Movement Kinematic and Electrophysiological Signatures of Sensorimotor Integration in Autism

By

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DEDICATION

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Chapter 1

Introduction

Stereotyped motor behavior is traditionally defined as rhythmic, repetitive, invariant movement. It occurs in a vast number of species ranging from invertebrates such as worms and insects to vertebrates such as birds and mammals – including humans (Berman, Choi, Bialek, & Shaevitz, 2014; Garner, Mason, & Smith, 2003; Mark Lewis & Kim, 2009; Stephens, Bueno de Mesquita, Ryu, & Bialek, 2011; Thelen, 1979). Despite its ubiquity, there is a conflict surrounding the phenomenon of motor stereotypy. It can be adaptive, as it is in healthy human infants, where it is a transitional state in motor development. It can also be maladaptive, as it is in a variety of neurodevelopmental, neuropsychiatric and neurologic disorders, where it interferes with goal-directed behavior. Research on motor stereotypy and the conceptual and neurobiological models aimed at understanding its genesis focus on either the adaptive or the maladaptive aspects of the behavior. Currently, there is no framework that accounts for both manifestations. Here we present a mechanistic framework that accounts for both the adaptive and maladaptive presentation of motor stereotypy.

1.1 Stereotypy as a transitional state in healthy motor development

Stereotyped motor behaviors occur in early infancy as a transitional state of motor development. Thelen (1979) observed that simple, repetitive behaviors including arm waving and body rocking preceded complex motor behaviors – goal-directed reaching and crawling, respectively – that involved the use of the same body segments. In a study of infant repetitive kicking, Thelen and Fisher (1983b) measured electromyography and joint-angle rotation in infants' legs. At around one month of age, kicks were characterized by tight temporal and spatial synchrony of the hip, knee, and ankle joints and a

simultaneous contraction of antagonistic muscle groups during the flexion phase followed by passive movement during the extension phase. Similar muscle activation and joint angle relationships occur during supported stepping in one month old infants (Thelen & Cooke, 1987). By two months of age, the ankle rotation is less correlated with the knee and hip joints, eventually reaching an adult-like negative correlation by the time infants are walking independently. Additionally, complex, phasic muscle activation replaces simple, tonic co-contraction of the muscles.

A similar transition occurs in the arm when infants are learning how to reach for a toy. Before they are able to execute controlled, accurate reaches, infants generate repetitive arm movements with patterns of motor activity that are inefficient relative to the dynamic physical properties of the arm and the goal of reaching the toy (Konczak, Borutta, Topka, & Dichgans, 1995; Thelen et al., 1993). Using these inefficient reach approximations as a starting point, infants explore the dynamics of their arms through adjusting the amplitude and timing of muscle activation, ultimately allowing them to generate more accurate and efficient reaches with muscle activation patterns that more closely resemble adult-like patterns. These findings demonstrate that simple, stereotyped motor behavior in infants is the foundation on which complex, functional behavior is built. However, this adaptive view of motor stereotypy does not account for stereotyped behavior in clinical conditions.

1.2 Stereotypy in developmental, neurologic, and psychiatric disorders

Stereotyped motor behavior is present in a variety of developmental, neurologic and psychiatric disorders including fronto-temportal dementia (Mendez, Shapira, & Miller, 2005), schizophrenia (Morrens, Hulstijn, Lewi, De Hert, & Sabbe, 2006), and neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD; American Psychatric Association, 2013; Goldman et al., 2009). It can be induced in animals via lesions (e.g., ventromedial thalamic nucleus (Zainos, DeAnda, Chavez, & Garcia-Munoz, 1984), nigrostriatal dopamine projections (Simola, Morelli, & Carta, 2007)), pharmacological agents, genetic manipulations, or barren cage environments (M Lewis, Tanimura, Lee, & Bodfish, 2007;

Peça et al., 2011; Stearns et al., 2007). In clinical populations, motor stereotypy is considered abnormal, maladaptive, and apparently purposeless (Cooper & Dourish, 1990) as it is not goal-directed. Unlike in normative development, stereotypy in disease states poses a functional impairment by interfering with complex, adaptive behavior. For example, stereotypy in individuals with ASD has been shown to interfere with play (Koegel, Firestone, Kramme, & Dunlap, 1974) and learning (Koegel & Covert, 1972; K. Morrison & Rosales-Ruiz, 1997).

Because motor stereotypy is highly prevalent in disease, it is often indicative of neural pathology. It is primarily associated with deficits in cortico-striatal-thalamic circuitry. Parkinson's disease patients have degeneration of dopaminergic medium spiny neurons that project to the striatum (Braak & Del Tredici, 2008). Lesioning these dopaminergic projections in animals recapitulates many symptoms of Parkinson's disease including tremor and levadopa induced dyskinesia (Simola et al., 2007). Additionally, injecting dopamine agonists into the striatum induces stereotypy in rodents (Delfs & Kelley, 1990; Kelley, Lang, & Gauthier, 1988). Animal studies of autism associated genes (Peça et al., 2011; Stearns et al., 2007) and cage-induced stereotypy (Presti & Lewis, 2005; Tanimura, Yang, Ottens, & Lewis, 2010) also implicate alterations of basal ganglia circuitry in the phenomenology of stereotyped motor behavior. However, neurologic disorder or insult does not account for motor stereotypy in healthy infant development.

1.3 A coherent framework for stereotypy in typical and atypical development

Hypothesis: *poor sensorimotor integration results in low motor complexity leading to the presence of stereotyped behavior in both normative development and disease states.*

Motor complexity provides an adaptive advantage for interacting with the environment since higher complexity permits more flexibility in motor output. This is based on Bernstein's (1967) concept of skill as a reflection of mastering redundant degrees of freedom in motor learning. He posited that the body is composed of multiple biomechanical degrees of freedom that can be utilized in several ways to

achieve the same goal. Motor control is contingent on the ability to use these degrees of freedom to flexibly interact with the environment. In normative development, when the motor system is immature or in a state of early motor learning, the system constrains the degrees of freedom to gain some control and produce stable movements for a given task. This results in simple movements such as the repetitive kicking that Thelen and Fisher (1983b) observed. As the motor system matures or learning progresses, degrees of freedom are released to permit greater specificity and efficiency of movement. This is supported by findings that higher motor complexity is associated with more accurate motor task performance (Deutsch & Newell, 2001; M. W. Mosconi et al., 2015).

Our model elaborates on Bernstein's (1967) postulate by emphasizing an important role of sensorimotor integration in the ability to release biomechanical degrees of freedom to produce controlled, complex movements. Sensorimotor integration involves communication between the sensory and motor systems in the brain allowing for a) the use of sensory input to generate an accurate and efficient motor plan (e.g., through an inverse model) and b) the use of self-generated and external sensory feedback to monitor and correct error in the movement (e.g., updating the forward model in the ongoing movement or for future movements; see (Wolpert, Miall, & Kawato, 1998) for a description of these processes in the cerebellum). Under our framework, sensory input allows the motor system to plan and execute accurate movements by making optimal use of the available degrees of freedom and to correct error in the movement by exploiting the available degrees of freedom to make adjustments that are appropriate to the error.

In the case of stereotyped behavior in healthy infants, our model suggests that the infant brain does not efficiently integrate sensory information with the motor system because either the sensory and motor regions of the brain are immature, or the infant has limited experience with or access to sensory information (e.g., due to immobility). Poor sensorimotor integration prevents the infant from using his/her degrees of freedom flexibly and efficiently, limiting his movements to simple, stereotyped behaviors. With maturity, the infant is able to integrate sensory information with motor behavior permitting him to release degrees of freedom to produce complex movements.

Similarly, our model posits that deficits in sensorimotor integration contribute to the emergence and maintenance of stereotyped behavior in clinical disorders. Whether it is caused by atypical development of sensorimotor circuitry, degenerative processes, or another form of altered neural function, these alterations could contribute to the persistence of stereotyped behavior by disrupting the sensory inputs that are required to inform and diversify motor repertoires.

1.4 Neural circuitry supporting sensory influence on motor function

The role of sensorimotor integration in motor control and complexity is consistent with the structural and functional connectivity of sensorimotor neural circuitry. While this sensorimotor connectivity occurs in several brain regions involved in motor control, including cortex, basal ganglia (Flaherty & Graybiel, 1994), and cerebellum (Proville et al., 2014; Wiestler, McGonigle, & Diedrichsen, 2011), we will describe the cortical reach pathway, depicted in **Figure 1**, as it is a well-studied example of this phenomenon.

Visual information from prestriate (V2) and extrastriate (V3, V3a, MT/MST) cortices (Colby, Gattass, Olson, & Gross, 1988; J. W. Lewis & Van Essen, 2000; Maunsell & van Essen, 1983) and somatosensory information from primary (SI) and secondary (SII) somatosensory cortices (Cipolloni & Pandya, 1999; Jones & Powell, 1969; Pandya & Seltzer, 1982) projects to sensorimotor regions including the lateral (LIP), ventral (VIP), and medial (MIP) intraparietal areas and Brodmann's area 5. SI and SII also project to frontal regions including primary motor cortex (M1), and supplementary motor area (SMA; Cipolloni and Pandya, 1999; Jones and Powell, 1969; Pandya and Seltzer, 1982). The intraparietal areas are interconnected (Blatt, Andersen, & Stoner, 1990; J. W. Lewis & Van Essen, 2000) , and represent target, eye, and limb position in various reference frames (Bremner & Andersen, 2012; Brotchie, Andersen, Snyder, & Goodman, 1995; Duhamel, Bremmer, BenHamed, & Graf, 1997; Ferraina & Bianchi, 1994; Gnadt & Andersen, 1988; Johnson, Ferraina, Bianchi, & Caminiti, 1996; Pesaran, Nelson, & Andersen, 2006).

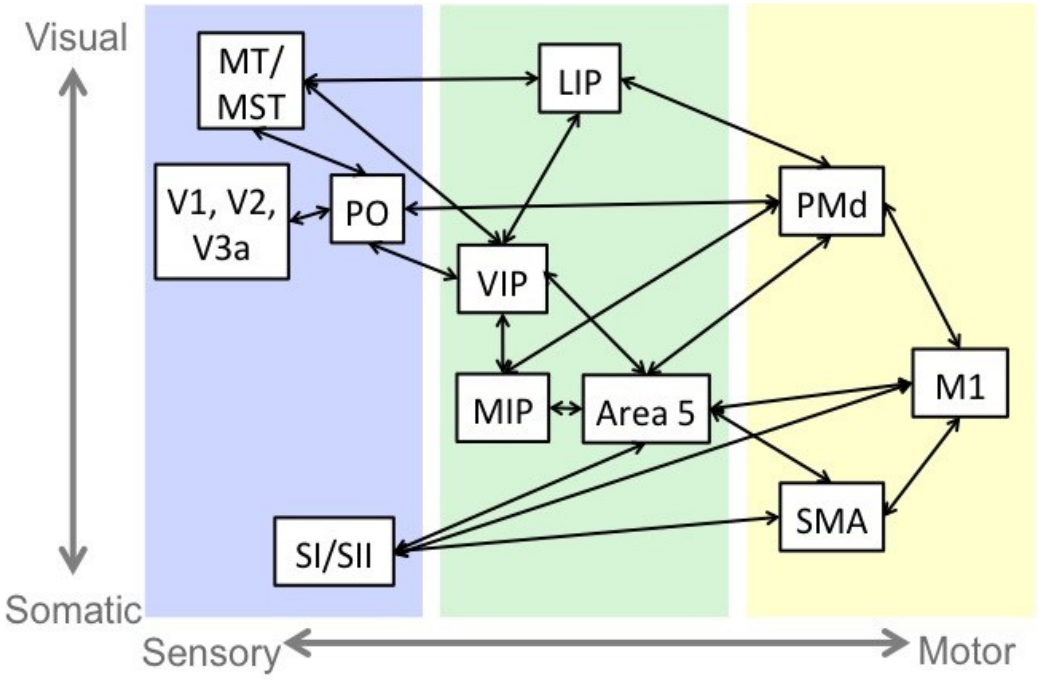

Figure 1: An example of sensorimotor circuitry: the reach pathway. Blue indicates regions that are primarily responsive to sensory stimulation. Green indicates regions that have sensory and motor responses, and yellow indicates regions that have primarily motor related activity. There is a tendency in the sensory and sensorimotor areas for regions near the top of the figure to represent visual information and the regions near the bottom to represent somatosensory information. Abbreviations: middle temporal area (MT), medial superior temporal area (MST), primary visual cortex (V1), secondary visual cortex (V2), visual area 3a (V3a), parieto-occipital area (PO), primary somatosensory cortex (SI), secondary somatosensory cortex (SII), lateral intraparietal cortex (LIP), medial intraparietal cortex (MIP), ventral intraparietal cortex (VIP), dorsal premotor cortex (PMd), primary motor cortex (MI), supplementary motor area (SMA).

The sensorimotor areas project to frontal motor regions including dorsal premotor cortex (PMd), SMA, and M1 (Johnson et al., 1996; Jones, Coulter, & Hendry, 1978; Jones & Powell, 1970; Jürgens, 1984; Pandya & Kuypers, 1969; Petrides & Pandya, 1984; Strick & Kim, 1978), which are active during motor planning (Alexander & Crutcher, 1990; Pesaran et al., 2006) and execution (Johnson et al., 1996). The motor cortices send the motor command to the body and to sensory and sensorimotor cortices to inform the sensorimotor system of the expected sensory consequences of the movement and monitor movement accuracy (Christensen et al., 2007; Desmurget & Grafton, 2000; Haggard & Whitford, 2004; MacDonald & Paus, 2003; Mulliken, Musallam, & Andersen, 2008; Nelson, 1996).

Additional studies of the functional role of sensorimotor connectivity indicate that visual

information influences the neural activity of an ongoing motor pattern (Archambault, Caminiti, & Battaglia-Mayer, 2009; Mulliken et al., 2008); voluntary movement induces activation in SI that is associated with PMC activity when proprioceptive input is blocked (Christensen et al., 2007), and the deactivation of the superior parietal lobule impairs the perception of visual-motor congruency for self-generated but not passive movements (MacDonald & Paus, 2003).

Our model suggests that poor functional integration in this circuitry may influence both the emergence of motor stereotypy in early typical development and its persistence in NDDs.

1.5 Motor complexity in typical development

In addition to Thelen and colleagues' studies in typical infants, the development of motor complexity has been studied in other contexts. When infants are first learning to sit and can support their posture only briefly, their motor profile, as measured via center-of-pressure, is less complex than it is a few months later, when they are able to support their posture for extended periods of time (Harbourne & Stergiou, 2003). Similarly, the center-of-pressure profiles of young children while standing still are less complex than those of school-age children or young adults (Newell, 1998). A developmental pattern is also observed in the force exertion profiles for isometric grip force tasks (Deutsch & Newell, 2001, 2002, 2003; Smits-Engelsman, Westenberg, & Duysens, 2003) and the temporal structure of gait (Hausdorff, Zemany, Peng, & Goldberger, 1999) such that young children have less complex motor profiles than older children or adults. These findings demonstrate that motor complexity increases over the course of normative development.

1.6 Sensory influence on motor complexity in typical development

In keeping with the proposed model, there is evidence that sensory feedback can influence developmental changes in motor complexity. Thelen (1980) found that rates of stereotyped movements

were inversely related to the amount of vestibular input (rocking, bouncing, swinging, etc.) provided by caregivers, and stereotypy persisted later in infants who received less vestibular input. The frequency of stereotypy also increased when movement was restricted (e.g., the infant was in a playpen, walker, or chair) compared to when the infant was allowed to move freely. Additionally, in pre-ambulatory infants, the rotation of the hip, knee, and ankle become less coupled and resemble mature ambulation if the infants are supported while stepping on a treadmill (Thelen, 1986). The pull of the treadmill on the infants' rear legs elicits stepping movements with more complex joint-angle relationships than the infants are able to generate independently at that stage.

Other paradigms have also elucidated developmental changes in motor complexity that depend on the sensory context. The double-step reaching task requires participants to reach to a visual target (Hyde & Wilson, 2013; Ruddock et al., 2015; Van Braeckel, Butcher, Geuze, Stremmelaar, & Bouma, 2007; Wilson & Hyde, 2013). On most of the trials, the target remains stationary, but on a subset of the trials, the target shifts mid-reach to a new location. This requires the participant to use continuous visual and proprioceptive feedback to efficiently alter the movement trajectory to accurately touch the target. Younger children are less efficient in correcting their movements when the target shifts than older children or adults. This developmental pattern is maintained when controlling for variables that measure motor planning and execution independently of the stimulus condition (e.g., reaction time, time to peak velocity).

Using a quantitative assessment of motor complexity, Deutsch and Newell (2001, 2002, 2003) measured approximate entropy and power spectral frequency of the force output during an isometric force task in children and adults. They found age-related increases in approximate entropy and frequency representation when the participants were provided with visual feedback of their force exertion. However, when visual feedback was removed, all age groups displayed relatively low complexity. These findings were replicated in a postural sway task (Newell, 1998), further supporting the contributions of age and sensory feedback to motor complexity.

1.7 Motor complexity in neural pathology

Motor complexity is atypical in several neurologic disorders that present with stereotypy (Bodfish, Parker, Lewis, Sprague, & Newell, 2001; Hong, Bodfish, & Newell, 2006a; Kent et al., 2012; Newell & Bodfish, 2007; Newell, Incledon, Bodfish, & Sprague, 1999; Sprague & Newell, 1996). Here, we will focus on the relation of motor complexity to stereotypy in NDDs. Most of this work has focused on adults with stereotyped body rocking (Bodfish et al., 2001; Hong et al., 2006a; Newell & Bodfish, 2007; Newell et al., 1999). Newell *et al.* (1999) analyzed the position time series of joint position during body rocking using approximate entropy. Individuals with stereotyped body rocking had less complex joint position profiles than typically developing individuals. Similarly, individuals with stereotyped body-rocking displayed lower complexity in their center-of-pressure profiles than typically developing individuals when they were sitting still (Hong et al., 2006a; Newell & Bodfish, 2007) or standing still (Bodfish et al., 2001) on a force platform. When participants engaged in body rocking, the typically developing participants reduced their motor complexity to the level of the individuals with stereotyped body rocking; whereas, the participants with stereotyped body rocking displayed low complexity in both conditions (Hong et al., 2006a; Newell & Bodfish, 2007). These studies indicate that motor stereotypy is a manifestation of low motor complexity.

Consistent with these findings, Mosconi and colleagues (2015) observed that individuals with ASD (ages 5-35 years), had lower approximate entropy of sustained grip force, relative to age-matched, typically developing individuals. They also found a trend for typically developing individuals to show a greater age-related increase in motor complexity than individuals with ASD indicating that individuals with ASD have an abnormal developmental trajectory of motor complexity.

1.8 Sensorimotor integration in developmental, neurologic, and psychiatric disorders

Many neurologic and psychiatric disorders that present with stereotypy have known sensorimotor

deficits (Lencer et al., 2010; S. L. Morris et al., 2015a; Nebel et al., 2015; Quednow et al., 2008; Takarae, Minshew, Luna, Krisky, & Sweeney, 2004; Z. Wang et al., 2015). Unfortunately, sensory abnormalities, motor deficits, and stereotyped behaviors in these disorders have largely been studied in isolation and without regard for how they may relate to one another.

In ASD, for example, stereotyped behavior is diagnostic (American Psychatric Association, 2013), but motor deficits (Duffield et al., 2013; Mostofsky et al., 2006) and unusual sensory behaviors (Kirby, Dickie, & Baranek, 2015; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Stewart et al., 2016) are also highly prevalent and are some of the earliest symptoms (Sacrey, Bennett, & Zwaigenbaum, 2015). Few studies have found associations between stereotyped behavior and sensory, motor, or sensorimotor abnormalities (Boyd et al., 2010; Boyd, McBee, Holtzclaw, Baranek, & Bodfish, 2009) underscoring the need for additional research exploring the relation between these symptom domains. Stereotyped behavior in ASD emerges in infancy as it does in typical development (Kim & Lord, 2010; Thelen, 1979), but unlike in typical development, stereotypy persists in individuals with ASD. While the literature in NDDs, including ASD supports the link between reduced motor complexity and the presence of motor stereotypy, there are currently no studies that assess the effect of sensory feedback on motor complexity in individuals with ASD or related NDDs. Given the importance of sensory feedback for motor complexity in typical development, we hypothesize that reduced motor complexity in individuals with ASD and related NDDs results from poor sensorimotor integration. However, additional research is needed to explore this hypothesis.

1.9 Conclusions

Traditionally, motor stereotypy has been studied from two distinct perspectives: it can serve a functional role, as in normative development where it provides a foundation for the development of goal-directed behavior, or it can be maladaptive, as in neurologic and psychiatric disorders where it interferes with functional behavior. At present, there is no unifying framework to explain these two manifestations

of motor stereotypy. We have introduced a model arguing that both healthy and pathologic forms of motor stereotypy manifest when motor complexity is low as a result of poor sensorimotor integration. This model is consistent with the established structure of sensorimotor neural circuitry. Support for this model comes from existing studies of stereotypy in typical development and NDDs that demonstrate a relation between stereotypy and motor complexity, as well as studies demonstrating the importance of sensory feedback for developmental increases in motor complexity in typical development.

There are several critical gaps in the research relating to early identification, treatment, and etiology of conditions associated with stereotypy that can be considered in relation to the proposed model:

1. Early Risk Markers:

Diagnosing children with pathologic conditions that present with stereotypy often is not possible until after symptoms manifest; however, under our model, careful tracking of the development of motor complexity may be used to determine when at-risk infants veer from the normative trajectory. Early identification of at-risk infants permits earlier treatment interventions, which could prevent or minimize the expression of stereotypy in these individuals.

2. Early Intervention:

If our model is accurate, interventions could aim to enhance motor complexity, for example by engagement with sensorimotor activities that require the child to vary his/her motor patterns. Treatment interventions that have enriched the home environments through exposure to various sensory and motor activities or have reinforced variability in behavior have successfully reduced repetitive behaviors in children with ASD (Boyd, McDonough, Rupp, Khan, & Bodfish, 2011; Woo, Donnelly, Steinberg-Epstein, & Leon, 2015; Woo & Leon, 2013). Importantly, these studies did not test whether decreased stereotypy was mediated by increased motor complexity, but this should be explored in future studies.

3. Pathogenesis:

Motor complexity and sensorimotor integration can be examined reliably in clinical populations and in animal models. Adapting tasks used to assess the influence of sensory feedback on motor complexity in typical development (e.g., Deutsch and Newell, 2001, 2002, 2003) for use in individuals with ASD or other NDDs would provide additional support for our conceptual framework, while the use of animal models provides a means for studying the etiology of stereotypy and the effect of sensory feedback on motor complexity at levels of behavioral, neuronal, and molecular analysis that are inaccessible in humans.

Chapter 2

Visual feedback during motor performance is associated with increased complexity and adaptability of motor and neural output

2.1 Introduction

Stereotyped behavior is rhythmic, repetitive behavior that shows little variation in form and is often considered maladaptive and atypical (Cooper & Dourish, 1990) due to its high prevalence in disorders including schizophrenia (Morrens et al., 2006), fronto-temporal dementia (Mendez et al., 2005), and neurodevelopmental conditions such as autism spectrum disorder (ASD; American Psychatric Association, 2013; Goldman et al., 2009). Stereotyped behavior also occurs in healthy human infants, however, indicating that it is not always associated with atypical development or pathology (Thelen, 1979). Unlike in pathologic conditions where stereotyped behavior can persist throughout life, in healthy infants, stereotyped movements (e.g., repetitive arm waving and kicking) are replaced by complex, goal-directed movements (e.g., reaching and locomotion, respectively). Normative stereotyped movements are believed, therefore, to serve as a foundation on which complex motor behavior is built (Konczak et al., 1995; Thelen & Cooke, 1987; Thelen & Fisher, 1983b, 1983a).

Studies of stereotypy have been conducted in either non-clinical or clinical populations based, presumably, on the assumption that these are distinct phenomena with distinct underlying mechanisms that contribute to their expression. Less research has considered that stereotyped behavior in different populations reflects a shared underlying mechanism (Shafer, Newell, Lewis, & Bodfish, 2017). In the present study, we explored the role that one such mechanism – sensorimotor integration – may play in the expression of stereotyped motor behavior. This study is based on previous findings that limiting the integration of sensory input with motor output reduces the complexity and adaptability of motor output

such that movements become less complex and more stereotyped.

Previous studies in healthy infants have found that infants display stereotyped motor behavior when their sensory and motor neural circuitry is immature and they have had limited sensory and motor experiences (Konczak et al., 1995; Thelen, 1979, 1980, 1986; Thelen et al., 1993). With experience and maturation, the stereotyped behavior is replaced by complex motor behavior that allows infants to interact adaptively and flexibly in the environment. Bernstein (1967) posited that motor control emerges through mastering the body's abundant biomechanical degrees of freedom. In early stages of motor learning in normative development, the motor system constrains these degrees of freedom in order to exert control over them and produce stable movements, such as the stereotyped movements that are present in healthy infants described by Thelen (1979). As the motor system matures or the individual gains experience, biomechanical degrees of freedom are released, permitting the individual to use his/her body more flexibly to enhance the specificity and efficiency of movement. This transition from stereotyped to complex motor patterns has been associated with infants' sensory environments. For example, infants who receive more sensory input from caregivers (e.g., rocking, swinging, bouncing) and infants who have more opportunities to explore their environments display lower rates of stereotyped behavior (Thelen, 1980). The infant's sensory environment can also induce more complex, adult-like patterns of movement than the infant is able to elicit spontaneously (Thelen, 1986). These findings suggest an important role of sensory input on the complexity and adaptability of infants' motor output. A recent longitudinal study in healthy infants revealed that neural complexity (measured at rest) increases over the age range (2-12mos.) that Thelen (1979) observed the transition from stereotyped to complex movements (Hasegawa et al., 2018). This finding indicates that the behavioral transition occurs in parallel with the development of greater neural integration.

Studies in animals have demonstrated that atypical sensory conditions such as barren cage environments can induce stereotyped patterns of behavior in otherwise healthy animals, and rates of stereotypy can be decreased or prevented by rearing animals in enriched cage environments that have a diversity of opportunities for sensorimotor experience (Bechard, Bliznyuk, & Lewis, 2017; Bechard,

Cacodcar, King, & Lewis, 2016; Campbell, Dallaire, & Mason, 2013; Meehan, Garner, & Mench, 2004; Muehlmann et al., 2012). Similar observations have occurred in human populations. Children who grew up in the impoverished environment of orphanages in Romania show high rates of stereotyped behavior and exhibit several other behaviors that resemble features of autism (Bos, Zeanah, Smyke, Fox, & Nelson, 2010; Levin, Fox, Zeanah, & Nelson, 2015). When these children were placed in more enriched homes (adoption or foster care), their rates of stereotyped behavior decreased. These studies indicate that stereotyped behavior can be induced (beyond infancy) in otherwise healthy individuals by manipulating the availability and integrity of the sensory environment.

In keeping with these findings, stereotypy may occur in several clinical disorders because these disorders present with deficits in sensorimotor integration. For example, schizophrenia, autism spectrum disorders, and other neurodevelopmental disorders, which are commonly associated with stereotyped behavior have been shown behaviorally and neurophysiologically to have deficits in sensorimotor integration (American Psychatric Association, 2013; Goldman et al., 2009; Lencer et al., 2010; Morrens et al., 2006; S. L. Morris et al., 2015b; Nebel et al., 2015; Quednow et al., 2008; Takarae et al., 2004; D. J. J. Wang et al., 2018). A few studies in autism have specifically found an association between stereotypy and sensory, motor, or sensorimotor abnormalities (Boyd et al., 2010, 2009). Interventions that targeted sensory integration and engagement with environmental stimuli have successfully reduced symptom severity in individuals with autism; however these studies did not specifically evaluate the effects on stereotyped behavior (Woo et al., 2015; Woo & Leon, 2013).

The sensorimotor integration model of stereotypy would predict that withholding access to sensory feedback or reducing the integrity of sensory feedback during a motor task in healthy individuals would result in transient reductions on neural complexity consistent with reduced complexity of the motor output. This prediction is supported by findings in healthy individuals of increased neural coherence between sensory and motor regions when feedback is provided during a motor task compared to when it is not (Lin, Shaw, Young, Lin, & Jung, 2012; Papadelis et al., 2016). Complexity of the neural signal has been shown to be positively associated with functional connectivity (D. J. J. Wang et al., 2018). Altered

sensorimotor integration is commonly observed in clinical populations that present with stereotyped behavior. Specifically, individuals with autism and schizophrenia have reduced functional connectivity in sensorimotor networks (X. Chen et al., 2015; Kaufmann et al., 2015; Nair, Treiber, Shukla, Shih, & Müller, 2013; Nebel et al., 2015). Studies have also found evidence that individuals with autism, infants at risk for developing autism, and individuals with schizophrenia have reduced complexity of the neural signal relative to healthy individuals (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011; Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011; Kotini & Anninos, 2002; Lee et al., 2001; Liu et al., 2017a; Sabeti, Katebi, & Boostani, 2009), though findings are mixed (Fernández, Gómez, Hornero, & López-Ibor, 2013; Takahashi et al., 2016), and these studies did not specifically relate these neural complexity differences to sensorimotor processing.

While previous studies suggest that stereotyped behavior is associated with sensorimotor integration, to date, there have been no studies that provide an empirical test of the sensorimotor integration model of stereotypy in healthy, typically developing adults and no studies in either clinical or nonclinical populations that have examined this model using simultaneous measurement of behavioral and neural function. In the present study, we aim to assess whether access to feedback influences sensorimotor integration and whether this relates to the complexity of motor output in typically developing adults. Specifically, we are testing whether reliable sensorimotor integration (through the availability and use of sensory feedback) permits greater complexity and adaptability of the neural and motor output, and conversely, whether poor sensorimotor integration (lack of access to – and, therefore, a lack of reliance on – sensory feedback) limits the adaptability of the neural and motor output resulting in low complexity, more stereotyped patterns of movement in healthy individuals.

2.2 Methods

2.2.1 Participants

Participants included 18 healthy, right-handed adults (10 females, 8 males) between the ages of 18 and 34 years (mean: 25.6 ± 4.9 years) with normal or corrected to normal vision. All participants were recruited from the Vanderbilt University and Vanderbilt University Medical Center communities and gave written informed consent to participate. This study was approved by the Vanderbilt University Institutional Review Board.

2.2.2 Equipment

Task stimuli were presented on a 24-inch high-definition (1920 x 1080 pixels) LCD computer monitor (ASUS VG248) from a PC (LG Electronics, Inc.) with 32GB of RAM at 4GHz. This PC is equipped with a NVIDIA GeForce GTX 770 graphics card and a dual monitor display. Participants used a wireless LED computer mouse to control the onscreen cursor during the sensorimotor task (described below). The sensorimotor task program was custom script programmed in MATLAB (The MathWorks, Inc., Natick, Massachusetts) using the Psychophysics Toolbox (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997).

EEG data were collected using 128-electrode Electrical Geodisics, Inc (EGI) HydroCel Sensor Nets through EGI Net Station v.5 software on a Macintosh computer. The electrodes in the HydroCel Nets use a mild saline and shampoo solution. Electrodes are embedded in soft sponges and housed in pedestals.

2.2.3 Sensorimotor Task

Participants were seated in a dimly lit room, ~90cm in front of a 24-inch flat-screen computer monitor on which task instructions and stimuli were presented. Participants performed a stimulus-tracking task during which they controlled a cursor (green dot subtending a visual angle of ~0.3°) and followed a moving target (grey square subtending a visual angle of ~1°) that moved at a constant velocity of ~2°/second across the computer screen. The task consisted of two sensory conditions: (1) Visual feedback: participants saw the moving target and the cursor on the computer screen for the duration of the trial, (2) No visual feedback: the target and cursor were visible on the screen at the beginning of the trial, but disappeared mid-trial, and participants were instructed to continue moving the computer mouse as if the target and cursor were still visible. The target and cursor reappeared at the end of the no visual feedback trials. The experiment consisted of eight experimental blocks, and each block consisted of 32 trials of a given sensory condition for a total of 256 trials (128 with visual feedback, 128 without visual feedback). The direction of target motion (up, down, left, right) was pseudo-randomized within a block, and all blocks contained 8 trials of each direction. The sensory feedback condition (with or without) alternated from one block to the next, and the condition of the first block was counterbalanced across participants. **Figure 2** illustrates the task stimuli and schema.

Each block began with a set of instructions pertaining to the sensory feedback condition of the proceeding trials. Forced breaks were built in to the task to minimize participant fatigue. A 10s break occurred after every 8 trials, and a 2min break occurred at the end of each block (32 trials). To ensure that participants were attending to the trials, they were presented with the instructions and prompted to press the space bar to continue the task after each break. Additionally, participants were required to move the cursor into the target to initiate each trial. The delay between the moment the participant moved the cursor into the target and the moment the target started moving was randomized between 1.5 and 2.25s to minimize anticipatory movements.

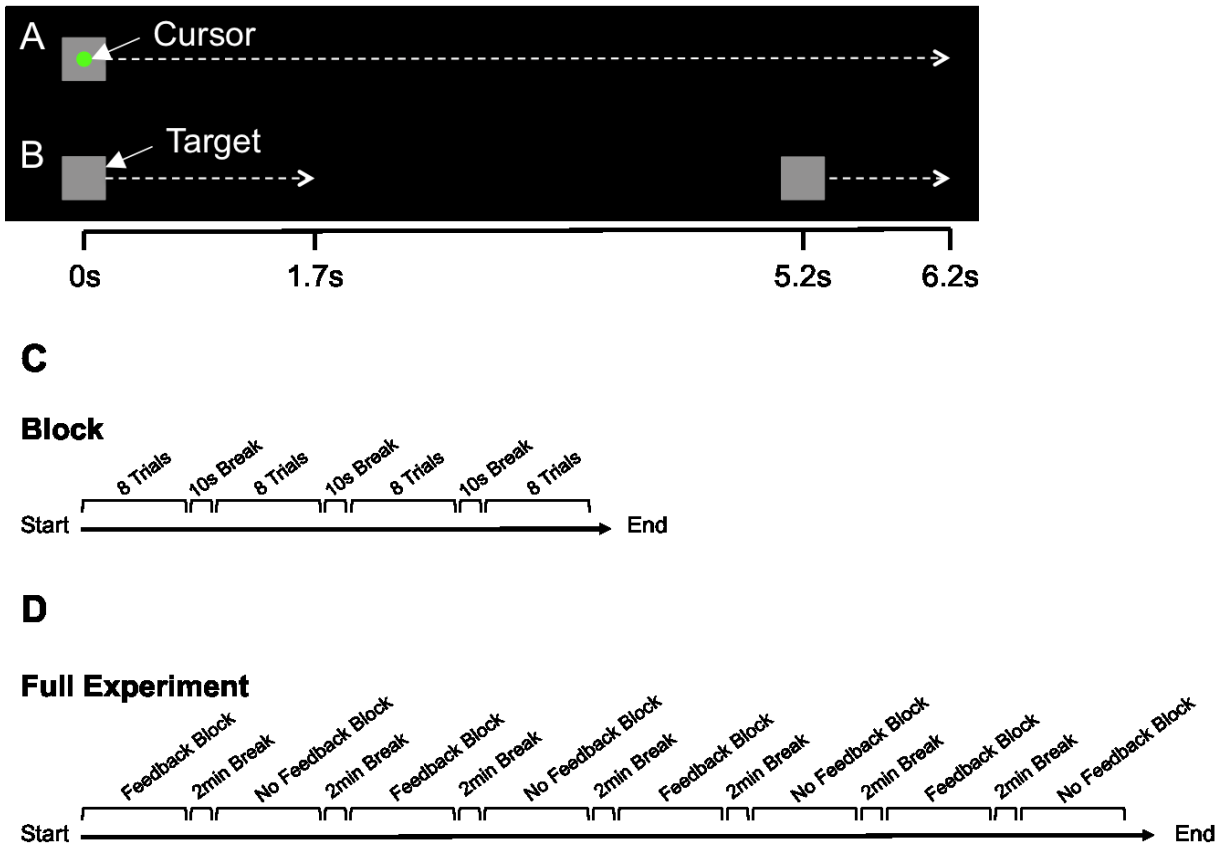

Figure 2: Task Design. A) Depiction of a Feedback trial with the target (grey) and the cursor (green). The target and cursor are visible for the duration of the trial. **B)** Depiction of a No Feedback trial. The target and cursor disappear 1.7s after the target starts moving. They are invisible for 3.5s before reappearing at the end of the trial. **C)** Structure of a block of trials. All trials within a block are the same sensory feedback condition. **D)** Structure of the task. Blocks alternate between Feedback and No Feedback. The condition of the starting block is randomly decided for each participant.

2.2.4 EEG Data Collection and Processing

EEG data were collected in Net Station v.5 software continuously throughout the sensorimotor task. Data were sampled at 1000Hz and online referenced to the vertex electrode (corresponding to Cz in the International 10-20 system). The initiation and termination of the EEG recording, and the signaling of event triggers were controlled by custom MATLAB script on the stimulus PC via hard wired signals sent through the amplifier. Event triggers marked the moment during each trial in the sensorimotor task when the target and cursor disappeared (No Feedback trials) or the corresponding time point in the Feedback

trials (~1.7s after the onset of target motion). EEG data were processed and cleaned in EEGLAB version 14.1.1b software (Delorme & Makeig, 2004) for MATLAB. Data were high pass filtered at 0.5 Hz and low pass filtered at 30 Hz and re-referenced to the average of all electrodes. Data were epoched from the window of -1s to 3.6s surrounding the moment during each trial when the target and cursor disappeared (No Feedback trials) or the corresponding time point in the Feedback trials. This epoch encompassed a baseline period of 1 second of target movement while the target and cursor were present (consistent across both feedback conditions) and the entire segment of the trial when the conditions differed (target and cursor were not visible during the No Feedback trials but were visible during the Feedback trials).

Impedance of all electrodes was maintained below 50kΩ. Noisy and bad electrode channels were identified based on visual inspection and spherically interpolated. No more than 12/128 channels (~10%) per participant were interpolated. Eye blink artifact was identified using independent components analysis. Components related to blinks were identified based on strong frontal topography and punctate activation of the component, and these components were removed. For other types of artifact, epochs containing artifact were identified based on visual inspection and were removed. A minimum of 45 clean trials per condition was required for the participant's data to be included in the analyses. Based on these criteria, none of the participants' data were excluded from the analyses. There was no significant difference between sensory feedback conditions in the number of trials that were retained ($t(17)$: 2.07, $p = 0.054$).

2.2.5 Data Analysis

Participant movement was monitored through the position of the cursor on the screen. Only the data from the time the cursor and target disappeared to the time they reappeared (for the No Feedback trials) and the corresponding time segment from the Feedback trials were considered for the analyses as these represent the time segments during which the two conditions differed. Motor performance was analyzed according to two axes of movement: the axis of cursor movement that was parallel to the motion

of the target, and the axis of cursor movement that was perpendicular to the motion of the target (e.g., if the target was moving rightward or leftward, parallel movements would be rightward or leftward movements made by the participant, and perpendicular movements would be upward and downward movements made by the participant). Error was calculated as the root mean squared error (RMSE) of the cursor position relative to the target position. The RMSE was calculated for each trial separately and then averaged across a participant for each condition and axis of motion such that each participant had two averaged RMSE values (parallel and perpendicular) for each feedback condition. All participants' average RMSE values were included as dependent variables in a 2x2 ANOVA with feedback condition (Feedback, No Feedback) and axis of motion (Parallel, Perpendicular) as independent repeated measures variables.

Movement complexity was assessed using the sample entropy (SampEn; Richman & Moorman, 2000; Yentes et al., 2013) of the cursor position relative to the target over time. SampEn was calculated for each trial separately and then averaged across the participant for each condition and axis of motion such that each participant had two averaged SampEn values (parallel and perpendicular) for each feedback condition. All participants' average SampEn values were included as dependent variables in a 2x2 ANOVA with feedback condition and axis of motion as independent repeated measures variables. SampEn(m, r, N) is a calculation of the self-similarity or regularity of a time series, and it is defined as the negative natural logarithm of the conditional probability that two similar sequences of m points in a data series of length N remain similar within a tolerance level of r at the next point in the time series, where m is the embedding dimension, r is the tolerance, and N is the length of the data series (Richman & Moorman, 2000; Yentes et al., 2013). Lower values of SampEn indicate greater self-similarity or regularity in the data series. SampEn is relatively robust to the length of the data series, and it has been shown to be reliable with data series as short as 200 data points.

Neural complexity was assessed using multi-scale sample entropy (MSE; Costa, Goldberger, & Peng, 2002, 2005) of the time series of the EEG data. MSE is calculated as the SampEn at different time scales of the time series. The SampEn of the original time series is the value for scale one. For scale two,

the original time series is essentially down sampled by averaging across every 2 consecutive data points in the series and then calculating the SampEn for the down sampled time series. Each subsequent scale down samples across increasing numbers of consecutive data points in the original time series and calculating SampEn for each of these down sampled time series. MSE can be represented as a curve of SampEn across scales, or the average value across all scales can be used as a general measure of complexity.

The MSE for the broad-spectrum EEG signal (0.5-30Hz) was calculated for each electrode on each trial separately and then averaged across electrodes and participant for each condition such that each participant had two sets of averaged MSE values – one for the Feedback condition and one for the No Feedback condition. The broad-spectrum data were analyzed using a 2x17 repeated measures ANOVA with feedback condition (Feedback vs. No Feedback) and time scale (1-17) as the independent factors. Regional MSE analyses were conducted on the specific frequency bands alpha/mu (8-13Hz) and beta (13-30Hz). MSE analyses on specific frequency bands have been done in previous studies (Ghanbari et al., 2015; Mišić, Mills, Taylor, & McIntosh, 2010). Alpha/mu and beta were selected due to the relevance of these frequency bands to sensorimotor processing (Lin et al., 2012; McFarland, Miner, Vaughan, & Wolpaw, 2000; Mizuhara, 2012). Additionally, previous papers assessing motor-related neural complexity have looked specifically at complexity in these frequency bands (Gao, Wang, & Chen, 2013; Martínez-Vargas, Castro-Hoyos, & Castellanos-Dominguez, 2014).

For regional analyses, electrode clusters were defined according to scalp region. These included left and right frontal clusters centered around F3 and F4 of the 10-20 System, respectively; left and right central clusters centered around C3 and C4 of the 10-20 system; left and right parietal clusters centered around P3 and P4 of the 10-20 system; left and right occipital clusters centered around O1 and O2 of the 10-20 System, respectively; and left and right temporal clusters centered around T7 and T8 of the 10-20 System, respectively. Frontal clusters were chosen based on their likelihood of capturing a signal relative to executive functioning. Central and parietal clusters were chosen based on their likelihood of capturing a motor relevant signal. Occipital clusters were chosen based on their likelihood of capturing a visually

relevant signal, and the temporal clusters were chosen as control regions, as these scalp regions are unlikely to capture task-relevant activity. MSE values for each cluster were calculated per participant per condition as the average MSE values across trials of all electrodes in the cluster. Regional data were analyzed according to region and feedback condition for each time scale. Additionally, the average MSE values across time scales were calculated for each region and condition. These averaged MSE values were included as the dependent variable in a 2 x 5 x 2 repeated measures ANOVA with feedback condition (Feedback, No Feedback), region (Frontal, Central, Parietal, Occipital, Temporal), and laterality (Left, Right) as the independent variables.

For whole brain analyses, MSE values were calculated per participant as the average across trials within a condition and across all electrodes on the scalp. Whole brain data were analyzed according to condition for each time scale. Additionally, the average MSE values across time scales were calculated for each condition, and a Tukey test was used to analyze differences in feedback conditions for these averaged values.

To relate the motor complexity findings to the neural complexity findings, correlational analyses between the motor complexity data and the neural complexity were run for each feedback condition. Only the motor data corresponding to the parallel axis of motion were used, since this axis had the greatest variability.

2.3 Results

2.3.1 Motor Performance

Motor performance was assessed using the root mean square error (RMSE) of the cursor position relative to the target position in the axes of motion perpendicular to and parallel to the motion of the target. The results of a 2x2 rmANOVA with feedback condition (Feedback, No Feedback) and axis of motion (Perpendicular, Parallel) as independent variables are summarized in **Figure 3**. This analysis

revealed a significant main effect of feedback condition driven by greater RMSE in the No Feedback condition compared to the Feedback condition ($F(1,17)=210.25$, $p<0.001$, $\eta_p^2 = 0.925$), a significant main effect of axis of motion driven by greater RMSE in the Parallel axis than in the Perpendicular axis ($F(1,17)=11.04$, $p=0.004$, $\eta_p^2 = 0.394$), and a significant feedback condition x axis of motion interaction ($F(1,17)=9.96$, $p=0.006$, $\eta_p^2 = 0.370$). Follow-up analyses revealed that RMSE was greater in the No Feedback condition than the Feedback condition for both the Parallel ($F(1,17)=76.11$, $p<0.001$, $\eta_p^2=0.817$) and Perpendicular ($F(1,17)=65.74$, $p<0.001$, $\eta_p^2=0.795$) axes of movement; however, the magnitude of the differences between sensory feedback conditions was significantly greater in the Parallel axis than the Perpendicular axis ($t(17)=3.16$, $p=0.006$, $d=1.229$).

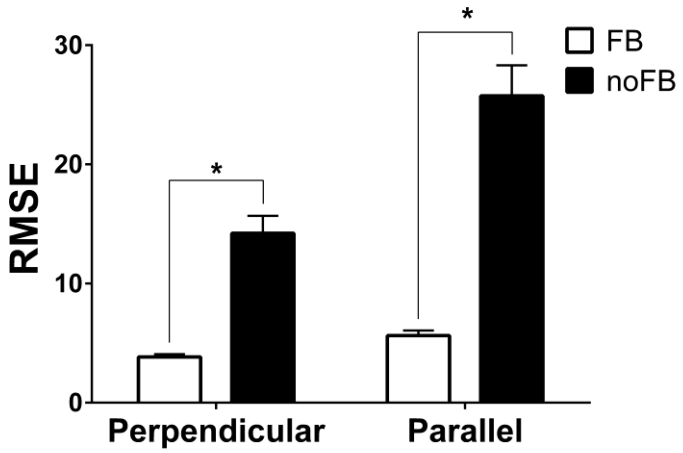

Figure 3: Motor Performance. Performance was measured using the root mean square error (RMSE) of the cursor position relative to the target. Higher values represent poorer performance. Error is indicated for the perpendicular axis of motion (left) and parallel axis of motion (right) for the Feedback condition (white) and the No Feedback condition (black). Significant differences between feedback conditions are indicated by *. Error bars represent standard error of the mean.

2.3.2 Motor Complexity

Motor complexity was assessed using the sample entropy (SampEn) of the time series of the cursor position in both axes of motion. The results of a 2x2 rmANOVA with feedback condition and axis of motion as independent variables are summarized in **Figure 4**. This analysis revealed a significant main effect of feedback condition driven by greater SampEn in the Feedback condition relative to the No Feedback Condition ($F(1,17)=779.25$, $p<0.001$, $\eta_p^2 = 0.979$), a significant main effect of axis of motion driven by greater SampEn in the Parallel axis of motion than in the Perpendicular axis ($F(1,17)=564.1$,

$p<0.001$, $\eta_p^2 = 0.971$), and a significant feedback condition x axis of motion interaction ($F(1,17)=690.63$, $p<0.001$, $\eta_p^2 = 0.976$). Follow-up analyses revealed the SampEn was greater in the Feedback condition than the No Feedback condition for both the Parallel ($F(1,17)=762.22$, $p<0.001$, $\eta_p^2=0.978$) and Perpendicular ($F(1,17)=301.46$, $p<0.001$, $\eta_p^2=0.947$) axes of movement; however the magnitude of the differences between sensory feedback conditions was significantly greater in the Parallel axis than the Perpendicular axis ($t(17)=26.28$, $p<0.001$, $d=7.843$).

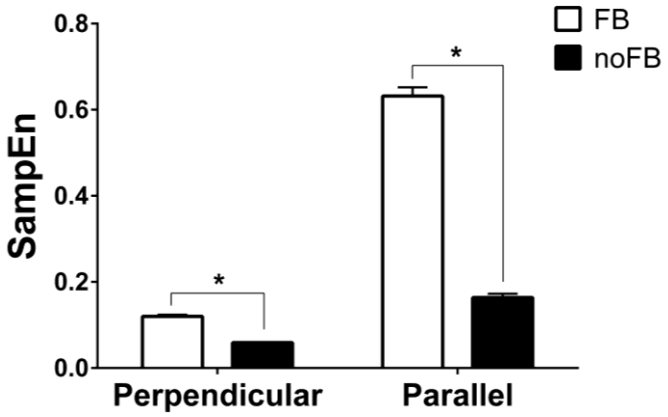

Figure 4: Motor Complexity. Motor complexity on the task was calculated using sample entropy (SampEn) of the time series of the cursor position relative to the target. Motor complexity is indicated for the perpendicular axis of motion (left) and parallel axis of motion (right) for the Feedback condition (white) and the No Feedback condition (black). Significant differences between feedback conditions are indicated by *. Error bars represent standard error of the mean.

2.3.3 Neural Complexity

To assess general effects of feedback condition on neural complexity, SampEn values of the broad-spectrum signal were averaged across electrodes for each time scale for each participant. These data were analyzed for each frequency band using a repeated measures ANOVA with feedback condition and time scale as the independent variables. Differences that remained significant after correcting for multiple comparisons using Least Squares Difference are reported. Results of this ANOVA revealed a significant main effect of sensory feedback condition ($F(1,17)=7.75$, $p=0.013$, $\eta_p^2=0.313$), a main effect of time scale ($F(1.55,17)=3642.60$, $p<0.001$, $\eta_p^2=0.995$), and a sensory feedback condition by time scale interaction ($F(1.234,17)=10.11$, $p=0.003$, $\eta_p^2=0.373$). The main effect of sensory feedback condition was driven by the Feedback condition having higher complexity than the No Feedback condition. Results are depicted in **Figure 5**.

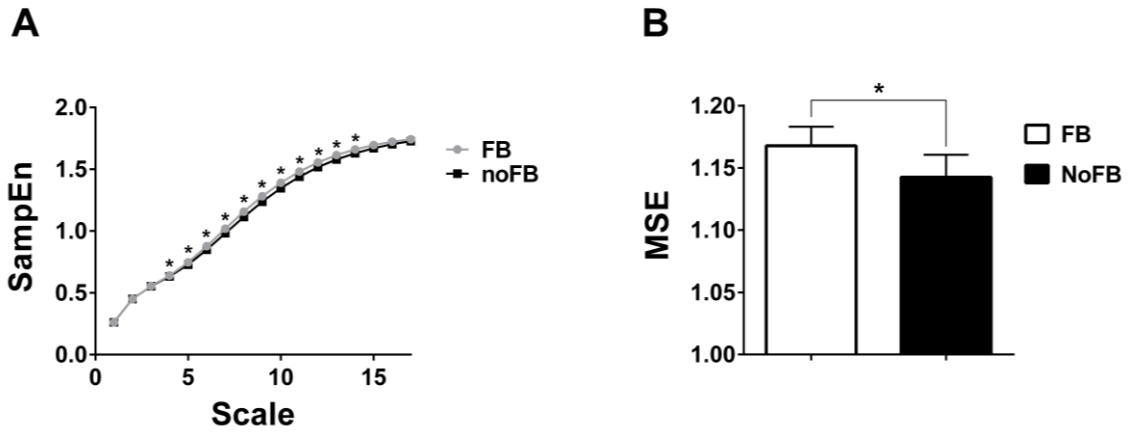

Figure 5: Overall Neural Complexity. A) Sample entropy (SampEn) averaged across all electrodes for each time scale for each sensory feedback condition (Feedback: grey circles, No Feedback: black squares). Time scales for which the Feedback and No Feedback conditions significantly differed are indicated by *. **B)** Multi-scale Sample Entropy (MSE) values calculated by averaging across all electrodes and all time scales for each sensory feedback condition (Feedback: white, No Feedback: black). The significant difference between sensory feedback conditions is indicated by *. Error bars represent standard error of the mean.

Regional neural complexity was assessed using multiscale sample entropy (MSE) of the EEG signal at 10 different scalp regions (Left Frontal, Right Frontal, Left Central, Right Central, Left Parietal, Right Parietal, Left Occipital, Right Occipital, Left Temporal, Right Temporal) for the alpha frequency band and the beta frequency band. SampEn values were averaged across time scales and electrodes within each region and feedback condition for each participant. These averaged values were included in a 2 x 5 x 2 repeated measures ANOVA (separately for each frequency band) with feedback condition (Feedback, No Feedback), region (Frontal, Central, Parietal, Occipital, Temporal), and laterality (Left, Right) as the independent variables. Additionally, for each scalp region, and each frequency band, a 2 (Feedback, No Feedback) x 17 (Timescales 1-17) repeated measures ANOVA was conducted. Results for the alpha frequency band analyses are depicted in **Figure 6** and results for the beta frequency band analyses are depicted in **Figure 7**. Condition differences at each scale that remained significant after correcting for multiple comparisons using Least Significant Difference are indicated.

The results of the alpha ANOVA including scalp region and laterality revealed significant main effects of feedback condition ($F(1,17) = 15.83$, $p = 0.001$, $\eta_p^2=0.482$), laterality ($F(1,17) = 4.92$, $p = 0.040$, $\eta_p^2= 0.224$), and region ($F(2.28, 17)$, $p < 0.001$, $\eta_p^2= 0.522$). The main effect of feedback condition

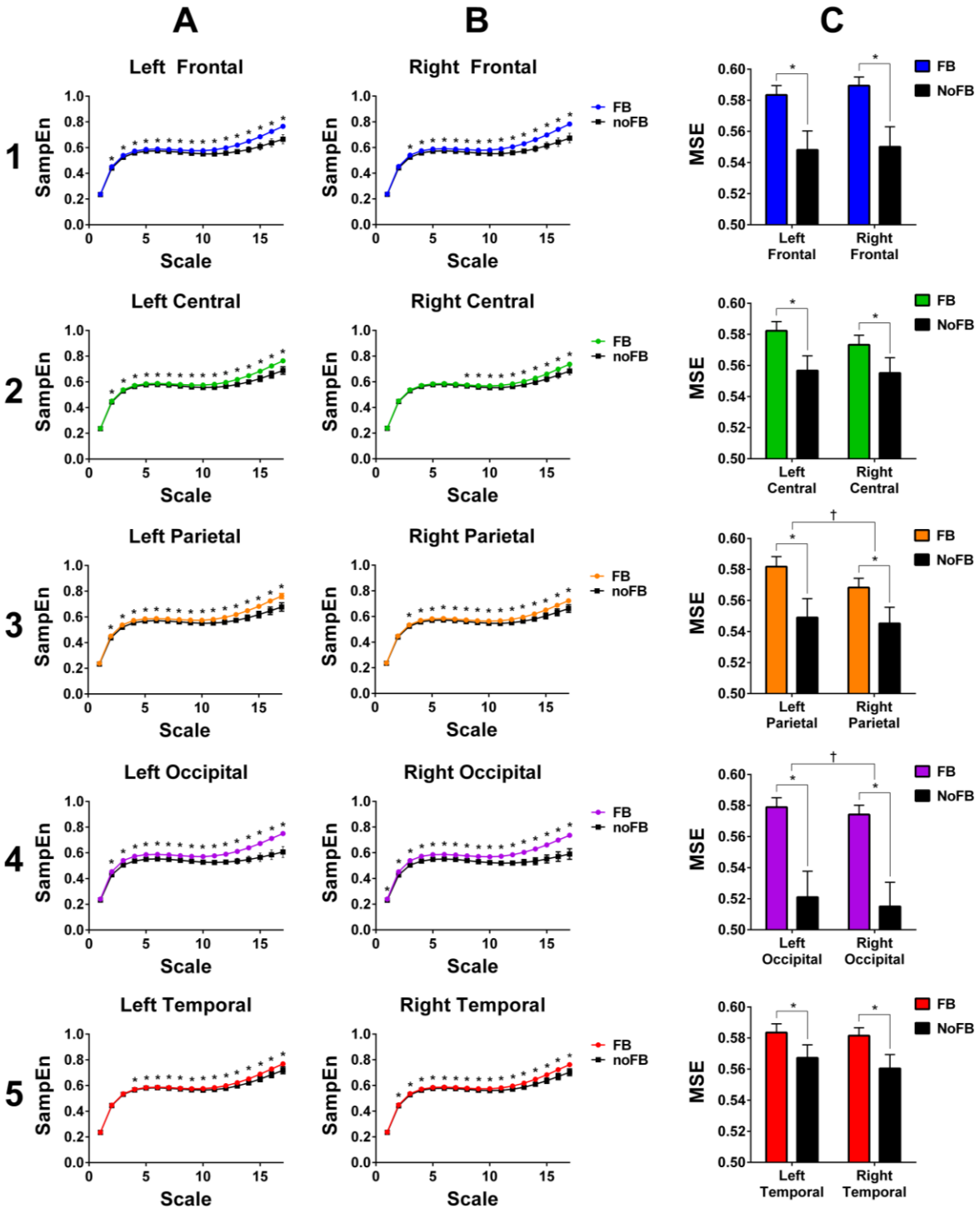

Figure 6: Alpha Band Neural Complexity. Rows are different scalp regions: **1)** Frontal, **2)** Central, **3)** Occipital, **4)** Temporal. Columns **A** and **B** depict the neural complexity (SampEn) at each time scale for the left and right hemispheres, respectively. The * shows significant differences between the Feedback (colored circles) and the No Feedback condition (black squares). Column **C** depicts the across-scales average for each scalp region and sensory feedback condition. The * shows significant differences between the Feedback (colored bars) and No Feedback condition (black bars). The † shows significant differences between Left and Right hemisphere activity. Error bars depict standard error of the mean.

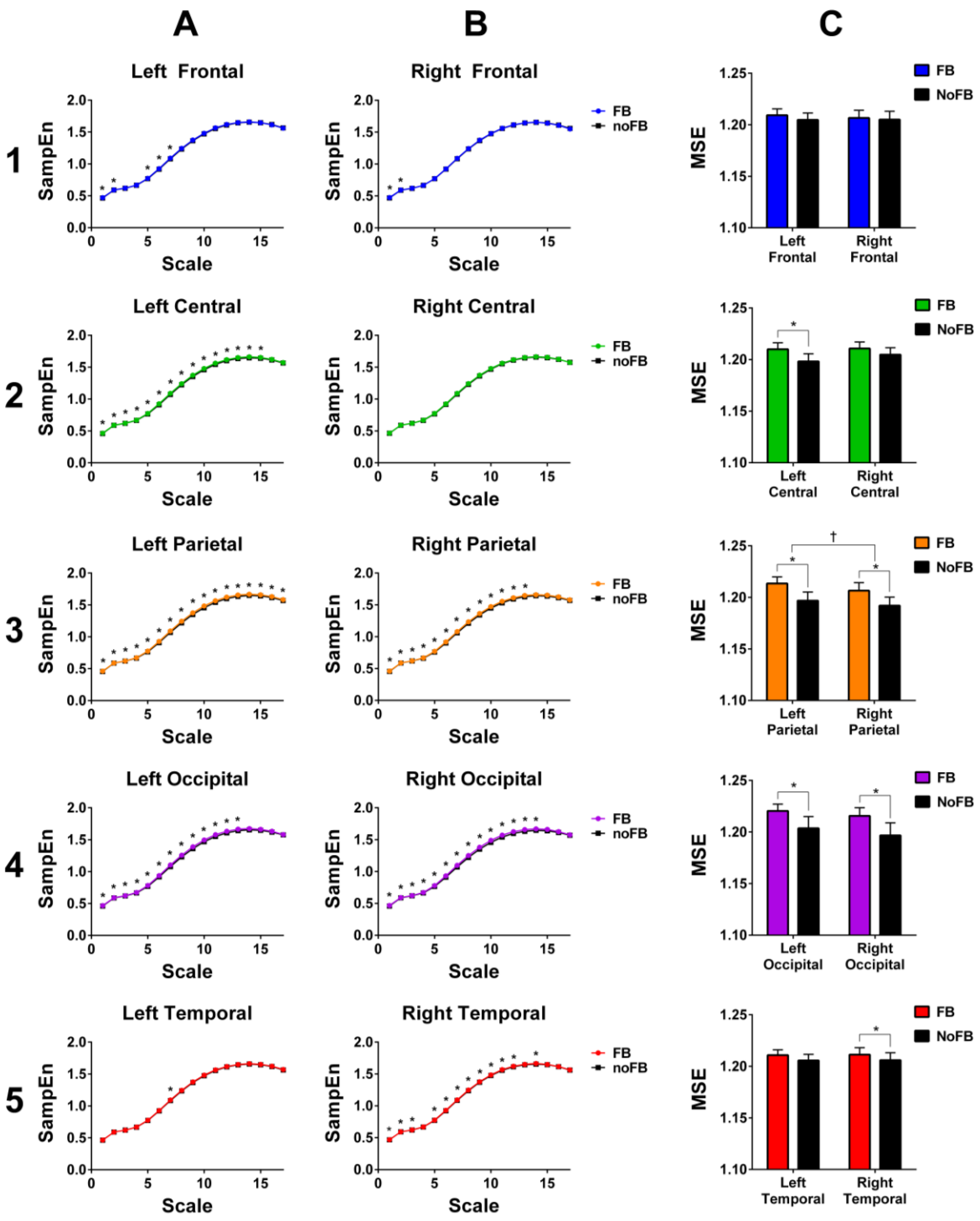

Figure 7: Beta Band Neural Complexity. Rows are different scalp regions: **1)** Frontal, **2)** Central, **3)** Occipital, **4)** Temporal. Columns **A** and **B** depict neural complexity (SampEn) at each time scale for the left and right hemispheres, respectively. The * shows significant differences between the Feedback (colored circles) and No Feedback condition (black squares). Column **C** depicts the across-scales average for each scalp region and sensory feedback condition. The * shows significant differences between the Feedback (colored bars) and No Feedback condition (black bars). The † shows significant differences between Left and Right hemisphere activity. Error bars depict standard error of

was driven by greater MSE in the Feedback condition. The main effect of laterality was driven by greater MSE in the Left hemisphere. The main effect of cluster was driven by lower MSE in the occipital region than in all other regions (Frontal: $t(17) = 5.53$, $p < 0.001$, $d = 1.30$; Central: $t(17) = 4.83$, $p < 0.001$, $d = 1.11$; Parietal: $t(17) = 3.85$, $p = 0.001$, $d = 0.907$; Temporal: $t(17) = 5.29$, $p < 0.001$, $d = 1.25$) and greater MSE in the temporal region than in Central ($t(17) = 2.82$, $p < 0.001$, $d = 0.665$) and Parietal ($t(17) = 4.71$, $p < 0.001$, $d = 1.11$) regions. There were significant interactions between feedback condition and region ($F(1.50, 17) = 14.99$, $p < 0.001$, $\eta_p^2 = 0.469$) and laterality and region ($F(2.09, 17) = 3.69$, $p = 0.033$, $\eta_p^2 = 0.178$). Follow-up comparisons revealed that the feedback condition by region was driven by the strongest reduction in MSE in the occipital region in the No Feedback condition relative to the Feedback condition. Follow-up comparisons revealed that the laterality by region interaction was driven by greater MSE in the left hemisphere for the Parietal ($t(17) = 2.36$, $p = 0.030$, $d = 0.557$) and Occipital ($t(17) = 2.13$, $p = 0.047$, $d = 0.504$) regions only.

Results of the beta ANOVA including scalp region and laterality revealed a significant main effect of feedback condition ($F(1,17) = 8.66$, $p = 0.009$, $\eta_p^2 = 0.338$). Follow-up analyses revealed that this main effect was driven by greater MSE in the Feedback condition. No other main effects were significant. There was a significant interaction between feedback condition and region ($F(1.86, 17) = 5.18$, $p = 0.013$, $\eta_p^2 = 0.234$). Follow-up analyses revealed that this interaction was driven by higher MSE in the Feedback condition for the Central ($t(17) = 2.43$, $p = 0.026$, $d = 0.573$), Parietal ($t(17) = 3.73$, $p = 0.002$, $d = 0.880$), Occipital ($t(17) = 2.63$, $p = 0.018$, $d = 0.620$), and Temporal ($t(17) = 2.34$, $p = 0.032$, $d = 0.551$) regions, but not the Frontal region. No other interactions were significant.

2.3.4 Relation of Motor and Neural Complexity

Correlations between motor complexity (SampEn) and neural complexity (overall MSE) were run for each sensory feedback condition using the SampEn values and MSE values for each trial and each participant. There was no significant correlation between motor complexity and neural complexity in the

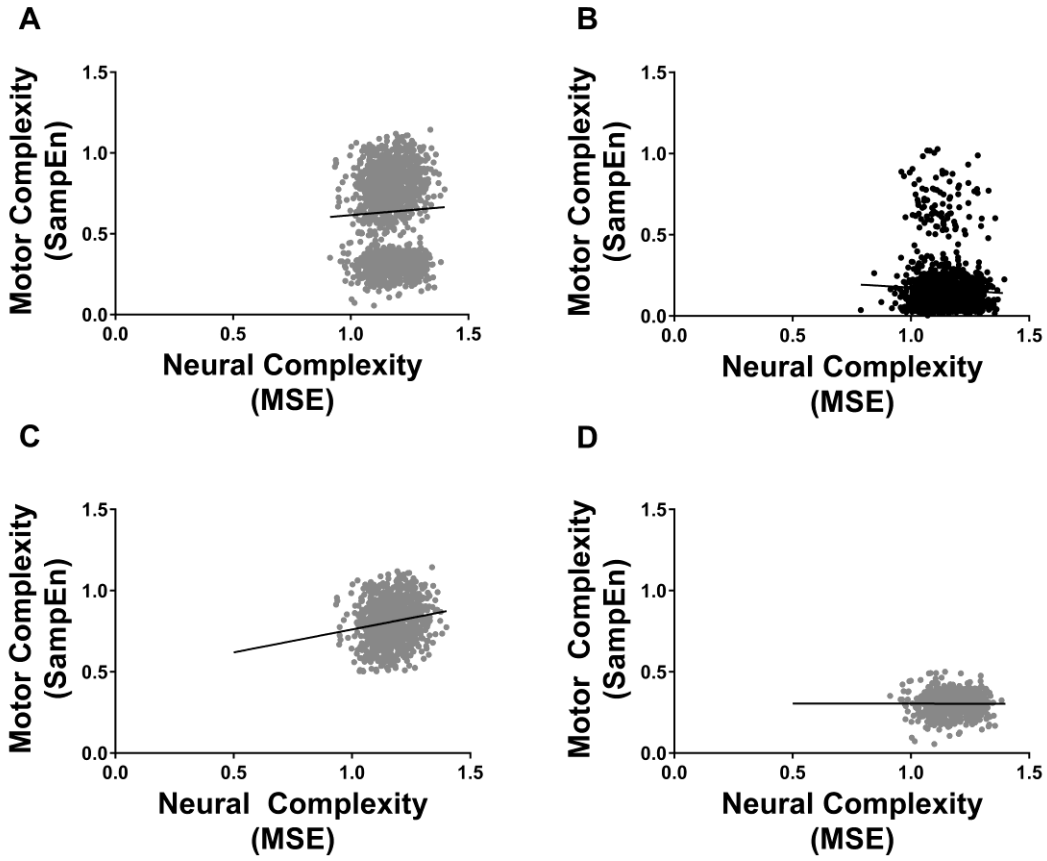

Figure 8: Relation between Motor and Neural Complexity. Correlations between motor complexity (SampEn) and neural complexity (MSE) for: **A)** trials in the Feedback condition, **B)** trials in the No Feedback condition, **C)** the trials in the high motor complexity cluster of the Feedback condition, and **D)** trials in the low motor complexity cluster.

No Feedback condition. There was no significant correlation between motor complexity and neural complexity in the Feedback condition. However, visual inspection of the motor complexity data from the Feedback condition revealed a bimodal distribution with two distinct clusters of trials. Based on visual inspection, these clusters were separated into a "high complexity" cluster (mean: 0.81±0.13) including trials with SampEn above 0.5, and a "low complexity" cluster (mean: 0.30±0.07) including trials with SampEn below 0.5. An independent samples t-test between the low motor complexity cluster and the SampEn of the No Feedback trials revealed that the low motor complexity Feedback trials had a significantly greater SampEn than the No Feedback trials ($t(3004.23) = 30.13$, $p < 0.001$, $d = 2.45$). Further evaluation of the data revealed that these clusters emerged within participants and were present in all 18 participants, indicating that individual participants were not driving the bimodal distribution.

Additionally, they occurred in both early and late blocks of trials for each participant eliminating the possibility that the bimodal distribution was due to learning effects. The clusters are also not associated with the direction of the trials. In light of the bimodal distribution of the SampEn data, Pearson correlations between motor complexity and neural complexity were run separately for each cluster. There was a significant correlation between SampEn and MSE for the high motor complexity cluster ($r(934)=0.175$, $p<0.001$). There was no significant correlation between SampEn and MSE for the low motor complexity cluster. These data are depicted in **Figure 8**.

2.4 Discussion

Stereotyped motor behavior is often associated with neurodevelopmental, neuropsychiatric, and neurodegenerative disorders, and it is described as lacking variability in form and maladaptive. However, stereotyped movements also occur in typically developing infants, where they serve as a foundation for the development of more complex, goal-directed behavior (Konczak et al., 1995; Thelen, 1979; Thelen et al., 1993; Thelen & Fisher, 1983b), and thus are not always associated with brain disorders. Studies in typical development indicate that sensory input and feedback is important for the transition from simple, stereotyped movements to the expression of complex, adaptive behavior (Thelen, 1980, 1986). In an attempt to provide a mechanistic model of stereotypy that could be applied to both clinical and nonclinical populations, we proposed in Shafer et al. (2017) that low complexity, stereotyped behavior manifests when there is a lack of integration of sensory information with the motor system. This could be due to a lack of access to sensory feedback or deficits in the sensorimotor neural circuitry. This lack of sensorimotor integration limits the information that the motor system has access to when generating a motor output, resulting in a low complexity, stereotyped output. Proper sensorimotor integration (and greater access to sensory input) provides greater sensory information to the motor system, allowing the motor system to access more biomechanical degrees of freedom to efficiently and appropriately respond to the environmental context.

The present study was designed to test the model proposed in Shafer et al (2017) to determine if diminished sensory input in healthy adults is associated with lower complexity of both motor output and time-locked neural activity. We tested the hypothesis that visual feedback enhances the complexity and adaptability of neural and motor output in healthy adults by assessing task performance, motor complexity, and neural complexity during a visuomotor task with simultaneous EEG. Our results indicated that motor performance and motor complexity are higher when visual feedback is available compared to when it is not. This is consistent with previous studies (Deutsch & Newell, 2001, 2002, 2003) and with our hypotheses. Also consistent with our hypotheses, neural complexity is increased when visual feedback is available compared to when it is not, indicating that visual feedback induces higher neural complexity which may lead to higher complexity, adaptability, and consequently, accuracy in the motor output. Conversely, when visual feedback is unavailable, the neural signal is limited in complexity, which limits the adaptability of the motor output resulting in poor performance and stereotyped patterns of behavior.

Based on our hypotheses of how the availability of sensory information influences the motor output, we expected that access to visual feedback would provide more information to the visual system, which would communicate that information to the motor system and be used to generate a complex motor output. Thus, we expected both the visual-related (occipital) and the motor-related (central and parietal) neural signal to be higher in complexity when visual feedback was available compared to when it was not. Given that all participants were right-handed and used their right hand to perform the task, we expected a motor-related signal located centrally and parietally in the contralateral (left) hemisphere to the movement, as has been observed in previous studies of motor and visuomotor related cortical potentials and frequency-based analyses of motor processing (Cespón, Galdo-Álvarez, & Díaz, 2013; Duann & Chiou, 2016; Naranjo et al., 2007; Veldman et al., 2018).

For both the alpha and beta frequencies, we observed feedback related increases in neural complexity in the occipital scalp regions indicating, as hypothesized, that access to visual feedback increases the information available to and processed by visual cortex. Our results for both the alpha and

beta frequency bands also revealed significantly greater complexity in left parietal regions compared to right parietal regions as well as significantly greater complexity when visual feedback was available compared to when it was not. We also observed increased neural complexity in the central scalp regions for both the alpha and beta analyses; however, neither of these analyses indicated an effect of laterality, so it is not clear whether these signals correspond to motor activity. The neural findings in occipital left parietal scalp regions, combined with the motor performance and complexity findings support that when visual feedback is available, the visual system has access to more information, which is integrated into the motor system to produce a complex, adaptive motor output consistent with our conceptual model.

Of note, the alpha frequency band analyses revealed Feedback related increases in neural complexity in all scalp regions and increased neural complexity in the left occipital region hemisphere, in addition to the left parietal region. Similarly, the beta band analyses revealed feedback related increases in temporal scalp regions in addition to the motor and visually relevant regions. The distributed task related activity in the alpha frequency band is not surprising, as alpha has been associated with visual processing and attention in addition to sensorimotor processing (Foster, Sutterer, Serences, Vogel, & Awh, 2017; Limbach & Corballis, 2017; Lobier, Palva, & Palva, 2018; Thut, 2006). The effects of laterality in the left occipital region for the alpha analyses and the effect of feedback on temporal regions could also be related to the poor spatial resolution inherent in EEG. It is possible the spread of the motor-related signal is being captured in the analyses of these neighboring regions.

In the alpha frequency analyses, we also observed increased neural complexity in the frontal scalp regions when visual feedback was available. This could be related to differences in error monitoring – when visual feedback is available, participants are able to assess errors in their movements online when they make errors in their movements (i.e., they can see when the cursor deviates from the target); however, when visual feedback is not available, participants are not able to monitor the accuracy of their movement to know when they are making errors. Frontal alpha has been found to be associated with error monitoring for errors that were not self-generated (Zhang, Chavarriaga, & Millán, 2015). Frontal scalp localization of error processing has been repeatedly found in evoked-response potential studies that assess

the error related negativity in various paradigms (Weinberg, Dieterich, & Riesel, 2015). Additionally, Arrighi and colleagues (2016) observed modulation of frontal (Fz) theta band activity that was time-locked to motor errors and event related spectral perturbations that were time locked to corrective movements when participants had visual feedback of their hand position during a reach-to-target task. These findings suggest that the differences in the effect of visual feedback on neural complexity at frontal electrode sites may be related to the processing of and response to errors that occur during the Feedback condition. Future studies should assess the effects of error processing on neural complexity.

An unexpected finding that emerged was the bimodal distribution of motor complexity for trials in the Feedback condition. We determined that these clusters emerged within each of our participants and ruled out learning effects and contributions of experimentally manipulated variables. We hypothesize that these clusters may have emerged as a result of the strategy that the participant used when completing a given Feedback trial. If for example, the participant is heavily reliant on the visual cues, focusing on the relative position of the target and cursor, s/he will have high motor complexity on that trial. If however, the participant is more focused on proprioceptive cues, focusing on the position of his hand and trying to keep the speed of the hand consistent, he will have low motor complexity on that trial, similarly to when feedback is not available and the participant is solely reliant on proprioceptive cues. Although, we observed that the low complexity Feedback trials were still significantly higher than the No Feedback trials, this could be explained by the fact that visual cues were still present during these trials, so participants are likely to be using the visual cues to some extent even if they are relying predominantly on proprioceptive cues. Future studies could test this hypothesis using a version of the visuomotor task that instructs participants on which strategy to use.

Previous studies have demonstrated that optimal motor complexity is task dependent, such that there are tasks for which low motor complexity is optimal (e.g., finger tapping tasks) and tasks for which high motor complexity is optimal (Newell, Broderick, Deutsch, & Slifkin, 2003). Our results support these findings by demonstrating that healthy individuals, depending on the sensory environment, can express both high and low motor complexity. In other words, low complexity, stereotyped patterns of

movement can be induced in healthy individuals through manipulating access to visual feedback. Importantly, this indicates that stereotyped behavior is not restricted to brain disorders or periods of immature brain development, and motor complexity is malleable within individuals. What may distinguish the low motor complexity in healthy, mature individuals from that in infants and individuals with pathologic forms of stereotyped behavior is the fact that healthy, mature individuals are able to reliably integrate sensory information, when it is available, and use it to access more biomechanical degrees of freedom and generate more complex, adaptive movements; whereas, infants or individuals with neuropathology may have difficulty integrating available sensory information and/or translating that sensory information into an adaptive motor output, restricting their motor output to low complexity, stereotyped movements.

Consistent with the hypotheses proposed in Shafer et al. (2017) withholding visual feedback in healthy adults resulted in a low complexity motor and neural output, comparable to the low motor and neural complexity states observed in disorders such as ASD (Bodfish et al., 2001; Bosl et al., 2011; Catarino et al., 2011; Fournier, Amano, Radonovich, Bleser, & Hass, 2014; Hong, Bodfish, & Newell, 2006b; Liu et al., 2017a; M. W. Mosconi et al., 2015; Newell & Bodfish, 2007; Newell et al., 1999) and Parkinson's disease (C. C. Chen et al., 2010; S. Morrison, Kerr, Newell, & Silburn, 2008; Park, Roemmich, Elrod, Hass, & Hsiao-Wecksler, 2016; Pasluosta et al., 2018; Vaillancourt, Slifkin, & Newell, 2001b; Yi, Wang, Deng, & Wei, 2017), which have characteristic repetitive motor behaviors. Importantly, there is also evidence in both ASD (Dowd, McGinley, Taffe, & Rinehart, 2012; Goh, Morris, Parsons, Ring, & Tan, 2017; Hannant, Cassidy, Tavassoli, & Mann, 2016; Izawa et al., 2012; Lim et al., 2018; Marko et al., 2015; Minshew, Sung, Jones, & Furman, 2004) and Parkinson's Disease (Almeida et al., 2005; Jacobs & Horak, 2006; G. N. Lewis & Byblow, 2002; Vaillancourt, Slifkin, & Newell, 2001a; Zhao et al., 2014) of sensorimotor disturbances. The common phenomenology of sensorimotor disturbances, repetitive motor behaviors, and low baseline neural and motor complexity found in these distinct clinical conditions suggests that these may be varied phenotypic expressions of deficits in sensorimotor integration. The possibility that a shared mechanism like sensorimotor integration may account for

multiple clinical features across distinct disorders is consistent with contemporary transdiagnostic models of neurodevelopmental and neuropsychiatric disorders (Cuthbert & Insel, 2013; Insel et al., 2010; S. E. Morris & Cuthbert, 2012).

2.5 Conclusions

Our study aimed to determine the role that sensorimotor integration plays in the expression of, stereotyped behavior by attempting to induce low complexity motor patterns in typically developing adults through manipulating access to visual feedback during a motor task. Withholding visual feedback from participants resulted in poorer motor performance, lower motor complexity, and lower neural complexity. Our results suggest that reliable access to visual feedback provides the nervous system with information that it can use to generate adaptive motor output through online monitoring and correction of movements. When visual feedback is withheld, there is limited information for the brain to use to monitor the accuracy of the movement and generate adaptive motor corrections. This results in less complex (more stereotyped) and less accurate motor behavior. Further, our findings indicate that motor complexity is flexible within individuals and may be influenced by both external factors (sensory feedback) and internal factors (strategy). Our findings have implications for understanding and treating disorders such as ASD that present with stereotyped behaviors.

Chapter 3

Altered neural processing during the execution of complex sensorimotor behavior in autism

3.1 Introduction

Stereotyped (i.e., rhythmic, repetitive) motor behavior is one of the diagnostic features of autism spectrum disorders (ASD), and it is highly prevalent in several other neurodevelopmental, neuropsychiatric, and neurodegenerative disorders (American Psychatric Association, 2013; Goldman et al., 2009; Mendez et al., 2005; Morrens et al., 2006). It is generally considered atypical, maladaptive and purposeless (Cooper & Dourish, 1990). For example, motor stereotypy in individuals with ASD has been shown to pose a functional impairment by interfering with play (Koegel et al., 1974) and learning (Koegel & Covert, 1972; K. Morrison & Rosales-Ruiz, 1997).

Stereotypy also occurs in healthy infants however, in the context of typical development stereotypy is viewed as an adaptive motor behavior which serves as a foundation for learning and executing the complex movements necessary for adaptive goal-directed behavior (Thelen, 1979). As complex goal-directed movements such as reaching and ambulation develop in infants as they age, these more complex patterns of movement replace the simple, stereotyped movements such as repetitive arm waving and kicking (Konczak et al., 1995; Thelen & Cooke, 1987; Thelen & Fisher, 1983b, 1983a).

Historically, stereotypy in typical development and clinical populations has been studied separately due to the assumption that it represents different phenomena in each case, and therefore, is driven by different mechanisms. Recently, we proposed a novel sensorimotor integration model of stereotyped behavior based on the functional integration of sensory and motor neural circuitry that is common to both early healthy brain development and the set of brain-based disorders in which stereotypy

is a common symptom, and thus may provide a single parsimonious account of these distinct aspects of stereotyped behavior (Shafer et al., 2017). In this model stereotyped actions can be conceptualized dimensionally along a continuum of complexity of motor behavior with simple stereotyped low complexity movements at one end and complex and more adaptive movements at the other end. Consistent with the established role that sensory input plays in the control of motor output within functional sensorimotor neural circuits, the availability of relevant sensory information may drive the complexity and adaptability of motor output such that low complexity, stereotyped patterned of motor output may be manifested when sensory input is restricted. This diminished sensory control of motor output could be present either as a result of insufficient maturation of sensorimotor neural circuitry in the case of typically developing infants or as a result of atypical development of this circuitry in the case of neurodevelopmental disorders.

Support for this sensorimotor integration model of stereotypy comes from previous studies of the influence of sensory experience on motor performance and motor development in both typically developing and clinical groups. Findings from previous research have demonstrated that sensory experience can influence both the development and complexity of motor behavior in typical development. Infants who receive more sensory input from caregivers and have more opportunities to explore their environments display lower rates of stereotyped behavior (Thelen, 1980). Conversely, children who are raised in impoverished environments (e.g., orphanages) display high rates of stereotyped behavior (Bos et al., 2010; Levin et al., 2015). When these children leave the orphanages and are placed in more enriched homes, their motor stereotypy decreases. In line with these findings on the role of sensory experience and motor development, other work has demonstrated that the availability of sensory information can influence the complexity of the motor output in typically developing individuals. For example, increased sensory feedback can elicit more complex motor patterns in infants than the stereotyped patterns of movement that infant generates spontaneously (Thelen, 1986). Conversely, studies have demonstrated that limiting the availability of sensory feedback and thus the integration of sensory information with motor output results in reduced complexity and adaptability of the motor output (Deutsch & Newell,

2001, 2002, 2003).

Sensorimotor function has also been examined in the context of the various clinical conditions that are associated with the development of stereotyped behaviors. For example, sensorimotor disturbances are observed in several disorders that present with motor stereotypy (Lencer et al., 2010; S. L. Morris et al., 2015b; Nebel et al., 2015; Quednow et al., 2008; Takarae et al., 2004; D. J. J. Wang et al., 2018). In ASD, structural and functional abnormalities have been observed in sensorimotor regions of cortex (Abbott et al., 2018; Müller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003), cerebellum (Catani et al., 2008; Marko et al., 2015), and striatum (Abbott et al., 2018; Di Martino et al., 2011; Hollander et al., 2005; Langen et al., 2014; Langen, Durston, Staal, Palmen, & van Engeland, 2007). Behaviorally, sensorimotor processing abnormalities in ASD have been observed in the oculomotor (Mosconi et al., 2013; Schmitt, Cook, Sweeney, & Mosconi, 2014; Shirama, Kanai, Kato, & Kashino, 2016; Takarae et al., 2004) and skeletomotor systems (Izawa et al., 2012; Lim et al., 2018; Lim, Partridge, Girdler, & Morris, 2017; Marko et al., 2015; Mosconi et al., 2015; Wang et al., 2015) and include deficits in motor planning (D'Cruz et al., 2009; Z. Wang et al., 2015), motor learning (Izawa et al., 2012; Marko et al., 2015), and the use of sensory feedback to control ongoing movements (Lim et al., 2018, 2017; Mosconi et al., 2015). Additionally, there is evidence that sensorimotor differences may be among the earliest signs of ASD (Baranek, 1999; Sacrey et al., 2015) indicating that they are present early enough to impact the development of later symptoms including social deficits and repetitive behaviors that are characteristic of ASD.

To date, support for a sensorimotor interpretation of stereotyped behavior has come primarily and only indirectly in the form of findings of atypical sensorimotor function in clinical groups that also have high rates of stereotyped behaviors. More direct evidence that links sensorimotor integration to stereotyped movement in both healthy and clinical populations is lacking. This study was designed to provide a more direct test of the sensorimotor integration model of stereotyped behavior through an examination of the effect of sensory feedback on the degree of complexity of motor output in adults with ASD and in a comparison sample of adults without ASD. For this study, we developed a novel visually-

guided tracking task that measures the impact of sensory (visual) feedback on the accuracy and complexity of motor performance. Concurrent EEG measurement of neural complexity during the visuomotor task provided a way to examine the effects of sensory feedback on both motor performance and neural function. We hypothesized: (a) that participants with ASD will be characterized by a pattern of increased movement error, decreased motor complexity, and decreased neural complexity during the sensory feedback condition, and (b) that this pattern of decreased complexity of motor and neural function during sensory feedback will be associated with greater severity on clinical measures of stereotyped behavior within the ASD sample.

3.2 Methods

3.2.1 Participants

Participants were recruited from the Vanderbilt University, Vanderbilt University Medical Center communities and surrounding areas. All participants or, when applicable, their guardians gave written informed consent to participate. This study was approved by the Vanderbilt University Institutional Review Board. 17 adults with ASD (5 female, 12 male) and 20 typically developing adults (7 females, 13 males) were recruited to participate in this study. Participants ranged in age from 18-36 years old. All potential participants were screened following recruitment. In order to proceed to enrollment, participants had to have normal or corrected to normal vision, and TD participants had to screen negative for history of mood disorders, traumatic brain injury, seizures, use of psychoactive medication, and other conditions that affect brain function. For participants in the ASD group, diagnosis of ASD was confirmed by administration of module 4 of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Gotham, Pickles, & Lord, 2009; Lord et al., 2012) by a trained member of our research team. One ASD participant did not complete the ADOS, but she was determined to have ASD based on family history of ASD, a recent diagnosis from a credible medical professional, and expert clinical opinion from a licensed

clinical psychiatrist on our research team. TD participants were screened for ASD using the Autism Spectrum Quotient and were excluded if they scored in the autism range. Participants were excluded from analyses if they had a verbal IQ of 70 or below due to the extent of verbal instruction and questionnaires in our study. Left-handed participants were also excluded from analyses due to the lateralization of motor activity in the brain. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Based on these exclusion criteria, two ASD participants (2 male) were excluded due to verbal intelligence quotient (IQ) below 70, and two TD participants (1 male, 1 female) were excluded because they were left handed. These exclusions resulted in 15 ASD participants (5 female, 10 male) and 18 TD participants (6 female, 12 male) included in the final analyses. One TD participant had experience administering the WASI-II, so the IQ scores for that participant are likely inflated and are not included in the group IQ comparison. After these exclusions, the groups did not differ on overall IQ ($t(30) = 1.38$, $p = 0.177$), age ($t(31) = 0.252$, $p = 0.803$), or gender (both groups were 66.7% male and 33.3% female). Full demographic data is listed in **Table 1**.

Table 1: Group Demographics and Phenotypes

	ASD			TD				
	N	Mean	SEM	N	Mean	SEM	t	p
Age	15	23.47	1.04	18	23.89	1.26	-0.25	0.80
ADOS	14	6.43	0.72	-	-	-	-	-
ADOS SA	14	6.64	0.60	-	-	-	-	-
ADOS RRB	14	5.71	0.81	-	-	-	-	-
FSIQ	15	106.33	3.46	17	112.12	2.47	-1.38	0.18
VIQ	15	106.87	2.57	17	113.53	3.13	-1.62	0.12
PIQ	15	103.80	4.70	17	107.24	2.56	-0.66	0.51
SRS	15	64.13	2.19	18	48.11	1.44	**6.31**	**<0.001**

ASD: Autism Spectrum Disorder, TD: Typical Development, ADOS: Autism Diagnostic Observation Schedule, SA: Social Affect Subscale, RRB: Restricted Repetitive Behavior Subscale, FSIQ: Full-Scale Intelligence Quotient, VIQ: Verbal IQ, PIQ: Perceptual IQ, SRS: Social Responsiveness Scale, N: Sample Size, SEM: Standard Error of the Mean

3.2.2 Behavioral and Cognitive Testing

Autism Spectrum Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001): The AQ is a 50 item questionnaire designed to measure behaviors and characteristics that are commonly associated with the ASD phenotype. A score of 32 or higher indicates clinically significant level of traits relevant to ASD. This value was used in this study as a screening cutoff for the inclusion of participants in the TD group.

Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Gotham et al., 2009; Lord et al., 2012): The ADOS-2 is a semi-structured diagnostic measure of the core features of ASD. This measure provides a score to measure against diagnostic thresholds as well as severity scores. The ADOS was only administered to participants in the ASD group, and module 4 (for adolescents/adults with fluent speech) was used for all participants due to the age and language ability of the participants in our study. The ADOS-2 was scored using the revised scoring algorithm developed in 2014 (Hus & Lord, 2014).

Wechsler Abbreviated Scales of Intelligence, Second Edition (WASI-II) (Wechsler & Zhou, 2011): The WASI-II is an intelligence assessment validated for individuals aged 6-89 years. This assessment gives an assessment of intelligence quotient (IQ) for verbal IQ, perceptual IQ, and full-scale IQ. For this study we report scores for the full-scale IQ value that is calculated from all four of the administered subscales.

Social Responsiveness Scale, Second Edition (SRS-2) (Constantino & Gruber, 2012): The SRS-2 is a questionnaire intended to measure behaviors associated with ASD, mostly related to social impairment including social awareness, social cognition, social communication, and social motivation. The SRS-2 also includes questions to measure restricted interests and repetitive behavior.

Repetitive Behavior Scale – Revised (RBS-R) (Bodfish, Symons, Parker, & Lewis, 2000): The RBS-R is a rating scale that assesses five categories of repetitive behavior (motor stereotypy, repetitive self-injury, compulsions, routines/sameness, restricted interests). These subscales have a high internal consistency with Cronbach's alpha values ranging from .78 (restricted interests) to .91

(routines/sameness) (Lam & Aman, 2007).

Adolescent/Adult Sensory Profile (SP) (Catana Brown & Dunn, 2002): The SP is a questionnaire intended to identify sensory processing patterns in individuals and their effects on function in daily life. It includes questions on six sensory processing categories including taste/smell processing, movement processing, visual processing, touch processing, activity level, and auditory processing.

3.2.3 Equipment

Task stimuli were presented on a 24-inch high-definition (1920 x 1080 pixels) LCD computer monitor (ASUS VG248) from a PC (LG Electronics, Inc.) with 32GB of RAM at 4GHz. This PC is equipped with a NVIDIA GeForce GTX 770 graphics card and a dual monitor display. Participants used a wireless LED computer mouse to control the onscreen cursor during the sensorimotor task (described below). The sensorimotor task program was custom script programmed in MATLAB (The MathWorks, Inc., Natick, Massachusetts) using the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997).

EEG data were collected using 128-electrode Electrical Geodisics, Inc (EGI) HydroCel Sensor Nets through EGI Net Station v.5 software on a Macintosh computer. The electrodes in the HydroCel Nets use a mild saline and shampoo solution. Electrodes are embedded in soft sponges and housed in pedestals.

3.2.4 Sensorimotor Task

Participants were seated in a dimly lit room, ~90cm in front of a 24-inch flat-screen computer monitor on which task instructions and stimuli were presented. Participants performed a stimulus-tracking task during which they controlled a cursor (green dot subtending a visual angle of ~0.3°) and followed a moving target (grey square subtending a visual angle of ~1°) that moved at a constant velocity of

~2°/second across the computer screen. A fixation cross appeared on the screen for 2 seconds at the beginning of each trial. The task consisted of two sensory conditions: (1) Visual feedback: participants saw the moving target and the cursor on the computer screen for the duration of the trial, (2) No visual feedback: the target and cursor were visible on the screen at the beginning of the trial, but disappeared mid-trial, and participants were instructed to continue moving the computer mouse as if the target and cursor were still visible. The target and cursor reappear at the end of the no visual feedback trials. The experiment consisted of eight experimental blocks, and each block consisted of 32 trials of a given sensory condition for a total of 256 trials (128 with visual feedback, 128 without visual feedback). The direction of target motion (up, down, left, right) was pseudo-randomized within a block, and all blocks contained 8 trials of each direction. The sensory feedback condition (with or without) alternated from one block to the next, and the condition of the first block was counterbalanced across participants. **Figure 1** illustrates the task stimuli and schema.

Each block began with a set of instructions pertaining to the sensory feedback condition of the proceeding trials. Forced breaks were built in to the task to minimize participant fatigue. A 10-second break occurred after every 8 trials, and a 2-minute break occurred at the end of each block (32 trials). To ensure that participants were attending to the trials, they were presented with the instructions and prompted to press the space bar to continue the task after each break. Additionally, participants were required to move the cursor into the target to initiate each trial. The delay between the moment the participant moved the cursor into the target and the moment the target started moving was randomized between 0.75 and 1.75 seconds to minimize anticipatory movements.

3.2.5 EEG Data Collection and Processing

EEG data were collected in Net Station v.5 software continuously throughout the sensorimotor task. Data were sampled at 1000Hz and online referenced to the vertex electrode (corresponding to Cz in the International 10-20 system). The initiation and termination of the EEG recording, and the signaling of

event triggers were controlled by custom MATLAB script on the stimulus PC via hard wired signals sent through the amplifier. Event triggers marked the moment during each trial in the sensorimotor task when the target and cursor disappeared (No Feedback trials) or the corresponding time point in the Feedback trials (1.7 seconds after the onset of target motion). EEG data were processed and cleaned in EEGLAB version 14.1.1b software (Delorme & Makeig, 2004) for MATLAB. Data were high pass filtered at 1 Hz and low pass filtered at 40 Hz and re-referenced to the average of all electrodes. Data were epoched from the window of -1 second to 3.6 seconds surrounding the moment during each trial when the target and cursor disappeared (No Feedback trials) or the corresponding time point in the Feedback trials. This epoch encompassed a baseline period of 1 second of target movement while the target and cursor were present (consistent across both feedback conditions) and the entire segment of the trial when the conditions differed (target and cursor were not visible during the No Feedback trials but were visible during the Feedback trials).

Impedance of all electrodes was maintained below 50kΩ. Noisy and bad electrode channels were identified based on visual inspection and spherically interpolated. No more than 6/128 channels (~5%) per participant were interpolated. Eye blink artifact was identified using independent components analysis. Components related to blinks were identified based on strong frontal topography and punctate activation of the component, and these components were removed. For other types of artifact, epochs containing artifact were identified based on visual inspection and were removed. As few studies have used MSE analyses in trial-based EEG studies, there is no standard for the number of trials that need to be retained to obtain a reliable sample for these analyses. We performed a jackknife procedure on the data from participants that had at least 60 clean trials in each feedback condition (Feedback: 4 ASD, 10 TD; No Feedback: 5 ASD, 8 TD) to determine how the mean and variance of the MSE calculation changed as fewer trials were included in the calculation. These analyses revealed that mean (Feedback: $t(13) = 1.71$, $p = 0.111$; No Feedback: $t(9) = 1.09$, $p = 0.306$) and variance did not change significantly between 60 trials retained and 20 trials retained (Feedback: $t(13) = 0.010$, $p = 0.992$; No Feedback: $t(9) = 1.93$, $p = 0.085$). The fewest trials retained for any given participant for either condition was 29, so no participants

were excluded from analyses based on EEG trial retention.

3.2.6 Data Analysis

Participant movement was monitored through the position of the cursor on the screen. Only the data from the time the cursor and target disappeared to the time they reappeared (for the No Feedback trials) and the corresponding time segment from the Feedback trials were considered for the analyses as these represent the time segments during which the two conditions differed. Motor performance was analyzed according to two axes of movement: the axis of cursor movement that was parallel to the motion of the target, and the axis of cursor movement that was perpendicular to the motion of the target (e.g., if the target was moving rightward or leftward, parallel movements would be rightward or leftward movements made by the participant, and perpendicular movements would be upward and downward movements made by the participant). Error was calculated as the root mean squared error (RMSE) of the cursor position relative to the target position. The RMSE was calculated for each trial separately and then averaged across a participant for each condition, and axis of motion such that each participant had two averaged RMSE values (parallel and perpendicular) for each feedback condition. All participants' average RMSE values were included as dependent variables in a 2x2x2 ANOVA with feedback condition (Feedback, No Feedback) and axis of motion (Parallel, Perpendicular) as independent within-subjects variables and group (ASD, TD) as the between-subjects variable.

Movement complexity was assessed using the sample entropy (SampEn) (Richman & Moorman, 2000; Yentes et al., 2013) of the cursor position relative to the target over time. SampEn was calculated for each trial separately and then averaged across the participant for each condition and axis of motion such that each participant had two averaged SampEn values (parallel and perpendicular) for each feedback condition. All participants' average SampEn values were included as dependent variables in a 2x2x2 ANOVA with feedback condition and axis of motion as independent within-subjects variables and group as the between-subjects variables.

SampEn(m, r, N) is a calculation of the self-similarity or regularity of a time series, and it is defined as the negative natural logarithm of the conditional probability that two similar sequences of m points in a data series of length N remain similar within a tolerance level of r at the next point in the time series, where m is the embedding dimension, r is the tolerance, and N is the length of the data series (Richman & Moorman, 2000; Yentes et al., 2013). Lower values of SampEn indicate greater self-similarity or regularity in the data series. SampEn is relatively robust to the length of the data series, and it has been shown to be reliable with data series as short as 200 data points.

Complexity of the EEG data were analyzed at both the broad spectrum EEG signal level (1-40Hz) and on specific frequency bands of the overall EEG signal. Neural complexity was assessed using multi-scale sample entropy (MSE) (Costa et al., 2002, 2005) of the time series of the EEG data. MSE is calculated as the SampEn at different time scales of the time series. The SampEn of the original time series is the value for scale one. For scale two, the original time series is essentially down sampled by averaging across every 2 consecutive data points in the series and then calculating the SampEn for the down sampled time series. Each subsequent scale down samples across increasing numbers of consecutive data points in the original time series and calculating SampEn for each of these down sampled time series. MSE can be represented as a curve of SampEn across scales, or the average value across all scales can be used as a general measure of complexity.

MSE values for the broad spectrum EEG signal (1-40Hz) were calculated for each electrode for each trial separately and then averaged across electrodes and participant for each condition such that each participant had two sets of averaged MSE values – one for the Feedback condition and one for the No Feedback condition. The broad-spectrum data were analyzed using a 2x2x17 repeated measures ANOVA with feedback condition (Feedback, No Feedback) and time scale (1-17) as the independent within-subjects factors and group (ASD, TD) as the between-subject factor.

Regional MSE analyses were conducted on the specific frequency bands alpha/mu (8-13Hz) and beta (13-30Hz). Analyses of MSE on neural data for specific frequency bands has been done in previous studies (Ghanbari et al., 2015; Mišić et al., 2010). Alpha/mu and beta were selected due to the relevance

of these frequency bands to sensorimotor processing (Lin et al., 2012; McFarland et al., 2000; Mizuhara, 2012). Additionally, previous papers assessing motor-related neural complexity have looked specifically at complexity in these frequency bands (Gao et al., 2013; Martínez-Vargas et al., 2014). For regional analyses, electrode clusters were defined according to scalp region. These included left and right frontal clusters centered around F3 and F4 of the 10-20 system, respectively; left and right parietal clusters centered around P3 and P4 of the 10-20 system, and left and right occipital clusters centered around O1 and O2 of the 10-20 system. Frontal clusters were chosen based on their likelihood of capturing a signal relative to executive functioning. Parietal clusters were chosen based on their likelihood of capturing a motor relevant signal. Occipital clusters were chosen based on their likelihood of capturing a visually relevant signal. We did not include the central scalp regions as previous data from our lab on a comparable task found that the central scalp region did not show effects of laterality, as would be expected for a motor signal. We also did not include the temporal scalp regions as a control (task irrelevant region) as previous data from our lab has found task relevant patterns of activity in this region. MSE values for each cluster were calculated per participant per condition as the average MSE values across trials of all electrodes in the cluster. Regional data were analyzed according to region and feedback condition for each time scale. Additionally, the average MSE values across time scales were calculated for each region and condition. These averaged MSE values were included as the dependent variable in a 2 x 3 x 2 x 2 repeated measures ANOVA with feedback condition (Feedback, No Feedback), region (Frontal, Parietal, Occipital), and laterality (Left, Right) as the within-subjects independent variables and group (ASD, TD) as the between-subjects variable.

3.3 Results

3.3.1 Motor Performance

The 2 (Sensory Condition: Visual Feedback, No Visual Feedback) x 2 (Group: ASD, TD) x 2

(Axis: Perpendicular, Parallel) repeated measures ANOVA with motor performance (RMSE) as the dependent variable revealed a main effect of Sensory Condition driven by lower RMSE in Visual Feedback condition ($F(1,31) = 160.68$, $p<0.001$, $\eta_p^2 = 0.838$), a main effect of Axis driven by higher RMSE in the Perpendicular axis ($F(1,31) = 107.09$, $p < 0.001$, $\eta_p^2 = 0.776$), and a significant Sensory Condition x Axis interaction ($F(1,31) = 77.91$, $p < 0.001$, $\eta_p^2 = 0.715$). Follow-up tests revealed that this interaction was driven by a greater difference between Sensory Conditions for the Parallel Axis than the Perpendicular Axis ($t(32) = 8.63$, $p < 0.001$, $d = 1.80$). There was no main effect of Group and no significant interactions that included the Group factor. To correct for violations of homogeneity of covariance, multivariate tests were reported and all results are reported after LSD corrections for multiple comparisons. These results are summarized in **Figure 9.**

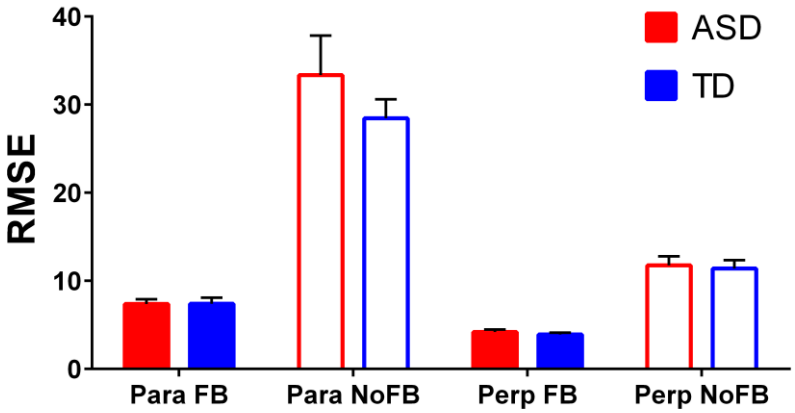

Figure 9: Motor Performance by Group. RMSE for the Parallel (left) and Perpendicular (right) axes of movement in the Feedback (solid bars) and No Feedback (empty bars) for the ASD (red) and TD (blue) groups. Error bars represent standard error of the mean. FB: Feedback; NoFB: No Feedback; Para: Parallel axis; Perp: Perpendicular axis.

3.3.2 Motor Complexity

The 2 (Sensory Condition: Visual Feedback, No Visual Feedback) x 2 (Group: ASD, TD) x 2 (Axis: Perpendicular, Parallel) repeated measures ANOVA with motor complexity (SampEn) as the dependent variable revealed a significant main effect of sensory condition driven by increased SampEn in the Visual Feedback condition ($F(1,31) = 1015.42$, $p < 0.001$, $\eta_p^2 = 0.970$), a main effect of Axis driven by greater SampEn in the Perpendicular axis ($F(1,31) = 752.29$, $p < 0.001$, $\eta_p^2 = 0.960$), and a significant

Sensory Condition x Axis interaction ($F(1,31) = 512.53$, $p < 0.001$, $\eta_p^2 = 0.943$). Follow-up analyses revealed that this interaction was driven by a greater difference between Sensory Conditions in the Parallel Axis than the Perpendicular Axis ($t(32) = 22.84$, $p < 0.001$, $d = 5.77$). There was no main effect of Group and no other significant interactions that included the Group factor. To correct for violations of homogeneity of variance, multivariate tests were reported, and all results are reported after LSD corrections for multiple comparisons. These results are summarized in **Figure 10**.

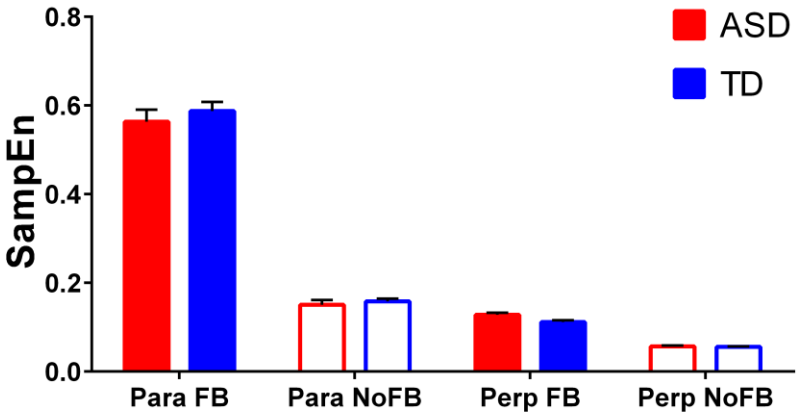

Figure 10. Motor Complexity by Group. SampEn for the Parallel (left) and Perpendicular (right) axes of movement in the Feedback (solid bars) and No Feedback (empty bars) for the ASD (red) and TD (blue) groups. Error bars represent standard error of the mean. FB: Feedback; NoFB: No Feedback; Para: Parallel axis; Perp: Perpendicular axis.

3.3.3 Neural Complexity

Broadband EEG complexity: Results of the 2 (Sensory Condition: Visual Feedback, No Visual Feedback) x 2 (Group: ASD, TD) x 17 (Timescale: 1-17) repeated measures ANOVA that included broadband MSE as the dependent variable are summarized in **Figure 11**. This ANOVA revealed a main effect of Sensory Condition driven by greater MSE in the Visual Feedback condition ($F(1,29) = 12.43$, $p = 0.002$, $\eta_p^2 = 0.332$), a main effect of Timescale ($F(1.41,35.23) = 2505.59$, $p < 0.001$, $\eta_p^2 = 0.990$), and a significant Sensory Condition x Timescale interaction ($F(2.06,51.58) = 11.30$, $p < 0.001$, $\eta_p^2 = 0.311$). The Sensory Condition x Timescale interaction was driven by scales 6-11 having a greater average difference between conditions than scales 12-17 ($t(30) = 4.46$, $p < 0.001$, $d = 0.32$), and scales 12-17 having a greater average difference between conditions than scales 1-5 ($t(30) = 2.92$, $p = 0.007$, $d = 0.47$). There

was no main effect of Group and no other significant interactions that included the Group factor. There were no violations of homogeneity of variance. All results are reported after LSD corrections for multiple comparisons and Huynh-Feldt ($\varepsilon > .75$) or Greenhouse-Geisser ($\varepsilon < .75$) corrections for violations of sphericity, where necessary.

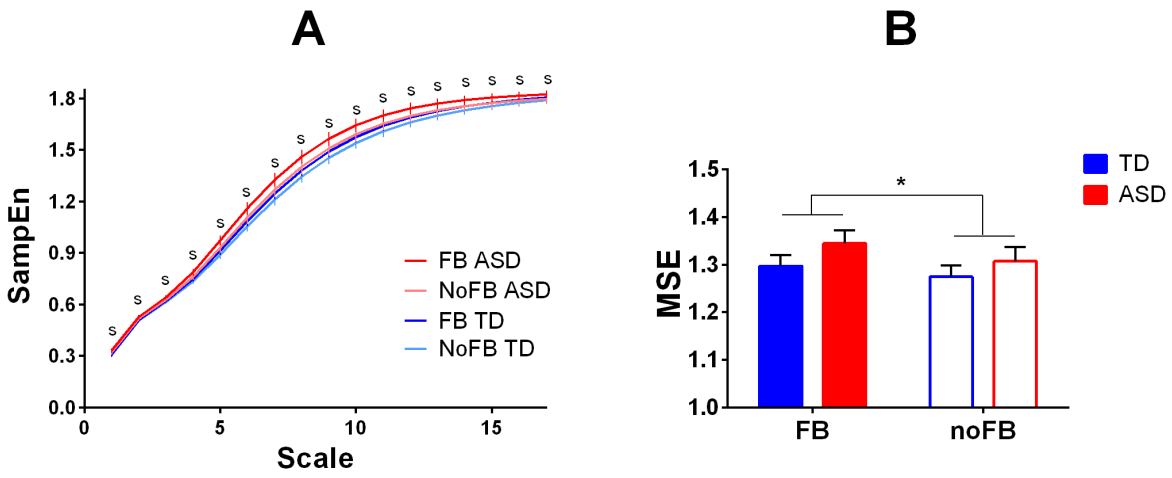

Figure 11: Broadband Neural Complexity by Group. A) SampEn of the broadband neural signal at each timescale for each group (ASD: red, TD: blue) and sensory feedback condition (Feedback: bold lines, No Feedback: pale lines). Error bars represent standard error of the mean. Significant differences between the sensory conditions are indicated with s. Significant group differences are indicated with g. B) Average broadband MSE across timescales for each group (ASD: red, TD: blue) and sensory condition (Feedback: solid bars, No Feedback: empty bars). Significant group and condition interactions are indicated with *. FB: Feedback; NoFB: No Feedback.

Alpha EEG complexity: The 2 (Feedback Condition: Feedback, No Feedback) x 3 (Scalp Region: Frontal, Parietal, Occipital) x 2 (Laterality: Left, Right) x 2 (Group: ASD, TD) repeated measures ANOVA that included alpha MSE as the dependent variable revealed a main effect of Sensory Condition driven by greater MSE in the Feedback condition ($F(1,25) = 21.35$, $p < 0.001$, $\eta_p^2 = 0.461$), a main effect of Scalp Region ($F(1.68,40.94) = 18.56$, $p < 0.001$, $\eta_p^2 = 0.426$), and a significant Sensory Condition x Scalp Region interaction ($F(2,50) = 10.67$, $p < 0.001$, $\eta_p^2 = 0.299$). Follow-up tests correcting for multiple comparisons using LSD revealed that the main effect of Scalp Region was driven by greater alpha MSE in the Frontal scalp region than in the Parietal ($t(30) = 8.16$, $p < 0.001$, $d = 0.396$) and greater alpha MSE in the Parietal scalp region than in the Occipital region ($t(30) = 3.04$, $p = 0.005$, $d = 0.265$). Follow-up tests correcting for multiple comparisons using LSD revealed that the interaction effect of Sensory

Condition x Scalp Region was driven by higher beta MSE in the Occipital region than the Parietal region ($t(30) = 3.97$, $p < 0.001$, $d = 0.402$) for the No Feedback Condition only. All results are reported after LSD corrections for multiple comparisons and Huynh-Feldt ($\varepsilon > .75$) or Greenhouse-Geisser ($\varepsilon < .75$) corrections for violations of sphericity, where necessary. Results are depicted in **Figure 12**.

Beta EEG complexity: The 2 (Feedback Condition: Feedback, No Feedback) x 3 (Scalp Region: Frontal, Parietal, Occipital) x 2 (Laterality: Left, Right) x 2 (Group: ASD, TD) repeated measures ANOVA that included beta MSE as the dependent variable revealed a main effect of Sensory Condition driven by greater beta MSE in the Feedback condition ($F(1,25) = 16.78$, $p < 0.001$, $\eta_p^2 = 0.402$). This ANOVA also revealed a significant Scalp Region x Group interaction ($F(2,24) = 4.43$, $p = 0.023$, $\eta_p^2 = 0.270$) driven by the ASD group having greater beta MSE than the TD group at Parietal ($F(1,25) = 6.30$, $p = 0.019$, $\eta_p^2 = 0.201$) and Occipital ($F(1,25) = 8.05$, $p = 0.009$, $\eta_p^2 = 0.244$) scalp regions but not at Frontal scalp regions. There was a significant Sensory Condition by Scalp Region interaction ($F(2,25) = 12.24$, $p < 0.001$, $\eta_p^2 = 0.505$) driven by greater beta MSE in the Feedback condition relative to the No Feedback condition for Parietal ($F(1,25) = 13.48$, $p = 0.001$, $\eta_p^2 = 0.350$) and Occipital ($F(1,25) = 14.13$, $p = 0.001$, $\eta_p^2 = 0.361$) scalp regions but not for the Frontal region. There was a significant Laterality by Scalp Region interaction ($F(2,24) = 6.44$, $p = 0.006$, $\eta_p^2 = 0.349$) driven by greater beta MSE in the Occipital region than the Parietal region only in the Right hemisphere ($t(30) = 2.98$, $p = 0.006$, $d = 0.346$). There was also a significant Group by Sensory Condition by Scalp Region interaction ($F(2,24) = 4.55$, $p = 0.021$, $\eta_p^2 = 0.275$). This 3-way interaction was driven by greater Condition differences for the ASD group than the TD group at Parietal ($F(1,25) = 6.30$, $p = 0.019$, $\eta_p^2 = 0.201$) and Occipital ($F(1,25) = 8.05$, $p = 0.009$, $\eta_p^2 = 0.244$) regions only. All follow up analyses reported were corrected for multiple comparisons using LSD corrections. These results are depicted in **Figure 13**.

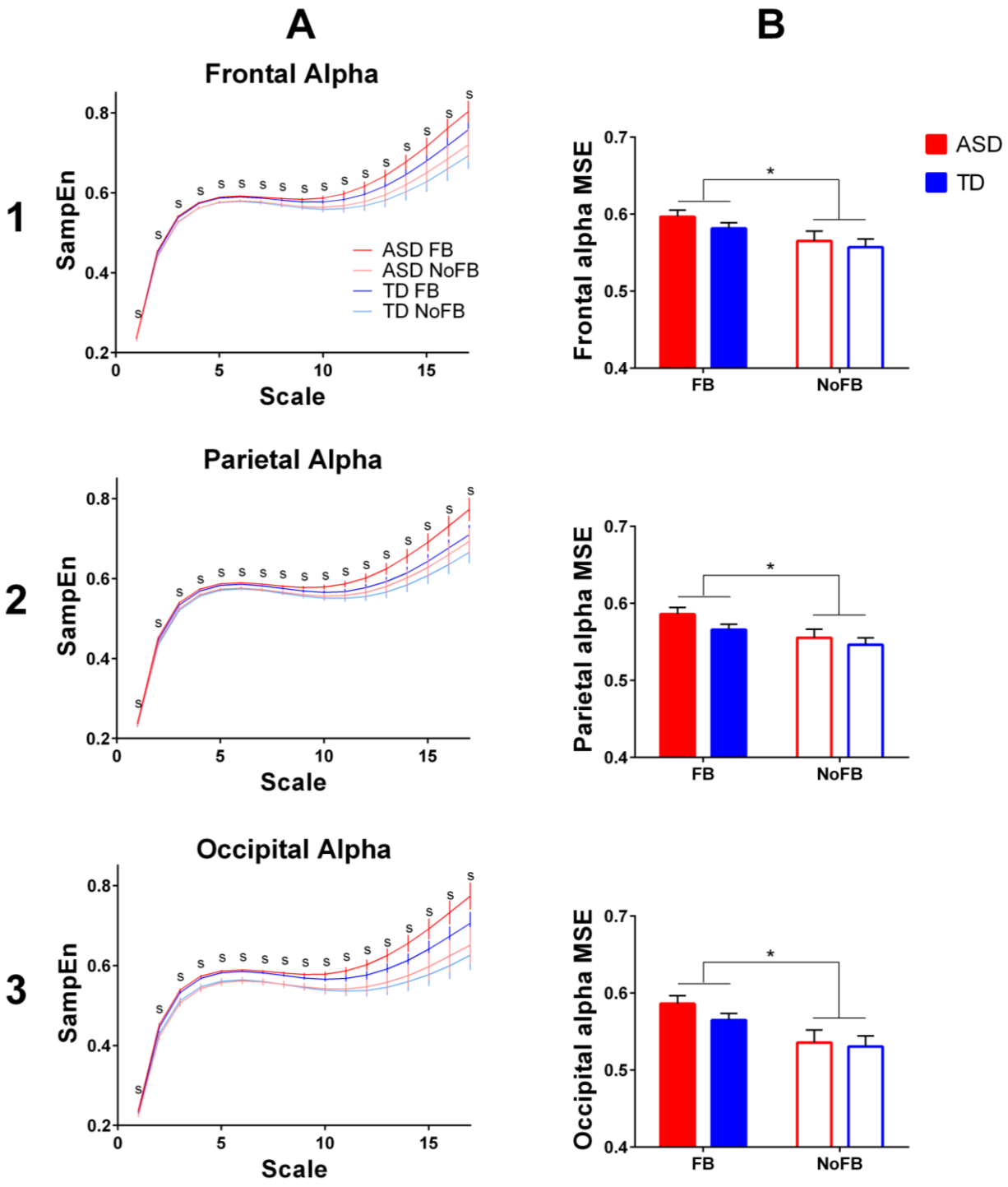

Figure 12: Alpha Neural Complexity by Group. A) SampEn of the alpha neural signal at each timescale for each group (ASD: red, TD: blue) and sensory feedback condition (Feedback: bold lines, No Feedback: pale lines) and each scalp region (Row 1: frontal; Row 2: Parietal; Row 3: occipital). Error bars represent standard error of the mean. Significant differences between the sensory conditions are indicated with s. Significant group differences are indicated with g. B) Average alpha MSE across timescales for each group (ASD: red, TD: blue) and sensory condition (Feedback: solid bars, No Feedback: empty bars) at each corresponding scalp region. Significant group and condition interactions are indicated with *. FB: Feedback; NoFB: No Feedback.

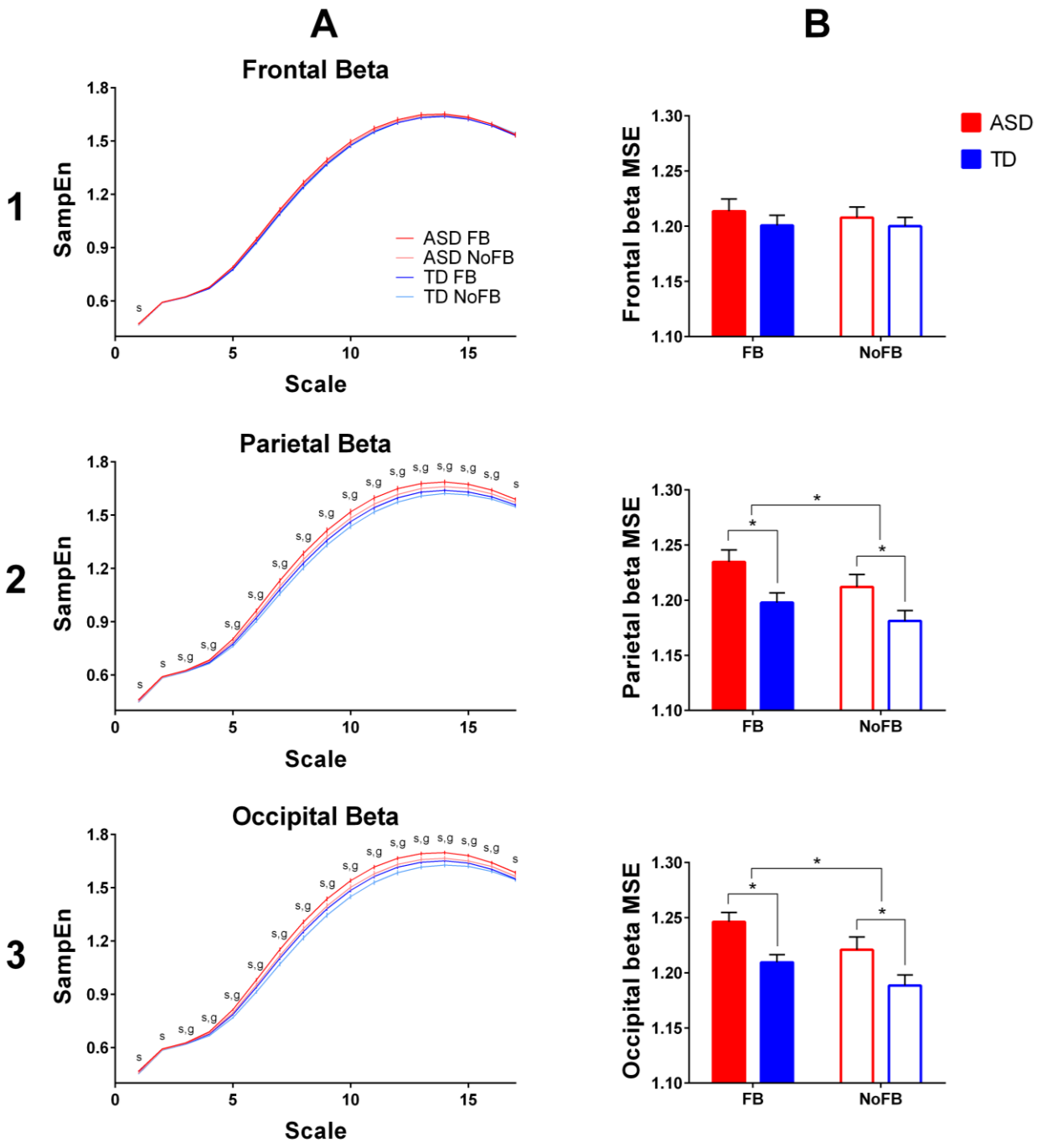

Figure 13: Beta Neural Complexity by Group. A) SampEn of the beta neural signal at each timescale for each group (ASD: red, TD: blue) and sensory feedback condition (Feedback: bold lines, No Feedback: pale lines) and each scalp region (Row 1: frontal; Row 2: Parietal; Row 3: occipital). Error bars represent standard error of the mean. Significant differences between the sensory conditions are indicated with s. Significant group differences are indicated with g. B) Average beta MSE across timescales for each group (ASD: red, TD: blue) and sensory condition (Feedback: solid bars, No Feedback: empty bars) at each corresponding scalp region. Significant group and condition interactions are indicated with *. FB: Feedback; NoFB: No Feedback.

3.3.4 Correlations with Behavioral Assessments

To examine the relation between the experimental measures and stereotyped behavior in the ASD group, we correlated motor performance (RMSE), motor complexity (SampEn), and neural complexity (MSE) with the stereotypy subscale of the RBS-R. All correlations were run using data from the parallel axis of movement as this was the axis along which target movements were directed. Severity of stereotypy was positively correlated with broadband MSE during the Feedback condition ($r(13) = 0.570$, $p = 0.026$), RMSE for both the Feedback ($r(13) = 0.557$, $p = 0.031$) and No Feedback conditions ($r(13) = 0.660$, $p = 0.007$) and negatively correlated with SampEn for both the Feedback ($r(13) = -0.566$, $p = 0.028$) and No Feedback conditions ($r(13) = -0.599$, $p = 0.018$). The correlations between stereotypy and both RMSE and SampEn are depicted in **Figure 14**. To test whether these findings were specific to stereotypy, we ran post hoc Pearson correlations for the total RBS-R score and the remaining subscale scores. The restricted interests subscale of the RBS-R was positively correlated with RMSE for the No Feedback condition ($r(13) = 0.532$, $p = 0.041$). No other correlations were significant for the RBS-R subscales or total score.

To assess the relation between the experimental measures and sensory processing behaviors, we ran Pearson correlations between the vision and movement domains of the Sensory Profile and motor performance, motor complexity, and neural complexity for the ASD and TD groups separately. The ASD group showed a positive correlation between the scores from the movement domain of the SP and broadband MSE in the No Feedback condition ($r(13) = 0.551$, $p = 0.033$). No other correlations between the experimental measures and the vision or movement domains reached significance for the ASD group. The TD group did not have any significant correlations between the experimental measures and the vision or movement domains of the SP.

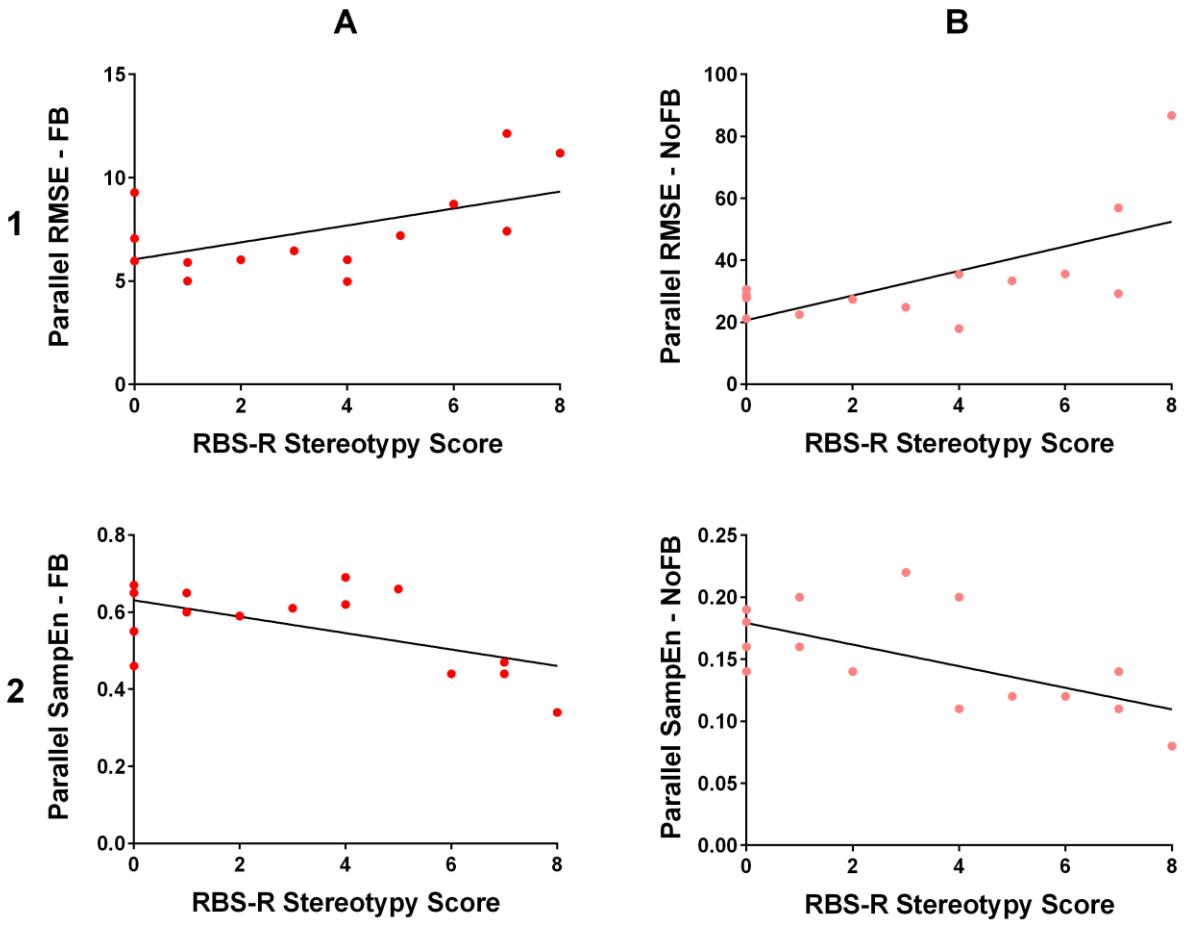

Figure 14: Correlations with RBS-R Stereotypy Subscale. Pearson Correlations for the ASD group between motor error (RMSE; Row 1) and motor complexity (SampEn; Row 2) for the Parallel axes of movement in the Feedback (Column A) and No Feedback (Column B) conditions.

3.4 Discussion

The present study was designed to test the sensorimotor integration model of stereotyped behavior (Shafer et al., 2017) and to examine the hypothesis that diminished sensorimotor integration in individuals with ASD may be contributing to reduced complexity of motor output and the manifestation of stereotyped behaviors.

Adult participants with and without ASD performed a stimulus-tracking task in the presence and absence of visual feedback while we monitored their position and EEG signal during the task. Contrary to

our hypothesis, participants with ASD performed similarly to TD participants in terms of both motor errors and motor complexity. For both groups significant decreases in motor errors and increases in motor complexity were seen in the presence of visual feedback relative to the absence of visual feedback. This provides evidence for sensorimotor capability in adults with ASD and indicates that, under explicit feedback and instructional conditions, individuals with and ASD are able to integrate visual feedback to increase the adaptability of their movements.

Inconsistent with previous literature (Izawa et al., 2012; Lim et al., 2018, 2017; Marko et al., 2015; M. W. Mosconi et al., 2015; Matthew W. Mosconi et al., 2013; Schmitt et al., 2014; Shirama et al., 2016; Takarae et al., 2004; Z. Wang et al., 2015), the ASD group and the TD group performed equivalently on the sensorimotor task. Prior studies have demonstrated deficits in sensorimotor performance in individuals with ASD. It is possible that our task was not as challenging to the sensorimotor system as other sensorimotor task paradigms (e.g., oculomotor tasks, posture tasks) that have shown deficits in sensorimotor performance in individuals with ASD (Lim et al., 2018, 2017; S. L. Morris et al., 2015a; Matthew W. Mosconi et al., 2013; Schmitt et al., 2014; Shirama et al., 2016; Takarae et al., 2004). Additionally, our task explicitly defined that accurate performance required the participants to keep the cursor inside of the target. The defined boundaries of movement accuracy in our task differ from other sensorimotor paradigms such as posture, gait, and grip force tasks for which participants are asked to perform naturalistic movements (e.g., posture) (Lim et al., 2018, 2017; S. L. Morris et al., 2015a)or accuracy is not defined by specific movement boundaries (e.g., isometric force tasks that instruct participants to keep their performance as close to the target as possible but do not define a window of accuracy) (M. W. Mosconi et al., 2015; Z. Wang et al., 2015). Having an explicit definition of accuracy in our task may aid participants both with and without ASD in performing the task accurately.

In the present study, we were able to look at sensory feedback related changes in motor performance and complexity in the context of concomitant changes in neural function as measured by EEG. Although we did not find group differences in either broadband neural complexity or alpha bands neural complexity, analysis of beta band activity did reveal that individuals with ASD had significantly

greater neural complexity at parietal and occipital scalp regions than individuals with TD. We selected the beta frequency bands as previous studies outside of ASD have demonstrated that activity in this frequency band is selective to sensorimotor processing (Lin et al., 2012; McFarland et al., 2000; Mizuhara, 2012) and also changes in motor-related neural complexity (Gao et al., 2013; Martínez-Vargas et al., 2014). In addition to these group related differences in the complexity of beta band activity, we also found that individuals with ASD showed the greatest sensory feedback related effects on beta band complexity in the parietal and occipital scalp regions relative to frontal regions. Parietal clusters were chosen based on their likelihood of capturing a motor relevant signal and occipital clusters were chosen based on their likelihood of capturing a visually relevant signal. The frontal scalp region in this analysis served as a control region that was likely less involved in the neural processing of sensory or motor relevant signals. Thus, the scalp region specific differences in the complexity of the beta band signal that we found in the ASD group provide some evidence that these ASD-related differences reflect alterations in brain network activity involved in processing the sensorimotor relevant information available to the participants to perform the experimental task. A significant limitation of this EEG approach is that EEG has poor spatial resolution and therefore the presumed link between EEG signals measured from parietal and occipital scalp region and sensorimotor function can only be inferred indirectly. Offsetting this limitation to some extent is the superior temporal resolution afforded by EEG analysis that provides more direct support for the presumed link between beta frequency activity and sensorimotor function (Lin et al., 2012; McFarland et al., 2000; Mizuhara, 2012). The pattern of ASD-releated increases in the complexity of beta frequency band activity in parietal and occipital scalp regions indicates that a greater degree of neural complexity was generated by the ASD participants in order to achieve a similar level of motor performance accuracy as the TD participants (i.e. the TD participants achieved a similar level of visually-guided motor accruarcy at a lower level of neural complexity). Although the directionality of group differences in neural complexity was opposite of our hypotheses, and therefore, any interpretation of these results is speculative, this finding could be indicative that individuals with ASD are recruiting additional neural resources as a compensatory mechanism to process the visual information to adapt their movements and

perform sensorimotor tasks accurately.

The role that increased neural complexity serves during sensorimotor task performance has not been previously established. The pattern of increased neural complexity that we observed for the ASD group in parietal and occipital scalp regions during our sensorimotor task may index alterations in functional connectivity in sensorimotor and visual networks in this group. Previous studies in healthy controls have found that neural complexity as measured by MSE is positively associated with functional connectivity (Wang et al., 2018), and thus the ASD-related differences in neural complexity during sensorimotor task performance that we found may be related to the well-established alterations in functional neural connectivity that has been documented in previous neuroimaging studies (Abbott et al., 2018; Cerliani et al., 2015; Khan et al., 2015; Oldehinkel et al., 2018). Support for this interpretation of our neural complexity findings for the ASD group comes from several sources. First, dysfunction of sensorimotor circuitry is one of the most prominent findings in whole-brain, large-cohort studies volumetric and DTI studies of neural functioning in ASD (Cerliani et al., 2015; Oldehinkel et al., 2018). Second, structural and functional abnormalities have also been reported for sensorimotor regions of cortex (Abbott et al., 2018; Müller et al., 2003), cerebellum (Catani et al., 2008; Marko et al., 2015), and striatum (Abbott et al., 2018; Di Martino et al., 2011; Hollander et al., 2005; Langen et al., 2014, 2007). Third, selective atypical connectivity of these discrete networks has been documented from infancy through adulthood in ASD (Cerliani et al., 2015; J. D. Lewis et al., 2017; Oldehinkel et al., 2018).

Previous studies that have used MSE to evaluate neural complexity in individuals with or at risk for ASD have found mixed results with some reporting greater neural complexity in individuals with ASD (Ghanbari et al., 2015; Takahashi et al., 2016) and others finding reduced neural complexity in ASD and at risk infants (Bosl et al., 2011; Catarino et al., 2011; Ghanbari et al., 2015; Liu et al., 2017b). One resting-state study in children observed greater MSE in the ASD group specifically at parietal and occipital scalp regions, consistent with our findings (Takahashi et al., 2016). However, this study found that this difference only occurred in the younger children (3-6yrs) and disappeared in older children 6-10yrs) due to an age-related increase in MSE in the TD children that did not occur in the ASD group. A

separate resting state study in children and adolescents (6-15yrs) looked at MSE for specific frequency bands (Ghanbari et al., 2015). This study found reduced parietal and occipital MSE in ASD in the alpha band and no group differences for beta MSE, inconsistent with our findings. However, the inconsistencies between previous studies and our findings could be due to differences in the age of the participants, the differences in task design, or differences in the approach to MSE analyses (e.g., regional vs. whole scalp, or broadband vs. specific frequency bands).

To more directly relate sensorimotor integration and motor complexity to stereotyped behavior in individuals with ASD, we correlated motor performance, motor complexity, and neural complexity with the severity of the stereotypy phenotype. These analyses revealed that severity of stereotypy in individuals with ASD is positively associated with motor error and negatively associated with motor complexity in both the presence and absence of visual feedback. This finding was specific to the stereotyped behavior subscale of the RBS-R (i.e., was not found for other non-sensorimotor varieties of repetitive behavior characteristic of ASD) and is consistent with our hypothesis that stereotyped behavior is a manifestation of low complexity in the motor system. The ASD group also demonstrated a positive correlation between broadband neural complexity in the visual feedback condition and severity of stereotyped behavior, providing further support for a link between clinical manifestations of atypical motor behavior and sensorimotor function in persons with ASD. Taken together with the group-level results found for ASD motor performance found in this study, these correlational findings for stereotyped behavior within the ASD group suggest that impairments in sensorimotor function may be present only in a specific subset of persons with ASD marked by the presence or severity of stereotyped behaviors as opposed to being present in persons with ASD more generally. This finding is consistent with other ASD studies that have found "subgroup" effects (Whitten, Unruh, Shafer, & Bodfish, 2018), and with a growing consensus that autism is a heterogeneous condition likely comprised of distinguishable subtypes of ASD (Happé & Ronald, 2008; Happé, Ronald, & Plomin, 2006; Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013; Whitten et al., 2018). Although the notion of distinct ASD subtypes is receiving increasing support in the field, precisely how distinct subgroups of persons with ASD differ from each other in

stable ways has yet to be determined. In this light, the present findings of individual differences within the ASD sample, if replicated and found to be stable overtime, suggest that objectively measured motor and neural indices of sensorimotor function may provide one means of identifying a distinct "sensorimotor" subtype within the autism spectrum.

We hypothesized that individuals with ASD would have poorer motor performance and decreased motor complexity relative to TD individuals based on the presence of stereotyped behavior in the ASD population; however, we did not find group differences in motor behavior. This may be due to the fact that our ASD group consisted of high-functioning adults who tend to have low rates of motor stereotypy than the broader ASD population. Future studies should assess motor performance and motor complexity under visual feedback manipulations in younger cohorts and in cohorts that include individuals with more severe cases of ASD to further elucidate the potential relation between sensorimotor integration, adaptive motor behavior, and stereotypy. Also the EEG methods used in this study have inherently poor spatial resolution. This prevented us from identifying the sources or specific neural networks that may be contributing to the group and condition differences that we observed in this study. Future studies could adapt this sensorimotor task to the functional MRI environment in order to reveal which brain regions are involved in performing the task, whether individuals with ASD differ from individuals with TD in the brain regions they recruit during the task, and how the activity at these regions differs between groups. Finally, our study was limited to manipulating visual feedback to explore visuomotor processing differences between individuals with ASD and TD. However, sensorimotor differences in ASD have also been observed the proprioceptive domain (Izawa et al., 2012; Marko et al., 2015; S. L. Morris et al., 2015b), so future work could extend our findings by manipulating both proprioceptive and visual feedback during a sensorimotor task to more fully explore sensorimotor differences in ASD.

Chapter 4

General Discussion

4.1 A novel framework for stereotypy in both typical and atypical development

Stereotyped behavior is one of the diagnostic features of ASD and is generally considered maladaptive, but it also occurs at an early stage of motor development in healthy infants. In the present body of work, I have proposed a conceptual model that implicates sensorimotor mechanisms to explain both pathologic and healthy forms of stereotyped behavior, and I have conducted two empirical studies to assess the validity of this conceptual model. The model postulates that inefficient or unreliable sensorimotor processing disrupts the transfer of sensory information to the motor system and limits the adaptive ability of the motor system to respond to sensory cues and results in movements that are low in complexity (i.e., stereotyped).

4.2 Empirical tests of the model

Study 1 assessed the role of visual feedback on motor performance, motor complexity, and sensorimotor neural complexity during a stimulus-tracking task in typically developing individuals. In study 2, a group of adults with ASD was compared to TD controls on the effect of visual feedback on motor performance, motor complexity, and sensorimotor neural complexity on the same sensorimotor task used in Study 1. Study 2 also compared the experimental measures from the sensorimotor task to behavioral features of ASD, specifically stereotyped behavior.

The conceptual model brings together literature from stereotyped behavior and sensorimotor integration in typical motor development and the literatures on stereotyped behavior and sensorimotor

deficits in ASD and other neurologic and neurodevelopmental disorders. Typically developing infants express stereotyped motor behavior before one year of age (Thelen, 1979). These behaviors have simple (low complexity) kinematics (Konczak et al., 1995; Thelen & Cooke, 1987; Thelen et al., 1993; Thelen & Fisher, 1983b). As infants develop, these stereotyped behaviors transition into more kinematically complex, goal-directed movements. Motor complexity continues to increase across development (Deutsch & Newell, 2001, 2002, 2003). Additional studies have demonstrated that rates of stereotyped behavior and the complexity of movement in healthy infants relates to their exposure to sensory stimuli (Thelen, 1980, 1986), and studies in older children have also demonstrated that in the absence of visual feedback during sustained movement reduces motor complexity relative to when visual feedback is provided (Deutsch & Newell, 2001, 2002, 2003). The conceptual model posits that stereotypy in healthy infants occurs when the sensorimotor systems in the brain are immature and infants have had limited sensorimotor experiences, limiting their ability to integrate sensory feedback with motor output resulting in low complexity, stereotyped movements. As the infants mature and gain experience, they are better able to integrate sensory feedback with motor output and generate complex, adaptive behavior.

Consistent with this model, and in keeping with previous studies, in Study 1 withholding visual feedback resulted in reduced motor performance and reduced motor complexity during the stimulus-tracking task compared to when visual feedback was provided. The neural complexity results paralleled the motor complexity results, with reduced complexity when visual feedback was withheld. This was most robust in alpha and beta frequency bands at central, parietal, and occipital scalp regions, which is consistent with sensorimotor processing. These findings support the role of sensorimotor integration in the expression of complex, controlled movement and indicate that low-complexity movements can be induced by manipulating access to sensory feedback in healthy individuals. Importantly, the findings in the TD group from Study 2 also provided a replication of these results from Study 1 in an independent sample, thus further verifying that visual feedback increases motor performance, motor complexity, and sensorimotor neural complexity in TD individuals.

Clinical populations that express stereotyped behavior often also demonstrate deficits in

sensorimotor processing (Lencer et al., 2010; S. L. Morris et al., 2015b; Nebel et al., 2015; Quednow et al., 2008; Takarae et al., 2004; Z. Wang et al., 2015). In ASD, sensory and motor signs precede the onset of the core social/communication deficits and repetitive behaviors (Sacrey et al., 2015). Sensorimotor deficits are also some of the most robust findings in large-cohort brain imaging studies in ASD (Cerliani et al., 2015; Oldehinkel et al., 2018). These findings indicate that sensorimotor dysfunction may play an important role in the ASD phenotype. The conceptual model posits that in clinical conditions, such as ASD, that express stereotyped behavior, the sensorimotor system is disrupted, either because of abnormal development or because there has been an insult to the system. This results in unreliable signaling between the sensory and motor systems, limiting the ability to use sensory feedback to generate complex, controlled movements, resulting in the expression of stereotyped behavior. Supporting the model, one postural control study demonstrated that individuals with ASD have reduced motor complexity relative to TD controls when visual feedback was available, but both groups showed low motor complexity when visual feedback was not provided, indicating that while the TD individuals were able to use the visual feedback to increase the complexity of their movement; whereas, the individuals with ASD were not (Lim et al., 2017).

Additionally, previous studies from our lab have demonstrated that individuals with neurodevelopmental disabilities who have high rates of stereotyped behavior demonstrate reduced motor complexity during postural sway tasks relative to TD individuals l(Bodfish et al., 2001; Hong et al., 2006a; Newell & Bodfish, 2007; Newell et al., 1999). While these studies did not manipulate sensory feedback, they do support a relation between stereotypy and motor complexity. Study 2 aimed to provide a more direct test of the role of sensorimotor integration on motor control and its relation to stereotyped behavior in ASD.

The results of Study 2 indicated that the pattern of both motor errors and motor complexity did not differ between groups regardless of sensory condition; however, both groups demonstrated improved motor performance and reduced motor complexity when visual feedback was available. Further, the ASD group demonstrated greater neural complexity and greater differences between feedback conditions than

individuals with TD, specifically in the beta frequency band at parietal and occipital scalp regions which are more circumscribed aspects of the broadband EEG signal that have been used to index sensorimotor function in previous studies. These EEG findings support the sensorimotor model of ASD developed to guide this work and indicate differences in sensorimotor processing in individuals with ASD at the level of neural functioning. The increased neural complexity observed at parietal and occipital scalp regions in the ASD group relative to the TD group could indicate that individuals with ASD are using compensatory sensorimotor mechanisms (e.g., recruiting additional neural resources) to increase their motor complexity and perform the task accurately.

Motor performance, motor complexity, and neural complexity were also associated with stereotyped behavior in the ASD group. Lower performance and lower motor complexity corresponded to more severe stereotyped behavior, consistent with the conceptual model. Higher neural complexity was also associated with more severe stereotypy. Given that the ASD group had greater neural complexity than the TD group, likely due to compensatory neural processing, this finding is suggestive that greater deficits in sensorimotor neural processing correspond with more severe stereotyped behavior. These findings were specific to stereotypy, as other types of repetitive behavior in ASD were not significantly related to the experimental measures further supporting that stereotypy manifests when complexity in the motor system is low.

4.3 Conclusions, implications, and future directions

Research in healthy development indicate that as an individual develops the ability to integrate sensory information with motor output, the motor behavior becomes more complex, permitting the individual to adapt movements to the environmental context. This occurs in healthy infants when they transition from stereotyped movements to complex, goal-directed behavior, which are mediated by their ability to predict and learn from the sensory consequences of their movements. The development of

complex motor behavior through sensorimotor integration in healthy development provides a mechanistic framework for understanding motor stereotypy in clinical populations with known sensory and motor abnormalities.

Traditionally, stereotyped motor behavior is associated with basal ganglia dysfunction, but the sensory influence on motor complexity and the relation of motor complexity to motor stereotypy in normative development implicates that sensorimotor cortex dysfunction may play a role in the presence of stereotyped motor behavior in clinical populations. Neural circuitry supporting sensorimotor integration links basal ganglia to sensorimotor cortex via corticostriatal connections, indicating that insults to basal ganglia likely impact the function of sensorimotor cortex. Future research should explore the role of sensorimotor cortex in the expression of motor stereotypy and whether basal ganglia dysfunction disrupts normal function in the sensorimotor cortex contributing to the expression of stereotyped motor behavior.

The proposed framework that implicates sensorimotor integration in the complexity and adaptability of the motor output and the manifestation of stereotyped behavior provides opportunities for studying stereotyped behavior in clinical disorders and identifying individuals at risk for developing motor stereotypy. Motor complexity can be measured and manipulated under a variety of sensory feedback conditions and concurrently with task performance and neural function as was done in Studies 1 and 2. This provides the means to assess the integrity of the sensorimotor systems in individuals with stereotyped behaviors at both a neural and behavioral level. Motor complexity can also be measured on a relatively short timescale with minimal task constraints (e.g. postural tasks) making it accessible for studying motor complexity in early human development and generalizable for studying animal models of motor stereotypy. Given its accessibility for use in infants, assessments of motor complexity can also be used to clinically screen and identify individuals who are at risk for developing motor stereotypy and the disorders associated with them, providing opportunities to intervene with therapy approaches aimed at increasing complexity in the motor system before symptoms manifest.

BIBLIOGRAPHY

Abbott, A. E., Linke, A. C., Nair, A., Jahedi, A., Alba, L. A., Keown, C. L., … Müller, R.-A. (2018). Repetitive behaviors in autism are linked to imbalance of corticostriatal connectivity: a functional connectivity MRI study. *Social Cognitive and Affective Neuroscience*, *13*(1), 32–42. https://doi.org/10.1093/scan/nsx129

Alexander, G. E., & Crutcher, M. D. (1990). Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *Journal of Neurophysiology*, *64*(1), 133–150.

Almeida, Q. J., Frank, J. S., Roy, E. A., Jenkins, M. E., Spaulding, S., Patla, A. E., & Jog, M. S. (2005). An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease. *Neuroscience*, *134*(1), 283–293. https://doi.org/10.1016/j.neuroscience.2005.02.050

American Psychatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Arlington, VA: American Psychiatric Publishing.

Archambault, P. S., Caminiti, R., & Battaglia-Mayer, A. (2009). Cortical Mechanisms for Online Control of Hand Movement Trajectory: The Role of the Posterior Parietal Cortex. *Cerebral Cortex*, *19*(12), 2848–2864. https://doi.org/10.1093/cercor/bhp058

Arrighi, P., Bonfiglio, L., Minichilli, F., Cantore, N., Carboncini, M. C., Piccotti, E., … Andre, P. (2016). EEG Theta Dynamics within Frontal and Parietal Cortices for Error Processing during Reaching Movements in a Prism Adaptation Study Altering Visuo-Motor Predictive Planning. *PLOS ONE*, *11*(3), e0150265. https://doi.org/10.1371/journal.pone.0150265

Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. *Journal of Autism and Developmental Disorders*, *29*(3), 213–224.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and

Females, Scientists and Mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 13.

Bechard, A. R., Bliznyuk, N., & Lewis, M. H. (2017). The development of repetitive motor behaviors in deer mice: Effects of environmental enrichment, repeated testing, and differential mediation by indirect basal ganglia pathway activation. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21503

Bechard, A. R., Cacodcar, N., King, M. A., & Lewis, M. H. (2016). How does environmental enrichment reduce repetitive motor behaviors? Neuronal activation and dendritic morphology in the indirect basal ganglia pathway of a mouse model. *Behavioural Brain Research*, *299*, 122–131. https://doi.org/10.1016/j.bbr.2015.11.029

Berman, G. J., Choi, D. M., Bialek, W., & Shaevitz, J. W. (2014). Mapping the stereotyped behaviour of freely moving fruit flies. *Journal of The Royal Society Interface*, *11*(20140672), 20140672–20140672. https://doi.org/10.1098/rsif.2014.0672

Bernstein, N. A. (1967). *The Co-ordination and Regulation of Movements*. Oxford: Pergamon Press Ltd.

Blatt, G. J., Andersen, R. A., & Stoner, G. R. (1990). Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the macaque. *Journal of Comparative Neurology*, *299*(4), 421–445.

Bodfish, J. W., Parker, D. E., Lewis, M. H., Sprague, R. L., & Newell, K. M. (2001). Stereotypy and motor control: differences in the postural stability dynamics of persons with stereotyped and dyskinetic movement disorders. *American Journal on Mental Retardation*, *106*(2), 123–134.

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders*, *30*(3), 237–243.

Bos, K. J., Zeanah, C. H., Smyke, A. T., Fox, N. A., & Nelson, C. A. (2010). Stereotypies in Children With a History of Early Institutional Care. *Archives of Pediatrics & Adolescent Medicine*, *164*(5), 406–411. https://doi.org/10.1001/archpediatrics.2010.47

Bosl, W., Tierney, A., Tager-Flusberg, H., & Nelson, C. (2011). EEG complexity as a biomarker for autism spectrum disorder risk. *BMC Medicine*, *9*(1), 1.

Boyd, B. A., Baranek, G. T., Sideris, J., Poe, M. D., Watson, L. R., Patten, E., & Miller, H. (2010). Sensory features and repetitive behaviors in children with autism and developmental delays. *Autism Research*, *3*(2), 78–87. https://doi.org/10.1002/aur.124

Boyd, B. A., McBee, M., Holtzclaw, T., Baranek, G. T., & Bodfish, J. W. (2009). Relationships among repetitive behaviors, sensory features, and executive functions in high functioning autism. *Research in Autism Spectrum Disorders*, *3*(4), 959–966. https://doi.org/10.1016/j.rasd.2009.05.003

Boyd, B. A., McDonough, S. G., Rupp, B., Khan, F., & Bodfish, J. W. (2011). Effects of a Family-Implemented Treatment on the Repetitive Behaviors of Children with Autism. *Journal of Autism and Developmental Disorders*, *41*(10), 1330–1341. https://doi.org/10.1007/s10803-010-1156-y

Braak, H., & Del Tredici, K. (2008). Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. *Experimental Neurology*, *212*(1), 226–229. https://doi.org/10.1016/j.expneurol.2008.04.001

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, *10*(4), 433–436.

Bremner, L. R., & Andersen, R. A. (2012). Coding of the Reach Vector in Parietal Area 5d. *Neuron*, *75*(2), 342–351. https://doi.org/10.1016/j.neuron.2012.03.041

Brotchie, P. R., Andersen, R. A., Snyder, L. H., & Goodman, S. J. (1995). Head position signals used be parietal neurons to encode locations of visual stimuli. *Nature*, *375*(18), 232–235.

Campbell, D. L. M., Dallaire, J. A., & Mason, G. J. (2013). Environmentally enriched rearing environments reduce repetitive perseveration in caged mink, but increase spontaneous alternation. *Behavioural Brain Research*, *239*, 177–187. https://doi.org/10.1016/j.bbr.2012.11.004

Catana Brown, & Dunn, W. (2002). *Adolescent/Adult Sensory Profile: User's Manual*. San Antonio, TX: The Psychological Corporation.

Catani, M., Jones, D. K., Daly, E., Embiricos, N., Deeley, Q., Pugliese, L., … Murphy, D. G. M. (2008).

Altered cerebellar feedback projections in Asperger syndrome. *NeuroImage*, *41*(4), 1184–1191. https://doi.org/10.1016/j.neuroimage.2008.03.041

Catarino, A., Churches, O., Baron-Cohen, S., Andrade, A., & Ring, H. (2011). Atypical EEG complexity in autism spectrum conditions: A multiscale entropy analysis. *Clinical Neurophysiology*, *122*(12), 2375–2383. https://doi.org/10.1016/j.clinph.2011.05.004

Cerliani, L., Mennes, M., Thomas, R. M., Martino, A. D., Thioux, M., & Keysers, C. (2015). Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder. *JAMA Psychiatry*, *72*(8), 767–777. https://doi.org/10.1001/jamapsychiatry.2015.0101

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2013). Age-related changes in ERP correlates of visuospatial and motor processes. *Psychophysiology*, *50*(8), 743–757. https://doi.org/10.1111/psyp.12063

Chen, C. C., Hsu, Y. T., Chan, H. L., Chiou, S. M., Tu, P. H., Lee, S. T., … Brown, P. (2010). Complexity of subthalamic 13–35Hz oscillatory activity directly correlates with clinical impairment in patients with Parkinson's disease. *Experimental Neurology*, *224*(1), 234–240. https://doi.org/10.1016/j.expneurol.2010.03.015

Chen, X., Duan, M., Xie, Q., Lai, Y., Dong, L., Cao, W., … Luo, C. (2015). Functional disconnection between the visual cortex and the sensorimotor cortex suggests a potential mechanism for self-disorder in schizophrenia. *Schizophrenia Research*, *166*(1–3), 151–157. https://doi.org/10.1016/j.schres.2015.06.014

Christensen, M. S., Lundbye-Jensen, J., Geertsen, S. S., Petersen, T. H., Paulson, O. B., & Nielsen, J. B. (2007). Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. *Nature Neuroscience*, *10*(4), 417–419. https://doi.org/10.1038/nn1873

Cipolloni, P. B., & Pandya, D. N. (1999). Cortical connections of the frontoparietal opercular areas in the rhesus monkey. *Journal of Comparative Neurology*, *403*(4), 431–458.

Colby, C. L., Gattass, R., Olson, C. R., & Gross, C. G. (1988). Topographical organization of cortical afferents to extrastriate visual area PO in the macaque: a dual tracer study. *Journal of*

Comparative Neurology, *269*(3), 392–413.

Constantino, J. N., & Gruber, C. P. (2012). *The Social Responsiveness Scale Manual (SRS-2)* (Second). Los Angeles, CA: Western Psychological Services.

Cooper, S. J., & Dourish, C. T. (1990). *Neurobiology of Stereotyped Behavior*. New York, NY: Clarendon Press/Oxford University Press. Retrieved from http://ovidsp.tx.ovid.com.proxy.library.vanderbilt.edu/ovftpdfs/FPDDNCFBCFKOKD00/fs046/ovft/live/gv023/00004850/00004850-199100620-00012.pdf

Costa, M., Goldberger, A. L., & Peng, C.-K. (2002). Multiscale Entropy Analysis of Complex Physiologic Time Series. *Physical Review Letters*, *89*(6). https://doi.org/10.1103/PhysRevLett.89.068102

Costa, M., Goldberger, A. L., & Peng, C.-K. (2005). Multiscale entropy analysis of biological signals. *Physical Review E*, *71*(2). https://doi.org/10.1103/PhysRevE.71.021906

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine*, *11*(1). https://doi.org/10.1186/1741-7015-11-126

D'Cruz, A.-M., Mosconi, M. W., Steele, S., Rubin, L. H., Luna, B., Minshew, N., & Sweeney, J. A. (2009). Lateralized Response Timing Deficits in Autism. *Biological Psychiatry*, *66*(4), 393–397. https://doi.org/10.1016/j.biopsych.2009.01.008

Delfs, J. M., & Kelley, A. E. (1990). The role of D1 and D2 dopamine receptors in oral stereotypy induced by dopaminergic stimulation of the ventrolateral striatum. *Neuroscience*, *39*(1), 59–67.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Desmurget, M., & Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends in Cognitive Sciences*, *4*(11), 423–431.

Deutsch, K. M., & Newell, K. M. (2001). Age Differences in Noise and Variability of Isometric Force Production. *Journal of Experimental Child Psychology*, *80*(4), 392–408.

https://doi.org/10.1006/jecp.2001.2642

Deutsch, K. M., & Newell, K. M. (2002). Children's coordination of force output in a pinch grip task. *Developmental Psychobiology*, *41*(3), 253–264. https://doi.org/10.1002/dev.10051

Deutsch, K. M., & Newell, K. M. (2003). Deterministic and stochastic processes in children's isometric force variability. *Developmental Psychobiology*, *43*(4), 335–345. https://doi.org/10.1002/dev.10140

Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.-N., Mennes, M., Mairena, M. A., … Milham, M. P. (2011). Aberrant Striatal Functional Connectivity in Children with Autism. *Biological Psychiatry*, *69*(9), 847–856. https://doi.org/10.1016/j.biopsych.2010.10.029

Dowd, A. M., McGinley, J. L., Taffe, J. R., & Rinehart, N. J. (2012). Do Planning and Visual Integration Difficulties Underpin Motor Dysfunction in Autism? A Kinematic Study of Young Children with Autism. *Journal of Autism and Developmental Disorders*, *42*(8), 1539–1548. https://doi.org/10.1007/s10803-011-1385-8

Duann, J.-R., & Chiou, J.-C. (2016). A Comparison of Independent Event-Related Desynchronization Responses in Motor-Related Brain Areas to Movement Execution, Movement Imagery, and Movement Observation. *PLOS ONE*, *11*(9), e0162546. https://doi.org/10.1371/journal.pone.0162546

Duffield, T. C., Trontel, H. G., Bigler, E. D., Froehlich, A., Prigge, M. B., Travers, B., … Lainhart, J. (2013). Neuropsychological investigation of motor impairments in autism. *Journal of Clinical and Experimental Neuropsychology*, *35*(8), 867–881. https://doi.org/10.1080/13803395.2013.827156

Duhamel, J.-R., Bremmer, F., BenHamed, S., & Graf, W. (1997). Spatial invariance of visual receptive fields in parietal cortex neurons. *Nature*, *389*(6653), 845–848.

Fernández, A., Gómez, C., Hornero, R., & López-Ibor, J. J. (2013). Complexity and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *45*, 267–276. https://doi.org/10.1016/j.pnpbp.2012.03.015

Ferraina, S., & Bianchi, L. (1994). Posterior parietal cortex: functional properties of neurons in area 5 during an instructed-delay reaching task within different parts of space. *Experimental Brain Research*, *99*(1), 175–178.

Flaherty, A. W., & Graybiel, A. M. (1994). Input-output organization of the sensorimotor striatum in the squirrel monkey. *Journal of Neuroscience*, *14*(2), 599–610.

Foster, J. J., Sutterer, D. W., Serences, J. T., Vogel, E. K., & Awh, E. (2017). Alpha-Band Oscillations Enable Spatially and Temporally Resolved Tracking of Covert Spatial Attention. *Psychological Science*, *28*(7), 929–941. https://doi.org/10.1177/0956797617699167

Fournier, K. A., Amano, S., Radonovich, K. J., Bleser, T. M., & Hass, C. J. (2014). Decreased dynamical complexity during quiet stance in children with Autism Spectrum Disorders. *Gait & Posture*, *39*(1), 420–423. https://doi.org/10.1016/j.gaitpost.2013.08.016

Gao, L., Wang, J., & Chen, L. (2013). Event-related desynchronization and synchronization quantification in motor-related EEG by Kolmogorov entropy. *Journal of Neural Engineering*, *10*(3), 036023. https://doi.org/10.1088/1741-2560/10/3/036023

Garner, J. P., Mason, G. J., & Smith, R. (2003). Stereotypic route-tracing in experimentally caged songbirds correlates with general behavioral disinhibition. *Animal Behaviour*, *66*, 711–727. https://doi.org/10.1006/anbe.2003.2254

Ghanbari, Y., Bloy, L., Christopher Edgar, J., Blaskey, L., Verma, R., & Roberts, T. P. L. (2015). Joint Analysis of Band-Specific Functional Connectivity and Signal Complexity in Autism. *Journal of Autism and Developmental Disorders*, *45*(2), 444–460. https://doi.org/10.1007/s10803-013-1915-7

Gnadt, J. W., & Andersen, R. A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. *Experimental Brain Research*, *70*(1), 216–220.

Goh, K. L., Morris, S., Parsons, R., Ring, A., & Tan, T. (2017). Postural and Cortical Responses Following Visual Occlusion in Adults With and Without ASD. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-017-3405-9

Goldman, S., Wang, C., Salgado, M. W., Greene, P. E., Kim, M., & Rapin, I. (2009). Motor stereotypies in children with autism and other developmental disorders. *Developmental Medicine & Child Neurology*, *51*(1), 30–38.

Gotham, K., Pickles, A., & Lord, C. (2009). Standardizing ADOS Scores for a Measure of Severity in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *39*(5), 693–705. https://doi.org/10.1007/s10803-008-0674-3

Haggard, P., & Whitford, B. (2004). Supplementary motor area provides an efferent signal for sensory suppression. *Cognitive Brain Research*, *19*(1), 52–58. https://doi.org/10.1016/j.cogbrainres.2003.10.018

Hannant, P., Cassidy, S., Tavassoli, T., & Mann, F. (2016). Sensorimotor Difficulties Are Associated with the Severity of Autism Spectrum Conditions. *Frontiers in Integrative Neuroscience*, *10*. https://doi.org/10.3389/fnint.2016.00028

Happé, F., & Ronald, A. (2008). The 'Fractionable Autism Triad': A Review of Evidence from Behavioural, Genetic, Cognitive and Neural Research. *Neuropsychology Review*, *18*(4), 287–304. https://doi.org/10.1007/s11065-008-9076-8

Happé, F., Ronald, A., & Plomin, R. (2006). Time to give up on a single explanation for autism. *Nature Neuroscience*, *9*(10), 1218–1220. https://doi.org/10.1038/nn1770

Harbourne, R. T., & Stergiou, N. (2003). Nonlinear analysis of the development of sitting postural control. *Developmental Psychobiology*, *42*(4), 368–377. https://doi.org/10.1002/dev.10110

Hasegawa, C., Takahashi, T., Yoshimura, Y., Nobukawa, S., Ikeda, T., Saito, D. N., … Kikuchi, M. (2018). Developmental Trajectory of Infant Brain Signal Variability: A Longitudinal Pilot Study. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00566

Hausdorff, J. M., Zemany, L., Peng, C.-K., & Goldberger, A. L. (1999). Maturation of gait dynamics: stride-to-stride variability and its temporal organization in children. *Journal of Applied Physiology*, *86*(3), 1040–1047.

Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M. M., Licalzi, E., … Buchsbaum,

M. (2005). Striatal Volume on Magnetic Resonance Imaging and Repetitive Behaviors in Autism. *Biological Psychiatry*, *58*(3), 226–232. https://doi.org/10.1016/j.biopsych.2005.03.040

Hong, S. L., Bodfish, J. W., & Newell, K. M. (2006a). Power-law scaling for macroscopic entropy and microscopic complexity: Evidence from human movement and posture. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *16*(1), 013135. https://doi.org/10.1063/1.2186765

Hong, S. L., Bodfish, J. W., & Newell, K. M. (2006b). Power-law scaling for macroscopic entropy and microscopic complexity: Evidence from human movement and posture. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, *16*(1), 013135. https://doi.org/10.1063/1.2186765

Hus, V., & Lord, C. (2014). The Autism Diagnostic Observation Schedule, Module 4: Revised Algorithm and Standardized Severity Scores. *Journal of Autism and Developmental Disorders*, *44*(8), 1996–2012. https://doi.org/10.1007/s10803-014-2080-3

Hyde, C. E., & Wilson, P. H. (2013). Impaired Online Control in Children With Developmental Coordination Disorder Reflects Developmental Immaturity. *Developmental Neuropsychology*, *38*(2), 81–97. https://doi.org/10.1080/87565641.2012.718820

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Izawa, J., Pekny, S. E., Marko, M. K., Haswell, C. C., Shadmehr, R., & Mostofsky, S. H. (2012). Motor Learning Relies on Integrated Sensory Inputs in ADHD, but Over-Selectively on Proprioception in Autism Spectrum Conditions: Distinct patterns of motor memory in Autism. *Autism Research*, *5*(2), 124–136. https://doi.org/10.1002/aur.1222

Jacobs, J. V., & Horak, F. B. (2006). Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with parkinson's disease. *Neuroscience*, *141*(2), 999–1009. https://doi.org/10.1016/j.neuroscience.2006.04.014

Johnson, P. B., Ferraina, S., Bianchi, L., & Caminiti, R. (1996). Cortical networks for visual reaching:

physiological and anatomical organization of frontal and parietal lobe arm regions. *Cerebral Cortex*, *6*(2), 102–119.

Jones, E. G., Coulter, J. D., & Hendry, S. H. C. (1978). Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *Journal of Comparative Neurology*, *181*(2), 291–347.

Jones, E. G., & Powell, T. P. S. (1969). Connexions of the somatic sensory cortex of the rhesus monkey. *Brain*, *92*(3), 477–502.

Jones, E. G., & Powell, T. P. S. (1970). An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, *93*(4), 793–820.

Jürgens, U. (1984). The efferent and afferent connections of the supplementary motor area. *Brain Research*, *300*(1), 63–81.

Kaufmann, T., Skåtun, K. C., Alnæs, D., Doan, N. T., Duff, E. P., Tønnesen, S., … Westlye, L. T. (2015). Disintegration of Sensorimotor Brain Networks in Schizophrenia. *Schizophrenia Bulletin*, *41*(6), 1326–1335. https://doi.org/10.1093/schbul/sbv060

Kelley, A. E., Lang, C. G., & Gauthier, A. M. (1988). Induction of oral stereotypy following amphetamine microinjection into a discrete subregion of the striatum. *Psychopharmacology*, *95*(4), 556–559.

Kent, J. S., Hong, S. L., Bolbecker, A. R., Klaunig, M. J., Forsyth, J. K., O'Donnell, B. F., & Hetrick, W. P. (2012). Motor Deficits in Schizophrenia Quantified by Nonlinear Analysis of Postural Sway. *PLoS ONE*, *7*(8), e41808. https://doi.org/10.1371/journal.pone.0041808

Khan, A. J., Nair, A., Keown, C. L., Datko, M. C., Lincoln, A. J., & Müller, R.-A. (2015). Cerebro-cerebellar Resting-State Functional Connectivity in Children and Adolescents with Autism Spectrum Disorder. *Biological Psychiatry*, *78*(9), 625–634. https://doi.org/10.1016/j.biopsych.2015.03.024

Kim, S. H., & Lord, C. (2010). Restricted and repetitive behaviors in toddlers and preschoolers with autism spectrum disorders based on the Autism Diagnostic Observation Schedule (ADOS).

Autism Research, *3*(4), 162–173. https://doi.org/10.1002/aur.142

Kirby, A. V., Dickie, V. A., & Baranek, G. T. (2015). Sensory experiences of children with autism spectrum disorder: In their own words. *Autism*, *19*(3), 316–326. https://doi.org/10.1177/1362361314520756

Kleiner, M., Brainard, D. H., & Pelli, D. G. (2007). What's new in Psychtoolbox-3? *Perception*, *36*(14), ECVP Abstract Supplement.

Koegel, R. L., & Covert, A. (1972). The relationship of self-stimulation to learning in autistic children. *Journal of Applied Behavior Analysis*, *5*(4), 381–387.

Koegel, R. L., Firestone, P. B., Kramme, K. W., & Dunlap, G. (1974). Increasing spontaneous play by suppressing self-stimulation in autistic children. *Journal of Applied Behavior Analysis*, *7*(4), 521–528.

Konczak, J., Borutta, M., Topka, H., & Dichgans, J. (1995). The development of goal-directed reaching in infants: hand trajectory formation and joint torque control. *Experimental Brain Research*, *106*(1), 156–168.

Kotini, A., & Anninos, P. (2002). Detection of non-linearity in schizophrenic patients using magnetoencephalography. *Brain Topography; New York*, *15*(2), 107–113.

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered Auditory and Multisensory Temporal Processing in Autism Spectrum Disorders. *Frontiers in Integrative Neuroscience*, *4*, 129. https://doi.org/10.3389/fnint.2010.00129

Lai, M.-C., Lombardo, M. V., Chakrabarti, B., & Baron-Cohen, S. (2013). Subgrouping the Autism "Spectrum": Reflections on DSM-5. *PLoS Biology*, *11*(4), e1001544. https://doi.org/10.1371/journal.pbio.1001544

Lam, K. S. L., & Aman, M. G. (2007). The Repetitive Behavior Scale-Revised: Independent Validation in Individuals with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866. https://doi.org/10.1007/s10803-006-0213-z

Langen, M., Bos, D., Noordermeer, S. D. S., Nederveen, H., van Engeland, H., & Durston, S. (2014).

Changes in the Development of Striatum Are Involved in Repetitive Behavior in Autism. *Biological Psychiatry*, *76*(5), 405–411. https://doi.org/10.1016/j.biopsych.2013.08.013

Langen, M., Durston, S., Staal, W. G., Palmen, S. J. M. C., & van Engeland, H. (2007). Caudate Nucleus Is Enlarged in High-Functioning Medication-Naive Subjects with Autism. *Biological Psychiatry*, *62*(3), 262–266. https://doi.org/10.1016/j.biopsych.2006.09.040

Lee, Y.-J., Zhu, Y.-S., Xu, Y.-H., Shen, M.-F., Zhang, H.-X., & Thakor, N. . (2001). Detection of non-linearity in the EEG of schizophrenic patients. *Clinical Neurophysiology*, *112*(7), 1288–1294. https://doi.org/10.1016/S1388-2457(01)00544-2

Lencer, R., Reilly, J. L., Harris, M. S., Sprenger, A., Keshavan, M. S., & Sweeney, J. A. (2010). Sensorimotor Transformation Deficits for Smooth Pursuit in First-Episode Affective Psychoses and Schizophrenia. *Biological Psychiatry*, *67*(3), 217–223. https://doi.org/10.1016/j.biopsych.2009.08.005

Levin, A. R., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2015). Social Communication Difficulties and Autism in Previously Institutionalized Children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(2), 108-115.e1. https://doi.org/10.1016/j.jaac.2014.11.011

Lewis, G. N., & Byblow, W. D. (2002). Altered sensorimotor integration in Parkinson's disease. *Brain*, *125*, 2089–2099.

Lewis, J. D., Evans, A. C., Pruett, J. R., Botteron, K. N., McKinstry, R. C., Zwaigenbaum, L., … Gu, H. (2017). The Emergence of Network Inefficiencies in Infants With Autism Spectrum Disorder. *Biological Psychiatry*, *82*(3), 176–185. https://doi.org/10.1016/j.biopsych.2017.03.006

Lewis, J. W., & Van Essen, D. C. (2000). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *Journal of Comparative Neurology*, *428*(1), 112–137.

Lewis, M, Tanimura, Y., Lee, L., & Bodfish, J. (2007). Animal models of restricted repetitive behavior in autism. *Behavioural Brain Research*, *176*(1), 66–74. https://doi.org/10.1016/j.bbr.2006.08.023

Lewis, Mark, & Kim, S.-J. (2009). The pathophysiology of restricted repetitive behavior. *Journal of*

Neurodevelopmental Disorders, *1*(2), 114–132. https://doi.org/10.1007/s11689-009-9019-6

Lim, Y. H., Lee, H. C., Falkmer, T., Allison, G. T., Tan, T., Lee, W. L., & Morris, S. L. (2018). Effect of Visual Information on Postural Control in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3634-6

Lim, Y. H., Partridge, K., Girdler, S., & Morris, S. L. (2017). Standing Postural Control in Individuals with Autism Spectrum Disorder: Systematic Review and Meta-analysis. *Journal of Autism and Developmental Disorders*, *47*(7), 2238–2253. https://doi.org/10.1007/s10803-017-3144-y

Limbach, K., & Corballis, P. M. (2017). Alpha-power modulation reflects the balancing of task requirements in a selective attention task. *Psychophysiology*, *54*(2), 224–234. https://doi.org/10.1111/psyp.12774

Lin, C.-L., Shaw, F.-Z., Young, K.-Y., Lin, C.-T., & Jung, T.-P. (2012). EEG correlates of haptic feedback in a visuomotor tracking task. *NeuroImage*, *60*(4), 2258–2273. https://doi.org/10.1016/j.neuroimage.2012.02.008

Liu, T., Chen, Y., Chen, D., Li, C., Qiu, Y., & Wang, J. (2017a). Altered electroencephalogram complexity in autistic children shown by the multiscale entropy approach. *Neuroreport*, *28*(3), 169–173. https://doi.org/10.1097/WNR.0000000000000724

Liu, T., Chen, Y., Chen, D., Li, C., Qiu, Y., & Wang, J. (2017b). Altered electroencephalogram complexity in autistic children shown by the multiscale entropy approach. *NeuroReport*, *28*(3), 169. https://doi.org/10.1097/WNR.0000000000000724

Lobier, M., Palva, J. M., & Palva, S. (2018). High-alpha band synchronization across frontal, parietal and visual cortex mediates behavioral and neuronal effects of visuospatial attention. *NeuroImage*, *165*, 222–237. https://doi.org/10.1016/j.neuroimage.2017.10.044

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. (2012). *Autism diagnostic observation schedule: ADOS-2*. Los Angeles, CA: Western Psychological Services.

MacDonald, P. A., & Paus, T. (2003). The role of parietal cortex in awareness of self-generated movements: a transcranial magnetic stimulation study. *Cerebral Cortex*, *13*(9), 962–967.

Marko, M. K., Crocetti, D., Hulst, T., Donchin, O., Shadmehr, R., & Mostofsky, S. H. (2015). Behavioural and neural basis of anomalous motor learning in children with autism. *Brain*, *138*(3), 784–797. https://doi.org/10.1093/brain/awu394

Martínez-Vargas, J. D., Castro-Hoyos, C., & Castellanos-Dominguez, G. (2014). Entropy-based multichannel measure of stationarity for characterization of motor imagery patterns. In *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (pp. 1469–1472). https://doi.org/10.1109/EMBC.2014.6943878

Maunsell, J. H., & van Essen, D. C. (1983). The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *The Journal of Neuroscience*, *3*(12), 2563–2586.

McFarland, D. J., Miner, L. A., Vaughan, T. M., & Wolpaw, J. R. (2000). Mu and beta rhythm topographies during motor imagery and actual movements. *Brain Topography; New York*, *12*(3), 177–186.

Meehan, C. L., Garner, J. P., & Mench, J. A. (2004). Environmental enrichment and development of cage stereotypy in Orange-winged Amazon parrots (Amazona amazonica). *Developmental Psychobiology*, *44*(4), 209–218. https://doi.org/10.1002/dev.20007

Mendez, M. F., Shapira, J. S., & Miller, B. L. (2005). Stereotypical movements and frontotemporal dementia. *Movement Disorders*, *20*(6), 742–745. https://doi.org/10.1002/mds.20465

Minshew, N. J., Sung, K., Jones, B. L., & Furman, J. M. (2004). Underdevelopment of the postural control system in autism. *Neurology*, *63*(11), 2056–2061. https://doi.org/10.1212/01.WNL.0000145771.98657.62

Mišić, B., Mills, T., Taylor, M. J., & McIntosh, A. R. (2010). Brain Noise Is Task Dependent and Region Specific. *Journal of Neurophysiology*, *104*(5), 2667–2676. https://doi.org/10.1152/jn.00648.2010

Mizuhara, H. (2012). Cortical dynamics of human scalp EEG origins in a visually guided motor execution. *NeuroImage*, *62*(3), 1884–1895. https://doi.org/10.1016/j.neuroimage.2012.05.072

Morrens, M., Hulstijn, W., Lewi, P. J., De Hert, M., & Sabbe, B. G. C. (2006). Stereotypy in

schizophrenia. *Schizophrenia Research*, *84*(2–3), 397–404. https://doi.org/10.1016/j.schres.2006.01.024

Morris, S. E., & Cuthbert, B. N. (2012). Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience*, *14*(1), 29–37.

Morris, S. L., Foster, C. J., Parsons, R., Falkmer, M., Falkmer, T., & Rosalie, S. M. (2015a). Differences in the use of vision and proprioception for postural control in autism spectrum disorder. *Neuroscience*, *307*, 273–280. https://doi.org/10.1016/j.neuroscience.2015.08.040

Morris, S. L., Foster, C. J., Parsons, R., Falkmer, M., Falkmer, T., & Rosalie, S. M. (2015b). Differences in the use of vision and proprioception for postural control in autism spectrum disorder. *Neuroscience*, *307*, 273–280. https://doi.org/10.1016/j.neuroscience.2015.08.040

Morrison, K., & Rosales-Ruiz, J. (1997). The effect of object preferences on task performance and stereotypy in a child with autism. *Research in Developmental Disabilities*, *18*(2), 127–137.

Morrison, S., Kerr, G., Newell, K. M., & Silburn, P. A. (2008). Differential time- and frequency-dependent structure of postural sway and finger tremor in Parkinson's disease. *Neuroscience Letters*, *443*(3), 123–128. https://doi.org/10.1016/j.neulet.2008.07.071

Mosconi, M. W., Mohanty, S., Greene, R. K., Cook, E. H., Vaillancourt, D. E., & Sweeney, J. A. (2015). Feedforward and Feedback Motor Control Abnormalities Implicate Cerebellar Dysfunctions in Autism Spectrum Disorder. *Journal of Neuroscience*, *35*(5), 2015–2025. https://doi.org/10.1523/JNEUROSCI.2731-14.2015

Mosconi, Matthew W., Luna, B., Kay-Stacey, M., Nowinski, C. V., Rubin, L. H., Scudder, C., … Sweeney, J. A. (2013). Saccade Adaptation Abnormalities Implicate Dysfunction of Cerebellar-Dependent Learning Mechanisms in Autism Spectrum Disorders (ASD). *PLoS ONE*, *8*(5), e63709. https://doi.org/10.1371/journal.pone.0063709

Mostofsky, S. H., Dubey, P., Jerath, V. K., Jansiewicz, E. M., Goldberg, M. C., & Denckla, M. B. (2006). Developmental dyspraxia is not limited to imitation in children with autism spectrum disorders. *Journal of the International Neuropsychological Society*, *12*(03), 314–326.

Muehlmann, A. M., Edington, G., Mihalik, A. C., Buchwald, Z., Koppuzha, D., Korah, M., & Lewis, M. H. (2012). Further characterization of repetitive behavior in C58 mice: Developmental trajectory and effects of environmental enrichment. *Behavioural Brain Research*, *235*(2), 143–149. https://doi.org/10.1016/j.bbr.2012.07.041

Müller, R.-A., Kleinhans, N., Kemmotsu, N., Pierce, K., & Courchesne, E. (2003). Abnormal variability and distribution of functional maps in autism: an FMRI study of visuomotor learning. *American Journal of Psychiatry*, *160*(10), 1847–1862.

Mulliken, G. H., Musallam, S., & Andersen, R. A. (2008). Forward estimation of movement state in posterior parietal cortex. *Proceedings of the National Academy of Sciences*, *105*(24), 8170–8177.

Nair, A., Treiber, J. M., Shukla, D. K., Shih, P., & Müller, R.-A. (2013). Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. *Brain*, *136*(6), 1942–1955. https://doi.org/10.1093/brain/awt079

Naranjo, J. R., Brovelli, A., Longo, R., Budai, R., Kristeva, R., & Battaglini, P. P. (2007). EEG dynamics of the frontoparietal network during reaching preparation in humans. *NeuroImage*, *34*(4), 1673–1682. https://doi.org/10.1016/j.neuroimage.2006.07.049

Nebel, M. B., Eloyan, A., Nettles, C. A., Sweeney, K. L., Ament, K., Ward, R. E., … Mostofsky, S. H. (2015). Intrinsic Visual-Motor Synchrony Correlates With Social Deficits in Autism. *Biological Psychiatry*, *79*(8), 633–641. https://doi.org/10.1016/j.biopsych.2015.08.029

Nelson, R. J. (1996). Interactions between motor commands and somatic perception in sensorimotor cortex. *Current Opinion in Neurobiology*, *6*, 801–810.

Newell, K. M. (1998). Degrees of freedom and the development of postural centure of pressure profiles. In K. M. Newell & P. C. M. Molenaar (Eds.), *Applications of Nonlinear Dynamics to Developmental Process Modeling* (pp. 63–84). Mahwah, NJ: Lawrence Erlbaum Associates, Publishers.

Newell, K. M., & Bodfish, J. W. (2007). Dynamical origins of stereotypy: Relation of postural movements during sitting to stereotyped movements during body-rocking. *American Journal on*

Mental Retardation, *112*(1), 66–75.

Newell, K. M., Broderick, M. P., Deutsch, K. M., & Slifkin, A. B. (2003). Task goals and change in dynamical degrees of freedom with motor learning. *Journal of Experimental Psychology: Human Perception and Performance*, *29*(2), 379–387. https://doi.org/10.1037/0096-1523.29.2.379

Newell, K. M., Incledon, T., Bodfish, J. W., & Sprague, R. L. (1999). Variability of stereotypic body-rocking in adults with mental retardation. *American Journal on Mental Retardation*, *104*(3), 279–288.

Oldehinkel, M., Mennes, M., Marquand, A., Charman, T., Tillmann, J., Ecker, C., … Zwiers, M. P. (2018). Altered Connectivity Between Cerebellum, Visual, and Sensory-Motor Networks in Autism Spectrum Disorder: Results from the EU-AIMS Longitudinal European Autism Project. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2018.11.010

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Pandya, D. N., & Kuypers, H. G. (1969). Cortico-cortical connections in the rhesus monkey. *Brain Research*, *13*(1), 13–36.

Pandya, D. N., & Seltzer, B. (1982). Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *Journal of Comparative Neurology*, *204*(2), 196–210.

Papadelis, C., Arfeller, C., Erla, S., Nollo, G., Cattaneo, L., & Braun, C. (2016). Inferior frontal gyrus links visual and motor cortices during a visuomotor precision grip force task. *Brain Research*, *1650*, 252–266. https://doi.org/10.1016/j.brainres.2016.09.011

Park, K., Roemmich, R. T., Elrod, J. M., Hass, C. J., & Hsiao-Wecksler, E. T. (2016). Effects of aging and Parkinson's disease on joint coupling, symmetry, complexity and variability of lower limb movements during gait. *Clinical Biomechanics*, *33*, 92–97. https://doi.org/10.1016/j.clinbiomech.2016.02.012

Pasluosta, C., Hannink, J., Gaßner, H., Von Tscharner, V., Winkler, J., Klucken, J., & Eskofier, B. M.

(2018). Motor output complexity in Parkinson's disease during quiet standing and walking: Analysis of short-term correlations using the entropic half-life. *Human Movement Science*, *58*, 185–194. https://doi.org/10.1016/j.humov.2018.02.005

Peça, J., Feliciano, C., Ting, J. T., Wang, W., Wells, M. F., Venkatraman, T. N., … Feng, G. (2011). Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. *Nature*, *472*(7344), 437–442. https://doi.org/10.1038/nature09965

Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spatial Vision*, *10*(4), 437–442.

Pesaran, B., Nelson, M. J., & Andersen, R. A. (2006). Dorsal Premotor Neurons Encode the Relative Position of the Hand, Eye, and Goal during Reach Planning. *Neuron*, *51*(1), 125–134. https://doi.org/10.1016/j.neuron.2006.05.025

Petrides, M., & Pandya, D. N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *Journal of Comparative Neurology*, *228*(1), 105–116.

Presti, M., & Lewis, M. (2005). Striatal opioid peptide content in an animal model of spontaneous stereotypic behavior. *Behavioural Brain Research*, *157*(2), 363–368. https://doi.org/10.1016/j.bbr.2004.08.003

Proville, R. D., Spolidoro, M., Guyon, N., Dugué, G. P., Selimi, F., Isope, P., … Léna, C. (2014). Cerebellum involvement in cortical sensorimotor circuits for the control of voluntary movements. *Nature Neuroscience*, *17*(9), 1233–1239. https://doi.org/10.1038/nn.3773

Quednow, B. B., Frommann, I., Berning, J., Kühn, K.-U., Maier, W., & Wagner, M. (2008). Impaired Sensorimotor Gating of the Acoustic Startle Response in the Prodrome of Schizophrenia. *Biological Psychiatry*, *64*(9), 766–773. https://doi.org/10.1016/j.biopsych.2008.04.019

Richman, J. S., & Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology-Heart and Circulatory Physiology*, *278*(6), H2039–H2049.

Ruddock, S., Piek, J., Sugden, D., Morris, S., Hyde, C., Caeyenberghs, K., & Wilson, P. (2015). Coupling

online control and inhibitory systems in children with Developmental Coordination Disorder: Goal-directed reaching. *Research in Developmental Disabilities*, *36*, 244–255. https://doi.org/10.1016/j.ridd.2014.10.013

Sabeti, M., Katebi, S., & Boostani, R. (2009). Entropy and complexity measures for EEG signal classification of schizophrenic and control participants. *Artificial Intelligence in Medicine*, *47*(3), 263–274. https://doi.org/10.1016/j.artmed.2009.03.003

Sacrey, L.-A. R., Bennett, J. A., & Zwaigenbaum, L. (2015). Early Infant Development and Intervention for Autism Spectrum Disorder. *Journal of Child Neurology*, *30*(14), 1921–1929. https://doi.org/10.1177/0883073815601500

Schmitt, L. M., Cook, E. H., Sweeney, J. A., & Mosconi, M. W. (2014). Saccadic eye movement abnormalities in autism spectrum disorder indicate dysfunctions in cerebellum and brainstem. *Molecular Autism*, *5*(1), 47. https://doi.org/10.1186/2040-2392-5-47

Shafer, R. L., Newell, K. M., Lewis, M. H., & Bodfish, J. W. (2017). A Cohesive Framework for Motor Stereotypy in Typical and Atypical Development: The Role of Sensorimotor Integration. *Frontiers in Integrative Neuroscience*, *11*. https://doi.org/10.3389/fnint.2017.00019

Shirama, A., Kanai, C., Kato, N., & Kashino, M. (2016). Ocular Fixation Abnormality in Patients with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-015-2688-y

Simola, N., Morelli, M., & Carta, A. R. (2007). The 6-hydroxydopamine model of Parkinson's disease. *Neurotoxicity Research*, *11*(3,4), 151–167.

Smits-Engelsman, B. C. M., Westenberg, Y., & Duysens, J. (2003). Development of isometric force and force control in children. *Cognitive Brain Research*, *17*(1), 68–74.

Sprague, R. L., & Newell, K. M. (Eds.). (1996). *Stereotyped Movements: Brain and Behavior Relationships*. Washington, DC: American Psychological Association.

Stearns, N. A., Schaevitz, L. R., Bowling, H., Nag, N., Berger, U. V., & Berger-Sweeney, J. (2007). Behavioral and anatomical abnormalities in Mecp2 mutant mice: A model for Rett syndrome.

Neuroscience, *146*(3), 907–921. https://doi.org/10.1016/j.neuroscience.2007.02.009

Stephens, G. J., Bueno de Mesquita, M., Ryu, W. S., & Bialek, W. (2011). Emergence of long timescales and stereotyped behaviors in Caenorhabditis elegans. *Proceedings of the National Academy of Sciences*, *108*(18), 7286–7289. https://doi.org/10.1073/pnas.1007868108

Stewart, C. R., Sanchez, S. S., Grenesko, E. L., Brown, C. M., Chen, C. P., Keehn, B., … Müller, R.-A. (2016). Sensory Symptoms and Processing of Nonverbal Auditory and Visual Stimuli in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *46*(5), 1590–1601. https://doi.org/10.1007/s10803-015-2367-z

Strick, P. L., & Kim, C. C. (1978). Input to primate motor cortex from posterior parietal cortex (area 5). I. Demonstration by retrograde transport. *Brain Research*, *157*(2), 325–330.

Takahashi, T., Yoshimura, Y., Hiraishi, H., Hasegawa, C., Munesue, T., Higashida, H., … Kikuchi, M. (2016). Enhanced brain signal variability in children with autism spectrum disorder during early childhood. *Human Brain Mapping*, *37*(3), 1038–1050. https://doi.org/10.1002/hbm.23089

Takarae, Y., Minshew, N. J., Luna, B., Krisky, C. M., & Sweeney, J. A. (2004). Pursuit eye movement deficits in autism. *Brain*, *127*(12), 2584–2594. https://doi.org/10.1093/brain/awh307

Tanimura, Y., Yang, M. C. K., Ottens, A. K., & Lewis, M. H. (2010). Development and temporal organization of repetitive behavior in an animal model. *Developmental Psychobiology*, *52*(8), 813–824. https://doi.org/10.1002/dev.20477

Thelen, E. (1979). Rhythmical stereotypies in normal human infants. *Animal Behaviour*, *27*, 699–715.

Thelen, E. (1980). Determinants of amount of stereotyped behavior in normal human infants. *Ethology and Sociobiology*, *1*, 141–150.

Thelen, E. (1986). Treadmill-Elicited Stepping in Seven-Month-Old Infants. *Child Development*, *57*(6), 1498–1506. https://doi.org/10.2307/1130427

Thelen, E., & Cooke, D. W. (1987). Relationship between newborn stepping and later walking: A new interpretation. *Developmental Medicine & Child Neurology*, *29*, 380–393.

Thelen, E., Corbetta, D., Kamm, K., Spencer, J. P., Schneider, K., & Zernicke, R. F. (1993). The

Transition to Reaching: Mapping Intention and Intrinsic Dynamics. *Child Development*, *64*(4), 1058–1098. https://doi.org/10.2307/1131327

Thelen, E., & Fisher, D. M. (1983a). From Spontaneous to Instrumental Behavior: Kinematic Analysis of Movement Changes during Very Early Learning. *Child Development*, *54*(1), 129. https://doi.org/10.2307/1129869

Thelen, E., & Fisher, D. M. (1983b). The organization of spontaneous leg movements in newborn infants. *Journal of Motor Behavior*, *15*(4), 353–377.

Thut, G. (2006). α-Band Electroencephalographic Activity over Occipital Cortex Indexes Visuospatial Attention Bias and Predicts Visual Target Detection. *Journal of Neuroscience*, *26*(37), 9494–9502. https://doi.org/10.1523/JNEUROSCI.0875-06.2006

Vaillancourt, D. E., Slifkin, A. B., & Newell, K. M. (2001a). Intermittency in the visual control of force in Parkinson's disease. *Experimental Brain Research*, *138*(1), 118–127. https://doi.org/10.1007/s002210100699

Vaillancourt, D. E., Slifkin, A. B., & Newell, K. M. (2001b). Regularity of force tremor in Parkinson's disease. *Clinical Neurophysiology*, *112*(9), 1594–1603.

Van Braeckel, K., Butcher, P. R., Geuze, R. H., Stremmelaar, E. F., & Bouma, A. (2007). Movement adaptations in 7- to 10-year-old typically developing children: Evidence for a transition in feedback-based motor control. *Human Movement Science*, *26*(6), 927–942. https://doi.org/10.1016/j.humov.2007.07.010

Veldman, M. P., Maurits, N. M., Nijland, M. A. M., Wolters, N. E., Mizelle, J. C., & Hortobágyi, T. (2018). Spectral and temporal electroencephalography measures reveal distinct neural networks for the acquisition, consolidation, and interlimb transfer of motor skills in healthy young adults. *Clinical Neurophysiology*, *129*(2), 419–430. https://doi.org/10.1016/j.clinph.2017.12.003

Wang, D. J. J., Jann, K., Fan, C., Qiao, Y., Zang, Y.-F., Lu, H., & Yang, Y. (2018). Neurophysiological Basis of Multi-Scale Entropy of Brain Complexity and Its Relationship With Functional Connectivity. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00352

Wang, Z., Magnon, G. C., White, S. P., Greene, R. K., Vaillancourt, D. E., & Mosconi, M. W. (2015). Individuals with autism spectrum disorder show abnormalities during initial and subsequent phases of precision gripping. *Journal of Neurophysiology*, *113*, 1989–2001. https://doi.org/10.1152/jn.00661.2014

Wechsler, D., & Zhou, X. (2011). *WASI-II: Wechsler Abbreviated Scale of Intelligence* (Second). San Antonio, TX: The Psychological Corporation.

Weinberg, A., Dieterich, R., & Riesel, A. (2015). Error-related brain activity in the age of RDoC: A review of the literature. *International Journal of Psychophysiology*, *98*(2), 276–299. https://doi.org/10.1016/j.ijpsycho.2015.02.029

Whitten, A., Unruh, K. E., Shafer, R. L., & Bodfish, J. W. (2018). Subgrouping Autism Based on Symptom Severity Leads to Differences in the Degree of Convergence Between Core Feature Domains. *Journal of Autism and Developmental Disorders*, *48*(6), 1908–1919. https://doi.org/10.1007/s10803-017-3451-3

Wiestler, T., McGonigle, D. J., & Diedrichsen, J. (2011). Integration of sensory and motor representations of single fingers in the human cerebellum. *Journal of Neurophysiology*, *105*(6), 3042–3053. https://doi.org/10.1152/jn.00106.2011

Wilson, P. H., & Hyde, C. (2013). The development of rapid online control in children aged 6–12years: Reaching performance. *Human Movement Science*, *32*(5), 1138–1150. https://doi.org/10.1016/j.humov.2013.02.008

Wolpert, D. M., Miall, R. C., & Kawato, M. (1998). Internal models in the cerebellum. *Trends in Cognitive Sciences*, *2*(9), 338–347.

Woo, C. C., Donnelly, J. H., Steinberg-Epstein, R., & Leon, M. (2015). Environmental enrichment as a therapy for autism: A clinical trial replication and extension. *Behavioral Neuroscience*, *129*(4), 412–422. https://doi.org/10.1037/bne0000068

Woo, C. C., & Leon, M. (2013). Environmental enrichment as an effective treatment for autism: A randomized controlled trial. *Behavioral Neuroscience*, *127*(4), 487–497.

https://doi.org/10.1037/a0033010

Yentes, J. M., Hunt, N., Schmid, K. K., Kaipust, J. P., McGrath, D., & Stergiou, N. (2013). The Appropriate Use of Approximate Entropy and Sample Entropy with Short Data Sets. *Annals of Biomedical Engineering*, *41*(2), 349–365. https://doi.org/10.1007/s10439-012-0668-3

Yi, G.-S., Wang, J., Deng, B., & Wei, X.-L. (2017). Complexity of resting-state EEG activity in the patients with early-stage Parkinson's disease. *Cognitive Neurodynamics*, *11*(2), 147–160. https://doi.org/10.1007/s11571-016-9415-z

Zainos, A., DeAnda, R., Chavez, L., & Garcia-Munoz, M. (1984). Turning Behavior, Barrel Rolling, and Sensory Neglect Induced by Picrotoxin in the Thalamus. *Experimental Neurology*, *83*, 534–547.

Zhang, H., Chavarriaga, R., & Millán, J. del R. (2015). Discriminant brain connectivity patterns of performance monitoring at average and single-trial levels. *NeuroImage*, *120*, 64–74. https://doi.org/10.1016/j.neuroimage.2015.07.012

Zhao, Y., Zheng, X., Wang, Q., Xu, J., Xu, X., & Zhang, M. (2014). Altered activation in visual cortex: Unusual functional magnetic resonance imaging finding in early Parkinson's disease. *Journal of International Medical Research*, *42*, 503–515. https://doi.org/10.1177/0300060513507647