Additionally, parents who had higher spouse-rated sub-clinical ASD symptoms, especially for pragmatic language deficits, demonstrated greater reductions in saccade velocity and acceleration. This finding is

difficult to interpret given that parents showed increased velocities and acceleration of their saccades, and thus pragmatic communication deficits appear to be associated with less severely affected ocular motor control. It is important to note that this was only found for spousal ratings, which have been shown to differ from self-ratings for the BAP (Sasson, et al., 2014). Research determining the mechanisms linking sensorimotor and BAP deficits in family members are needed to determine whether these areas of impairment reflect common pathogenic processes.

Importantly, our study expands upon literature regarding the broad autism phenotype in unaffected biological family members of individuals with ASD. Previous studies have focused on sub-clinical features that parallel core deficits of the disorder (e.g., rigid personality characteristics, deficient social-communication skills, and abnormal language and speech profiles) or cognition (Murphy, et al., 2000; Pickles, et al., 2000; Piven, 2001; Piven & Palmer, 1999; Sasson, Lam, Parlier, Daniels, & Piven, 2013; Sasson, Nowlin, & Pinkham, 2013). Here, we showed that ocular and manual motor abnormalities are present in biological parents of individuals with ASD, and that these impairments may be familial and related to sub-clinical features of ASD. A more comprehensive approach is needed to understand the breadth of phenotypic features associated with BAP, and the extent to which motor abnormalities should be included.

There are several limitations to the current study. First, we used a small sample of individuals with ASD and parents of individuals with ASD, which may have reduced statistical power to identify significant results. This was particularly evident when comparing findings between the larger sample of individuals with ASD and the FT sample, as fewer significant findings were identified in the smaller FT sample. Further, because we only studied a small number of family trios, our ability to detect familial relationships of motor impairments is limited, especially given the heterogeneous nature of the disorder. SOLAR analyses are typically completed with hundreds of family trios, which allow for more reliable estimates of familiality. While our results show promising differences in sensorimotor control between unaffected parents and controls and familiality of several of these deficits, further systematic analyses of

these relationships with a larger sample of family trios is needed to clarify the extent to which specific motor deficits are inter-correlated among probands and their parents. Lastly, the current study only examined three measures of motor functioning and specifically did not study feedback ocular motor control. Thus, our findings were limited in their ability to determine the extent to which feedback deficits are observed across effectors in ASD and their parents.

CONCLUSION

This study expanded our current understanding of motor abnormalities in ASD by characterizing ocular and manual motor impairments among affected individuals and their relationships with one another. These deficits implicate cerebellar-mediated *feedforward* and *feedback* mechanisms responsible for controlling rapid and sustained motor responses, respectively. Further, our novel results show that parents of individuals with ASD demonstrate a similar profile of *feedforward* and *feedback* deficits as probands, and that certain ocular and manual motor impairments are familial in ASD. Together, our findings implicate diffuse cerebellar pathology that has widespread effects on motor functioning in ASD, and that also may be related to core diagnostic features of the disorder. Thus, we conclude that motor impairments in individuals with ASD are not merely an associated feature, but rather a manifestation of the disorder and its underlying neurobiological mechanisms. Further, because similar cerebellar pathways are indicated for individuals with ASD and their unaffected parents of individuals with ASD, our results suggest that sensorimotor deficits provide strong potential intermediate phenotypes that may be biological markers of risk and provide important insights into pathways of transmission in this complex disorder.

TABLES

Table 1. *Demographic information for all participants*

	ASD n = 54	**ASD Controls** n = 38	**Parents** n = 106†	**Parent Controls** n = 50
Age	10.5 (4.0)	11.7 (4.9)	41.4 (5.5)	39.6 (7.3)
Gender (% male)	96*	82	48	44
FSIQ	18.1 (18.6)**	110.1 (13.8)	111.2 (10.5)	108.6 (11.7)
VIQ	95.5 (19.7)***	109.6 (13.3)	108.7 (11.4)	106.0 (12.2)
PIQ	102.0 (18.2)	107.8 (14.9)	111.0 (10.7)	109.1 (11.8)

Mean(SD)

* $p < .05$, ** $p < .01$

† one set of parents had two offspring in the study

Table 2. *2-sec task variables for participants with ASD and matched controls*

	Individuals with ASD	ASD Controls
Maximum voluntary contraction (N)		
	56.9 (20.5)*	75.5 (33.6)
Onset of force production (s)		
15% MVC	.403 (.126)	.372 (.129)
45% MVC	.421 (.132)	.402 (.129)
85% MVC	.424 (.120)	.392 (.129)
Accuracy of initial force contraction (end of initial force contraction / target force x 100; %)		
15% MVC	151 (68.3)*	126 (23.4)
45% MVC	103 (16.2)	99 (12.5)
85% MVC	85 (14.1)	88 (8.9)
Peak rate of force increase/end of initial force contraction		
15% MVC	4.79 (1.22)	4.82 (1.11)
45% MVC	4.06 (1.30)	3.95 (1.00)
85% MVC	3.75 (1.17)*¤	3.36 (0.74)
Duration of initial force contraction/end of initial force contraction		
15% MVC	.110 (.145)	.104 (.037)
45% MVC	.055 (.037)	.043 (.030)
85% MVC	.034 (.019)*¤	.019 (.043)

Mean (SD)

* $p < .05$ for full sample of individuals with ASD

¤ $p < .05$ for family trio sample of individuals with ASD

Table 3. *8-sec task variables for participants with ASD and matched controls*

	Individuals with ASD	ASD Controls
Maximum voluntary contraction (N)		
	57.2 (32.2)*	73.0 (24.7)
Onset of force production (s)		
15% MVC	.591 (.241) *¤	.494 (.164)
45% MVC	.610 (.241)	.526 (.166)
85% MVC	.665 (.281)	.578 (.237)
Accuracy of initial force contraction (end of initial force contraction / target force x 100; %)		
15% MVC	174 (95.8) *	134 (44.2)
45% MVC	98 (26.3) ¤	99 (17.4)
85% MVC	77 (16.2) ¤	76 (13.1)
Peak rate of force increase/end of initial force contraction		
15% MVC	4.93 (1.54)	4.36 (0.83)
45% MVC	4.12 (1.31) ¤	3.66 (0.97)
85% MVC	3.51 (1.23)	3.14 (0.95)
Duration of initial force contraction/end of initial force contraction		
15% MVC	.121 (.100)	.101 (.082)
45% MVC	.071 (.044)* ¤	.037 (.021)
85% MVC	.057 (.047)* ¤	.035 (.017)
Accuracy of sustained force contraction (mean force / target force x 100; %)		
15% MVC	111 (27.5)*	102 (7.7)
45% MVC	96 (5.7)	97 (3.5)
85% MVC	80 (12.3)* ¤	87 (9.2)
Coefficient of variation (SD of detrended force / mean force)		
15% MVC	.078 (.047)* ¤	.060 (.034)
45% MVC	.103 (.074)** ¤	.071 (.036)
85% MVC	.189 (.106)* ¤	.137 (.096)

Mean (SD)

* $p < .05$, ** $p < .01$ for full sample of individuals with ASD

¤ $p < .05$ for family trio sample of individuals with ASD

Table 4. *2-sec task variables for parents of individuals with ASD and matched controls*

	Parents of Individuals with ASD	Parent Controls
Maximum voluntary contraction (N)		
	104.0 (31.9)	100.0 (27.0)
Onset of force production (s)		
15% MVC	.321 (.090)	.322 (.091)
45% MVC	.354 (.106)	.356 (.107)
85% MVC	.364 (.102)	.362 (.102)
Accuracy of initial force contraction (end of initial force contraction / target force x 100; %)		
15% MVC	126 (31.2)	118 (16.7)
45% MVC	104 (8.7)	103 (8.3)
85% MVC	94 (6.7)	95 (6.6)
Peak rate of force increase/end of initial force contraction		
15% MVC	5.15 (1.32)	5.33 (1.14)
45% MVC	4.37 (1.16)	4.49 (1.20)
85% MVC	3.85 (0.99)	4.00 (0.95)
Duration of initial force contraction/end of initial force contraction		
15% MVC	.067 (.026)	.069 (.056)
45% MVC	.026 (.008)	.029 (.0123)
85% MVC	.016 (.005)	.017 (.008)

Mean (SD)

* $p < .05$ for full sample of parents of individuals with ASD

¤ $p < .05$ for family trio sample of parents of individuals with ASD

Table 5. *8-sec task variables for parents of individuals with ASD and matched controls*

	Parents of Individuals with ASD	Parent Controls
Maximum voluntary contraction (N)		
	105.6 (26.0)	96.5 (26.3)
Onset of force production (s)		
15% MVC	.415 (.158)	.403 (.107)
45% MVC	.458 (.182)	.454 (.163)
85% MVC	.487 (.201)	.470 (.178)
Accuracy of initial force contraction (end of initial force contraction / target force x 100; %)		
15% MVC	127 (30)	123 (40)
45% MVC	103 (13)	99 (17)
85% MVC	88 (14)	90 (16)
Peak rate of force increase/end of initial force contraction		
15% MVC	4.77 (1.50)	4.63 (1.29)
45% MVC	3.64 (1.04)	3.58 (1.12)
85% MVC	3.08 (0.94)	3.00 (0.74)
Duration of initial force contraction/end of initial force contraction		
15% MVC	.048 (.015)*	.058 (.027)
45% MVC	.017 (.010)	.023 (.019)
85% MVC	.017 (.016)	.016 (.008)
Accuracy of sustained force contraction (mean force / target force x 100; %)		
15% MVC	100.8 (2.5)	101.2 (2.2)
45% MVC	98.4 (1.9)* ¤	99.1 (1.2)
85% MVC	92.7 (6.2)	95.0 (5.4)
Coefficient of variation (SD of detrended force / mean force)		
15% MVC	.028 (.013)	.026 (.011)
45% MVC	.028 (.017)	.023 (.009)
85% MVC	.036 (.015)*	.030 (.011)

Mean (SD)

* $p < .05$ for full sample of individuals with ASD

¤ $p < .05$ for family trio sample of individuals with ASD

Table 6. *Familiality estimates for precision gripping and saccade variables*

Task	Variable	h^2
8-sec Precision Gripping	Sustained Force Variability (CoV)	0.326*
Visually-Guided Saccade	Peak Saccade Velocity	0.778**
	Peak Saccade Acceleration	0.874***
	Peak Saccade Deceleration	0.796**

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 7. *Visually-guided variables for individuals with ASD and matched controls*

	Individuals with ASD	ASD Controls
Saccade latency in ms		
12 deg	227 (34.2)	232 (35.0)
24 deg	238 (40.2)	253 (26.8)
Saccade error (absolute value in deg of visual angle)		
12 deg	1.28 (.546)	1.13 (.300)
24 deg	2.03 (.556)** ¤¤	1.49 (.460)
Trial-wise variability (SD) of saccade error (absolute value in deg)		
12 deg	.867 (.264)	.777 (.227)
24 deg	1.441 (.415)* ¤	1.108 (.385)
Saccade gain (saccade amplitude / target amplitude)		
12 deg	.914 (.058)	.926 (.039)
24 deg	.926 (.029)* ¤	.948 (.025)
Trial-wise variability (SD) of saccade gain		
12 deg	.092 (.026)	.081 (.024)
24 deg	.079 (.036)* ¤	.056 (.021)
Peak saccade velocity / saccade amplitude		
12 deg	35.69 (5.28)*	32.29 (4.66)
24 deg	24.33 (2.54)** ¤¤	21.20 (2.51)
Saccade duration / saccade amplitude		
12 deg	5.32 (0.56)	5.51 (0.48)
24 deg	3.51 (0.33)** ¤	3.91 (0.44)
Peak acceleration / saccade amplitude		
12 deg	3178 (621)*	2721 (646)
24 deg	1955 (337)** ¤	1633 (341)
Peak deceleration / saccade amplitude		
12 deg	2438 (523)*	2156 (446)
24 deg	1245 (254)** ¤¤	994 (212)
Duration of acceleration / saccade amplitude		
12 deg	1.20 (0.11)	1.28 (0.16)
24 deg	0.72 (0.11)	0.77 (0.13)
Duration of deceleration / saccade amplitudes		
12 deg	1.57 (0.18)	1.59 (0.17)
24 deg	1.09 (0.12)** ¤¤	1.26 (0.20)
Ratio duration of acceleration/duration of deceleration		
12 deg	.768 (.062)	.810 (.134)
24 deg	.671 (.121)	.619 (.129)

Mean (SD)

* $p < .05$, ** $p < .01$ for full sample of individuals with ASD

¤ $p < .05$, ¤¤ $p < .01$ for family trio sample of individuals with ASD

Table 8. *Visually-guided variables for parents of individuals with ASD and matched controls*

	Parents of Individuals with ASD	Parent Controls
Saccade latency in ms		
12 deg	229 (27)	239 (34)
24 deg	251 (30)	249 (25)
Saccade error (absolute value in deg of visual angle)		
12 deg	0.95 (0.39)	0.91 (0.36)
24 deg	1.50 (0.52)	1.41 (0.52)
Trial-wise variability (SD) of saccade error (absolute value in deg)		
12 deg	.684 (.251)	.712 (.298)
24 deg	.921 (.360)	.915 (.292)
Saccade gain (saccade amplitude / target amplitude)		
12 deg	.942 (.044)	.941 (.037)
24 deg	.943 (.027)^{M}	.950 (.029)
Trial-wise variability (SD) of saccade gain		
12 deg	.072 (.026)	.073 (.027)
24 deg	.046 (.018)	.047 (.016)
Peak saccade velocity / saccade amplitude		
12 deg	35.20 (4.52)*	22.52 (4.52)
24 deg	23.47 (2.35)*$^{D\,¤}$	22.10 (2.35)
Saccade duration / saccade amplitude		
12 deg	5.53 (0.72)*^{D}	5.89 (0.93)
24 deg	3.387 (0.63)^{D}	4.12 (0.85)
Peak acceleration / saccade amplitude		
12 deg	3156 (588)	2973 (646)
24 deg	1940 (326)	1823 (403)
Peak deceleration / saccade amplitude		
12 deg	2410 (558)	2212 (534)
24 deg	1033 (280)	987 (246)
Duration of acceleration / saccade amplitude		
12 deg	1.29 (.25)	1.36 (.27)
24 deg	0.74 (.22)	0.80 (.21)
Duration of deceleration / saccade amplitudes		
12 deg	1.61 (.24)**^{D}	1.73 (.23)
24 deg	1.23 (.23)^{D}	1.31 (.25)
Ratio duration of acceleration/duration of deceleration		
12 deg	.768 (.062)	.810 (.134)
24 deg	.671 (.121)	.619 (.129)

Mean (SD)

* $p < .05$, ** $p < .01$, *** $p < .001$ for full sample of individuals with ASD

¤ $p < .05$, ¤¤ $p < .01$, ¤¤¤ $p < .001$ for family trio sample of individuals with ASD

^{D} indicates fathers of individuals with ASD significantly different from control fathers

^{M} indicates mothers of individuals with ASD significantly different from control mothers

Table 9. *Demographic information for all family trios*

	ASD n = 40	**ASD Controls** n = 38	**Parents** n = 78[†]	**Parent Controls** n = 50
Age	10.4 (3.9)	11.7 (4.9)	41.4 (5.7)	39.6 (7.3)
Gender (% male)	95	82	50	44
FSIQ	100.0 (19.2)*	110.1 (13.8)	112.6 (10.2)	108.6 (11.7)
VIQ	96.1 (20.9)**	109.6 (13.3)	109.8 (10.9)	106.0 (12.2)
NVIQ	104.7 (17.8)	107.8 (14.9)	112.4 (10.5)	109.1 (11.8)

Mean (SD)
*$p < .05$, ** $p < .01$
[†] one set of parents had two offspring in the study

Table 10. *Correlation matrix of primary motor variables for individuals with ASD*

		2-sec Task	**8-sec Task**					**Visually-Guided Saccade Task**				
		Peak Rate of Increase (85%)	Accuracy of Initial Movement (15%)	Peak Rate of Increase	Accuracy of Sustained Movement (15%)	Accuracy of Sustained Movement (85%)	Variability of Sustained Movement	Saccade Error (24 deg)	Saccade Error Variability (24 deg)	Saccade Peak Velocity (24 deg)	Saccade Duration (24 deg)	Saccade Peak Acceleration
2-sec Task	Accuracy of Initial Movement (15%)	-.302	.707**^{Z}††	-.227	.440*†	-.527*^{Z}¤	.775**^{Z}††	.598*†	.543#¤	.012	-.276	.270
	Peak Rate of Increase (85%)		-.336#	.730**¤	-.347#	.296	-.430*¤	.045	.163	.018	.035	-.054
8-Sec Task	Accuracy of Initial Movement (15%)			.124	.588**†	-.144	.562**^{Z}††	.133	.044	.097	-.180	.091
	Peak Rate of Increase				-.192	.444*^{Z}	-.324#	.252	.343	.199	-.164	.050
	Accuracy of Sustained Movement (15%)					-.312#†	.358#†	-.102	-.347	-.287	.093	.150
	Accuracy of Sustained Movement (85%)						-.721**††	-.173	-.096	.217	-.145	.074
	Variability of Sustained Movement							.100	-.041	-.360	.227	-.181
	Saccade Error (24 deg)								.863**††	-.016	-.222	.138
Visually-Guided Saccade Task	Saccade Error Variability (24 deg)									.040	-.194	.290
	Saccade Peak Velocity (24 deg)										-.776**††	.698**††
	Saccade Duration											-.666**††

# p < .05 * p < .01 ** p < .001 in full sample

¤ p < .05, † p < .01, †† p < .001 in family trio sample

Table 11. *Correlation matrix of primary variables for controls matched to individuals with ASD*

		2-sec Task	**8-Sec Task**					**Visually-Guided Saccade Task**				
		Peak Velocity of Initial Movement (85%)	Accuracy of Initial Movement (15%)	Peak Rate of Increase	Accuracy of Sustained Movement (15%)	Accuracy of Sustained Movement (85%)	Variability of Sustained Movement	Saccade Error (24 deg)	Saccade Error Variability (24 deg)	Saccade Peak Velocity (24 deg)	Saccade Duration (24 deg)	Saccade Peak Acceleration
2-sec Task	Accuracy of Initial Movement (15%)	-.049	.107	.023	-.200	.100	.015	.245	.366	.049	-.116	.323
	Peak Velocity of Initial Movement (85%)		-.202	.853**	-.415#	.091	-.423#	.020	-.155	-.007	.192	.009
8-Sec Task	Accuracy of Initial Movement (15%)			.027	.707**	.000	.124	.394	.215	-.328	.379	.183
	Peak Rate of Increase				-.350#	-.100	-.263	.095	-.052	.129	.186	.177
	Accuracy of Sustained Movement (15%)					.204	.172	.099	.037	-.431	.168	-.007
	Accuracy of Sustained Movement (85%)						-.721**	-.296	-.299	.104	-.232	-.118
	Variability of Sustained Movement							.157	.304	-.187	.055	.027
	Saccade Error (24 deg)								.876**	-.110	-.183	.143
	Saccade Error Variability (24 deg)									.151	-.419	.266
Visually-Guided Saccade Task	Saccade Peak Velocity (24 deg)										-.752**	.519#
	Saccade Duration											-.241

# p < .05, * p < .01, ** p < .001

Table 12. *Correlation matrix of primary variables for parents of individuals with ASD*

		2-sec Task	**8-Sec Task**					**Visually-Guided Saccade Task**				
		Peak Velocity of Initial Movement (85%)	Accuracy of Initial Movement (15%)	Peak Rate of Increase	Accuracy of Sustained Movement (15%)	Accuracy of Sustained Movement (85%)	Variability of Sustained Movement	Saccade Error (24 deg)	Saccade Error Variability (24 deg)	Saccade Peak Velocity (24 deg)	Saccade Duration (24 deg)	Saccade Peak Acceleration
2-sec Task	Accuracy of Initial Movement (15%)	.280*¤	.401**††	.354*	.116	.130	.238#	-.251#	-.111	.340*^{Z}†	-.127	.127
	Peak Velocity of Initial Movement (85%)		.054	.848**††	-.071	-.292*††	-.055	-.224¤	-.041	.156	-.057	.081
8-Sec Task	Accuracy of Initial Movement (15%)			.327*	.334*†	.087	.437**^{Z}††	.010	-.044	.086	-.074	.094
	Peak Rate of Increase				.039	-.203¤	.102	-.234	-.089	.157	-.007	.179
	Accuracy of Sustained Movement (15%)					.186	.094	-.208	-.157	.132	-.067	.028
	Accuracy of Sustained Movement (85%)						-.438**††	-.028	-.142	.085	-.129	.047
	Variability of Sustained Movement							.042	.138	-.163	.184	-.042
	Saccade Error (24 deg)								.567**††	-.385**††	.077	-.211¤
Visually-Guided Saccade Task	Saccade Error Variability (24 deg)									-.284#†	.223#¤	-.212¤
	Saccade Peak Velocity (24 deg)										-.730**††	.670**††
	Saccade Duration											-.474**††

# p < .05 * p < .01 ** p < .001
¤ p < .05, † p < .01, †† p < .001 in family trio sample

Table 13. *Correlation matrix of primary variables for controls matched to parents of individuals with ASD*

		2-sec Task	**8-Sec Task**					**Visually-Guided Saccade Task**				
		Peak Velocity of Initial Movement (85%)	Accuracy of Initial Movement (15%)	Peak Rate of Increase	Accuracy of Sustained Movement (15%)	Accuracy of Sustained Movement (85%)	Variability of Sustained Movement	Saccade Error (24 deg)	Saccade Error Variability (24 deg)	Saccade Peak Velocity (24 deg)	Saccade Duration (24 deg)	Saccade Peak Acceleration
2-sec Task	Accuracy of Initial Movement (15%)	-.047	.676**	.061	.258	.214	.155	.118	.339#	-.064	.049	-.027
	Peak Velocity of Initial Movement (85%)		-.098	.722**	-.068	.021	-.216	.153	.077	.132	-.024	.310
8-Sec Task	Accuracy of Initial Movement (15%)			.209	.339#	.198	.030	-.059	.311#	-.008	.059	.053
	Peak Rate of Increase				.102	.013	-.189	.156	.236	-.006	.123	.208
	Accuracy of Sustained Movement (15%)					.299	-.024	.017	.109	-.013	.008	-.004
	Accuracy of Sustained Movement (85%)						-.556**	-.236	-.162	-.054	.092	-.029
	Variability of Sustained Movement							-.026	.047	-.073	-.033	-.067
	Saccade Error (24 deg)								.532**	-.157	.147	.034
Visually-Guided Saccade Task	Saccade Error Variability (24 deg)									-.147	.183	-.018
	Saccade Peak Velocity (24 deg)										-.724**	.684**
	Saccade Duration											-.520**

# p < .05 * p < .01 ** p < .001

Table 14. *Correlations with Clinical Features of ASD*

		ADI: A Total (Social)	**ADI: B Total (Comm)**	**ADI: C Total (RRBs)**	**ADOS: Soc-Comm Total**	**ADOS: RRBs**
2-sec Task	Accuracy of Primary Movement	.094	.236	.083	-.013	.497**
	Accuracy of Primary Movement (15%)	.144¤	.317	.178	-.072	.369#¤
8-sec Task	Accuracy of Primary Movement (15%)	-.045	.224	-.028	-.177¤	.140
	Peak Rate of Increase	-.121	-.326	-.393#	.070	-.040
	Accuracy of Sustained Movement (15%)	.074	.330	.112	-.116	.028
	Accuracy of Sustained Movement (85%)	.028	-.084	-.261	.205	.000
	Variability of Sustained Movement	-.142¤	-.002	.128	-.208	.069
Visually-Guided Saccade	Saccade Error (24 deg)	-.195	-.177	.034	-.123	.022
	Saccade Error Variability (24 deg)	-.262	-.290	.033	-.115	-.003
	Saccade Peak Velocity (24 deg)	.146	.234	.308	-.226	.254
	Saccade Duration	-.131	-.358	-.333	.115	-.228
	Saccade Peak Acceleration	.256	.307	.032	.137	.311

# $p < .05$, * $p < .01$, ** $p < .001$ for larger sample
¤ $p < .05$, † $p < .01$ for FT sample

APPENDIX A
Supplementary Tables

Supplementary Table 1**.** *Additional 2-sec task variables for participants with ASD and controls*

	Individuals with ASD	ASD Controls
End of initial force contraction (N)		
15% MVC	11.9 (3.86)	14.1 (5.98)
45% MVC	26.1 (9.49)	24.3 (17.7)
85% MVC	41.4 (17.1)*¤	57.5 (27.6)
Peak rate of force increase (N/s)		
15% MVC	56.4 (21.8)	69.8 (38.2)
45% MVC	105.4 (50.9)	140.7 (86.4)
85% MVC	147.3 (58.1)	195.8 (109.4)
Duration of initial force contraction (s)		
15% MVC	1.20 (.105)¤	1.22 (.367)
45% MVC	1.25 (.309)	1.14 (.409)
85% MVC	1.21 (.116)	0.82 (1.96)

Mean (SD)
* $p < .05$ for full sample of individuals with ASD
¤ $p < .05$ for family trio sample of individuals with ASD

Supplementary Table 2. *Additional 8-sec task variables for participants with ASD and controls*

	Individuals with ASD	ASD Controls
End of initial force contraction (N)		
15% MVC	13.9 (7.5)	14.2 (5.4)
45% MVC	25.0 (14.0) ¤	32.8 (13.9)
85% MVC	27.8 (21.7)*	47.8 (19.9)
Peak rate of force increase (N/s)		
15% MVC	69.3 (49.8)	63.6 (33.2)
45% MVC	102.7 (61.5)	118.5 (59.4)
85% MVC	127.0 (82.7)	146.4 (68.5)
Duration of initial force contraction (s)		
15% MVC	1.32 (0.73)	1.4 (1.30)
45% MVC	1.34 (0.47)	1.02 (0.35)
85% MVC	1.61 (0.79)	1.40 (0.47)
Mean force contraction (N)		
15% MVC	9.2 (4.44) *¤	11.1 (3.62)
45% MVC	24.9 (13.2)** ¤	31.9 (10.9)
85% MVC	40.8 (26.5) **¤	54.0 (12.7)
Variability of sustained force contraction (SD of detrended force; N)		
15% MVC	0.64 (0.33)	0.62 (0.31)
45% MVC	2.18 (1.13)	2.10 (0.92)
85% MVC	6.12 (2.80)	6.40 (3.51)

Mean (SD)

* $p < .05$, ** $p < .01$ for full sample of individuals with ASD

¤ $p < .05$, ¤¤ $p < .01$ for family trio sample of individuals with ASD

Supplementary Table 3. *Additional visually-guided saccade variables for individuals with ASD and matched controls*

	Individuals with ASD	ASD Controls
Peak saccade velocity (deg/s)		
12 deg	388 (63.2)	358 (47.1)
24 deg	537 (53.7)** ¤	481 (57.2)
Saccade duration (ms)		
12 deg	57.3 (5.43)*	60.9 (6.31)
24 deg	77.9 (7.24)*** ¤¤	88.8 (10.2)
Peak acceleration (deg/s/s)		
12 deg	34464 (6676)	30079 (6778)
24 deg	43219 (7361)* ¤	36998 (7628)
Peak deceleration (deg/s/s)		
12 deg	26522 (6033)*	23830 (4612)
24 deg	27328 (5285)** ¤	22472 (4655)
Duration of acceleration (ms)		
12 deg	12.9 (1.17)	14.1 (1.93)
24 deg	16.1 (2.61)	17.3 (2.81)
Duration of deceleration (ms)		
12 deg	16.9 (1.82)	17.5 (2.16)
24 deg	24.3 (2.73)** ¤¤	28.7 (4.62)

Mean (SD)

* $p < .05$, ** $p < .01$, *** $p < .001$ for full sample of individuals with ASD

¤ $p < .05$, ¤¤ $p < .01$ for family trio sample of individuals with ASD

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