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Motor Influences on Communication: Comparisons between Down Syndrome and Fragile X Syndrome

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Abstract:	Introduction: Motor skills, an important foundation for language and communication, are considerably delayed in children with Down syndrome (DS) and fragile X syndrome (FXS). However, the impact of these impairments on expressive and receptive communication and phenotypic specificity of these associations remains unknown. Method: Study participants included 37 children with DS (chronological ageM (CAM)=20.38; nonverbal mental ageM (NVMAM)=13.19) and 37 children with FXS (CAM=19.; NVMAM=13.16) matched on chronological and nonverbal mental age. Results: Results showed syndrome-specific profiles across motor and communication domains, where children with DS scored significantly higher than children with FXS on communication domains, but lower on gross motor. Findings revealed significant associations between domains of motor and communication for both groups, but phenotypic specificity in the magnitude of association between fine motor and receptive communication in that the strength of the association was significantly stronger for children with DS. Discussion: Findings demonstrate the importance of early motor abilities for the development of communication for both children with DS and those with FXS. Implications for phenotypic specificity and targeted intervention are discussed.

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Abstract

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Method: Study participants included 37 children with DS (chronological age$_M$ (CA_M)=20.38; nonverbal mental age$_M$ ($NVMA_M$)=13.19) and 37 children with FXS (CA_M=19.; $NVMA_M$=13.16) matched on chronological and nonverbal mental age.

Results: Results showed syndrome-specific profiles across motor and communication domains, where children with DS scored significantly higher than children with FXS on communication domains, but lower on gross motor. Findings revealed significant associations between domains of motor and communication for both groups, but phenotypic specificity in the magnitude of association between fine motor and receptive communication in that the strength of the association was significantly stronger for children with DS.

Discussion: Findings demonstrate the importance of early motor abilities for the development of communication for both children with DS and those with FXS. Implications for phenotypic specificity and targeted intervention are discussed.

Introduction

Early motor skills provide an important catalyst for concurrent and subsequent development across cognitive, language, and social communication domains (Iverson, 2010; Keen, 2011; Needham & Libertus, 2011; Mason, Goldstein, & Schwade, 2019; Needham, 2000). Connections between early motor development and advances in communication and language are particularly well established in typical development. Neurogenetic populations such as Down syndrome (DS) and fragile X syndrome (FXS) have pronounced delays in achieving important motor milestones and notable impairments in acquired motor skills; however, this is vastly understudied and poorly characterized in both DS and FXS. Importantly, the influence of motor delays and impaired motor functioning on language and communication in these populations remains unknown. In order to develop syndrome-specific interventions, it is critically important to gain a better understanding of the shared and unique features of motor and communication difficulties, and in particular, how motor impairments may differentially influence communication as a result of genetic etiology. As such, this study aims to address current knowledge gaps regarding the syndrome-specific nature and degree of impact motor impairments may have on communication in children with DS or FXS.

Motor and Communication in Typical Development

Motor development occurs in a largely sequential progression, with early gross motor milestones such as rolling over and independent sitting serving as foundational skills for more advanced abilities, such as rotating while seated, independent standing, and eventually, independent walking (Adolph & Franchchak, 2017; Adolph & Hoch, 2019; Francheck & Adolf, 2012; Thelen, 1995). Similarly, reaching facilitates advanced fine motor skills such as grasping, which is critical for enriched object explorations and social interactions around objects (Lobo &

Galloway, 2013; Needham et al., 2002; Sommerville & Decety, 2006). As such, motor development occurs within a narrow cascade, in which early motor skills support the emergence of subsequently advanced motor skills (Needham et al., 2014; Smith & Thelen, 2003; Thelen, 1995), but also within a broader cascade in which motor skills exert influence on other domains such as communication and language (Iverson, 2010; Libertus & Violi, 2016; Smith & Thelen, 2003; Thelen 1995; Walle & Campos, 2014).

Attainment of early motor abilities fundamentally changes the context of an infant's physical experiences, increasing opportunities for exploration and providing support for the emergence of language and communication (Iverson, 2010; Walle & Campos, 2014). For instance, acquiring the postural control required for independent sitting physically enables infants to produce more complex vocalizations and allows them to engage with caregivers, not only with these newly acquired communication skills, but also in a novel and expanded social context (i.e., sitting versus lying down). These new physical circumstances present the opportunity for joint attention between objects and caregivers (i.e., Iverson, 2010; Libertus & Violi, 2016), which, along with new vocal vocalization skills, contribute to greater social communication and reciprocity (Libertus & Violi, 2016). Likewise, independent walking allows a toddler to act with greater agency, offering enhanced opportunities for exploration, fostering language and communication (Karasik, Tamis-LeMonda, & Adolph, 2014; Walle & Campos, 2014). Walking infants are able to move more quickly and freely, carrying objects while locomoting, which affords infants a greater ability to *direct others' attention* and engage with distal objects (Clearfield, 2011). Substantial evidence also suggests that walking infants receive more attention and linguistic input from adults in their environment than non-walking infants of the same age (Karasik et al., 2014; Walle & Campos, 2014). These new and enriched

experiences driven by the ability to walk independently support both receptive and expressive communication abilities (Walle & Campos, 2014).

While there is less evidence for a developmental bridge between fine motor and communication, skills such as grasping clearly provide additional developmental opportunities that also support aspects of early communication (Barrett, Traupman, & Needham, 2008; Needham et al., 2002; Sommerville & Decety, 2006; Sommerville et al., 2008). As infants can grasp and manipulate objects in new ways, they are able to extend objects to others, share object experiences with others, and act with full agency (Claxton, McCarty, & Keen, 2009; Facaroli & Iverson, 2017; Needham et al., 2002; Needham & Libertus, 2010). Accordingly, the social context is further enriched and novel opportunities for verbal and nonverbal communication emerge (Focaroli & Iverson, 2017; Iverson, 2010; Needham et al., 2002; Libertus & Needham, 2010; Sommerville, et al., 2008; Walle & Campos, 2014). Collectively, the experiences afforded through gross and fine motor skill acquisition provide such a critical developmental foundation that delayed motor development or impaired motor functioning, such as that associated with neurogenetic conditions, may have significant implications for communicative development (Iverson et al., 2007; Focaroli & Iverson, 2017).

Down syndrome

Down syndrome (DS) is a neurogenetic condition affecting 1 in 691 live births (Canfield, et al., 2006; Parker et al., 2010) and the most common genetic cause of intellectual disability (ID) (Centers for Disease Control, 2006; Martin et al., 2009). The DS behavioral phenotype is characterized by moderate ID that is nearly universal with related difficulties across higher-order cognitive skills (Daunhauer, 2011), language development (Abbeduto, Warren, & Conners, 2007; Abbeduto & Murphy, 2004; Roberts et al., 2007; Martin et al., 2009), and motor

impairments (de Campos et al., 2010; Pereira et al., 2013; Will et al., 2018). Many areas of functioning exceed an expected degree of impairment given overall mental age or developmental status, and within a given area, there is significant within-syndrome variability in functioning (Daunhauer, 2011; Periera et al., 2013; Ulrich et al., 1995). Motor development and language/communication are two areas of development in DS that show significant impairment and a high degree of variability relative to typical development and other neurodevelopmental disorders (de Campos et al., 2013; Roberts et al., 2007; Tudella et al., 2011; van Duijn et al., 2010; Will et al., 2018).

Motor in DS. The degree, specific nature, and functional consequences of impaired motor development in DS are vastly understudied. However, it is clear that the atypical neurodevelopment associated with the underlying genetic etiology of DS predisposes infants and toddlers towards delayed acquisition of motor skills and continued motor impairments during later development (de Campos et al., 2010; de Campos et al., 2013; Periera et al., 2014; Will et al., 2018). The few existing studies on motor development in DS indicate that foundational as well as advanced motor skills are delayed and qualitatively impaired across gross and fine domains (de Campos et al., 2010; Periera et al., 2013, Ulrich et al., 1995). For example, in one study that included 20 infants with DS and 25 typically developing (TD) age-matched infants, infants with DS attained foundational motor skills like rolling over and sitting independently at a delayed rate of approximately two to five months, respectively (Periera et al., 2014). As infants with DS progressed towards more advanced skills in their motor development, a much lower proportion of infants with DS had acquired a given skill by a certain age compared to TD infants. Specifically, only 20% of DS infants were cruising (i.e., walking while holding onto furniture) when 100% of TD infants had achieved that milestone. Further, this achievement took

approximately four months longer for infants with DS to acquire than TD infants (Periera et al., 2013). Delayed acquisition of these foundational gross motor skills has implications for the timing and rate of emergence of subsequently advanced skills like independent walking, which is significantly delayed for most infants with DS (Pereira et al., 2013). In addition to gross motor skills, fine motor skills which are critical in facilitating object exploration and sharing, are also delayed for children with DS (de Campos et al., 2010; Periera et al., 2013). Once fundamental skills like reaching and grasping are attained, infants with DS reach and grasp at a significantly lower frequencies and produce more reaching errors than TD counterparts (de Campos et al., 2010). These gross and fine motor delays and qualitative motor differences likely have serious implications for developmental progress in other critical domains such as communication.

Communication and Language in DS. Communication and language skills are also considerably delayed in early development in DS, falling below mental age expectations and other developmental domains (Abbeduto, Warren, & Conners, 2007; Fidler, Hepburn, & Rogers, 2006; van Duijn et al., 2010; Will et al., 2018). Despite strengths in some aspects of expressive social communication like gesture use and reciprocal gaze, the prelinguistic period of communicative development becomes protracted for infants and toddlers with DS and verbal expressive communication is significantly delayed and compromised once present (Abbeduto & Murphy, 2004; Fidler, Philofsky, & Hepburn, 2005; Fidler, Philofsky, Hepburn, & Rogers, 2005; Roberts et al., 2007). Further, young children with DS have notable difficulty in the use and coordination of nonverbal and expressive modes of social communication (Abbeduto et al., 2007; Iverson et al., 2003; Roberts, 2007), particularly when organizing communication in more complex contexts, such as requesting (Fidler et al., 2005). In terms of language development, children with DS begin to produce language much later than typically developing same-aged

counterparts, and once expressive language does emerge, it develops at a much slower rate for children with DS (see Abbeduto et al., 2007 for review). Receptive language tends to be considered as a strength relative to expressive language in DS, but receptive vocabulary still expands at a slower rate, and individuals with DS are constrained in this area by their cognitive limitations (Abbeduto et al., 2007; Galeote, Sebastian, Checa, Rey & Soto, 2011). Although mechanisms of communication and language impairments in DS have been partially characterized (see Abbeduto et al., 2007 for review; Mason-Apps, Stojanovik, Houston-Price, & Buckley, 2018), the implications of gross and fine motor on communication and language impairments in DS remain unknown.

Fragile X syndrome

FXS is a single gene X-linked disorder caused by an overexpression of CGG repeats on the FMR1 gene (Loesch, Huggins, & Hagerman, 2004; Tassone et al., 2000) and occurs approximately 1 in 4,000-8,000 individuals, disproportionately affecting males (Hagerman, 2008). FXS also has a unique phenotypic expression and is broadly characterized by ID, challenges in social communication, and high rates of co-occurring psychiatric disorders (Hall, Lightbody, & Reiss, 2008; Harris et al., 2008; Klusek, Martin, & Losh, 2004; Talisa, Boyle, Crafa, & Kaufman, 2014). In addition to these broad phenotypic characteristics, impairments in both motor and communication/language are also pervasive in FXS during early development (Hinton et al., 2013; Roberts et al., 2016; Will et al., 2018; Will, Bishop, & Roberts, 2019), and the connection between these impaired developmental domains remains unknown.

Motor in FXS. Motor delays and atypical motor behaviors are among the first notable signs of impaired development in FXS (Baranek et al., 2005; Hinton et al., 2013), and these difficulties appear to persist into early childhood (Will et al., 2019; Will et al., 2018; Zingerevich

et al., 2009). Existing research on gross motor in FXS is limited, but evidence suggests notable delays within the first year of life (Hinton et al., 2013; Will, et al., 2019). For instance, general gross motor skills deviate from typical development prior to 12 months old (Will et al., 2019) and the average age of walking occurs at 17-months (Hinton et al., 2013) – approximately five months later than the average age of walking in typical development. In addition to gross motor, delays in fine motor development are evident as early as 9-months old (Roberts et al., 2009). Further, impaired fine motor development persists throughout early childhood, as children with FXS show slower rates of fine motor development throughout early childhood compared to TD counterparts (Roberts et al., 2009; Will et al., 2019). Investigations into the functional consequences of motor delays in FXS have emphasized social communication in relation to autism severity (Hinton et al., 2013; Roberts, Tonnsen, McCary, Caravella, & Shinkareva, 2016; Will et al., 2019). Importantly, the impact of such motor delays on outcomes other than severity of ASD symptomatology – such as language and communication – has yet to be examined.

Communication and Language in FXS. Similar to motor development, the development of language and communication is protracted in FXS (Abbeduto, Brady, & Kover, 2007; Roberts, Mirrett, Anderson, Burchinal, & Neebe, 2002). While challenges exist in both receptive and expressive communication (Caravella & Roberts, 2017; Roberts et al., 2012; Will et al., 2018), expressive skills generally trail receptive skill development and are a particular area of challenge (Abbeduto & Murphy, 2004; Roberts, Mirrett, & Burchinal, 2001; Roberts et al., 2002). For instance, first words emerge on average at 26-months (Hinton et al., 2013), which is a full year delayed compared to typical development. Further, functional aspects of receptive and expressive communication, such as social communication abilities, are especially compromised in FXS (Abbeduto & Murphy, 2004; Caravella & Roberts, 2017; Klusek et al.,

2014; Roberts et al., 2002). Recent evidence suggests these communication impairments emerge in infancy and present as decreased frequency and complexity of gestures and diminished social reciprocity (Hahn, Brady, McCary, Rague, & Roberts, 2017; Roberts et al., 2001). The consistency of these deficits across infancy, toddlerhood, and preschool in FXS, suggests these impairments are developmentally pervasive and warrants further examination of additional factors potentially influencing these difficulties (Marschik et al., 2014; Flenthrope & Brady, 2010), such as motor impairments.

Summary and Research Aims

Given the importance of motor skill acquisition in supporting communication and language in typical development, it is critical to ascertain a better understanding of these associations in DS and FXS. This is especially important when considering the early emergence and persistent nature of these impairments in either of these disorders. Furthermore, comparing these two neurogenetic conditions is clinically useful in identifying unique contributions of underlying genetic etiologies to developmental mechanisms and functional consequences. Identifying shared and unique features of each disorder can also provide useful information regarding early and targeted intervention. As such, the aims for this cross-sectional study are to 1) characterize motor (fine and gross) and language/communication (receptive and expressive) profiles in DS and FXS, and 2) determine the extent to which motor skills predict communication in children with DS or FXS, and whether this association differs as a function of neurogenetic syndrome.

Methods

Participants

Study participants included 37 children with DS between 10 and 44 months old (chronological age$_M$ (CA$_M$)=20.38; nonverbal mental age$_M$ (NVMA$_M$)=13.19) and 37 participants with FXS between nine and 43 months old (CA$_M$=19.51; NVMA$_M$=13.16). DS and FXS groups were well matched on CA (t=-0.23; p=.823) and NVMA (t=.40; p=.689). The DS group included 11 females (30%) and the FXS group also included 11 females (30%). Participants were drawn from two larger ongoing studies on either early foundations of cognitive development or prospective longitudinal studies on early temperament from [withheld for review] and [withheld for review]. At both sites, participants were primarily recruited from various medical, research or community social media sites specializing in FXS or DS.

Measures

Motor skills. The Mullen Scales of Early Learning (MSEL; Mullen, 1995) is a comprehensive developmental assessment that measures Fine Motor, Gross Motor, Visual Reception, Receptive Language, and Expressive Language, and also yields an Early Learning Composite (ELC) which has a mean of 100 and standard deviation of 15. We selected to use raw scores due to floor effects with standard scores that are common in populations with ID. Nonverbal mental age was derived from averaging the Fine Motor and Visual Reception age equivalent scores and used to establish cognitive equivalence between DS and FXS groups.

Communication. The Vineland Adaptive Behavior Scales Interview – second edition (VABS-II; Sparrow, Balla, & Cicchetti, 2005) is a comprehensive parent interview measure of adaptive behavior. This measure assesses adaptive skills across Motor, Communication, Socialization, and Daily Living Domains, and yields an Adaptive Behavior Composite score. Items are scored on a 0 – 2 likert scale, indicating the consistency with which an individual independently demonstrates the assessed skill: (0) never, (1) sometimes, or (2) usually.

Receptive and expressive communication domains include items specific to both communication skills (e.g., turning towards sounds, pointing to request) and language skills (e.g., following instructions and expressive use of words); hence, we use language and communication terminology interchangeably.

Procedures

Study procedures were approved by Institutional review boards at [withheld] and [withheld]. As part of the larger study batteries, participants completed developmental and temperament assessments, and their parents completed a series of interviews and surveys, and also provided demographic information. Parents received a report on their child's development and/or monetary compensation for participating. Assessments lasted between one and one-half hours and up to four hours, depending on age. Participants were provided with breaks as needed and caregivers were present during the assessments.

Analytic Approach

Descriptive statistics were used to calculate participant demographics. Groups were compared on CA and NVMA to establish group equivalence and confirm results from subsequent comparisons and regression models were not due to age or cognitive effects. Research Aim 1 focused on characterizing differences in motor and language/communication skills across DS and FXS to identify phenotypic patters. We addressed this aim using a descriptive approach, characterizing means and standard deviations for each domain across each etiological group and by sex, as well as by presenting effect sizes (Cohen's *d*) for between (DS versus FXS whole group) and within (males versus females) group differences. We also employed data visualization to characterize profiles of motor and communication across these groups (see Figures 1 and 2). Next, to address the second research aim we estimated a series of

moderated regression models to test whether gross or fine motor predicted receptive or expressive communication for either the DS or FXS groups, with DS specified as the reference group. For these models, we used motor domains from the MSEL as predictors of Communication domains on the VABS to avoid issues with measurement impurity. Interaction terms were included in each model to determine differences in the effect of motor on communication as a function of genetic etiology. Fine and Gross motor raw scores were centered at the mean for all models. Table 2 presents results from the full models that included interaction terms.

Results

Motor and Communication Profiles

Table 1 presents descriptive results on group differences across motor and communication domains.

<insert table 1 about here>

Results from descriptive analyses indicate that the DS group had lower scores on Gross Motor across both the MSEL and the VABS. Effect size estimates showed this group difference was to a medium effect on the MSEL (d=0.51) and to a small effect on the VABS (d=0.23). The DS and FXS groups showed minimal differences in mean Fine Motor scores across these measures (see Table 1; Figure 1). In terms of communication, the DS group had higher scores on Receptive Communication across both measures, and these effects were small (see Table 1). Expressive Communication scores were also higher across both the MSEL and the VABS for the DS group compared to the FXS group, and these differences were to a large effect (see Table 1). Figure 1 depicts profiles of performance on the MSEL and VABS across DS or FXS.

<insert Figure 1 about here>

Although not a primary aim of the study, we also explored within-group sex effects in motor and communication across the MSEL and VABS. Females with DS scored slightly higher on Fine Motor and Receptive Communication than males with DS, and these were small-to-medium effects (see Table 1). As for the FXS group, females scored slightly higher across MSEL and VABS domains, and effect sizes for these differences ranged from small (e.g., MSEL Receptive Communication and VABS Gross Motor) to large (e.g., MSEL Expressive Language). Figure 2 depicts profiles of performance on the MSEL and VABS across genetic groups by sex.

<insert Figure 2 about here>

Motor as a Predictor of Communication

Gross Motor. Results from models with gross motor as a predictor of receptive communication indicated that gross motor was in fact a significant predictor of receptive communication for children with DS ($b = 0.88$; $p < .001$), such that each additional point in gross motor raw scores was associated with an additional point on receptive communication. Interestingly, with gross motor held constant at the mean, a difference between DS and FXS on receptive communication emerged ($b = -3.54$; $p = .002$). This difference was such that accounting for differences in gross motor skills, the FXS group was predicted to score approximately 3 points lower in receptive communication raw scores. However, there was no difference in the effect of gross motor on receptive communication between DS and FXS groups ($b = -0.30$; $p = .162$), suggesting that gross motor is also a significant predictor of receptive communication for children with FXS.

Results from models with gross motor as a predictor of expressive communication indicated that gross motor was a significant predictor of expressive communication for children with DS ($b = 1.02$; $p < .001$), such that each additional 1-point increase in gross motor raw scores

was associated with a 1-point increase in expressive communication raw scores. Once accounting for gross motor differences, a difference between DS and FXS on expressive communication scores emerged (b = -5.89; p < .001), such that FXS were estimated to score significantly lower relative to the DS group. There was no difference in the effect of gross motor on expressive communication between children with DS and those with FXS (b = 0.13; p= .682), indicating that gross motor is a significant predictor of expressive communication for infants and toddlers with FXS as well.

Fine Motor. Results from models with fine motor as a predictor of receptive communication indicated a significant effect for children with DS (b = 1.19; p < .001), such that each additional point increase in fine motor raw scores predicted a 1-point increase in receptive communication raw scores. Holding fine motor constant at the mean, there was still no significant difference between DS and FXS groups on receptive communication outcomes (b = -1.44; p = .153). However, there was a significant difference in the effect of fine motor on receptive communication between the DS and FXS groups (b = - 0.57; p = .024). This effect was such that the association between fine motor and receptive communication was stronger for infants and toddlers with DS than infants and toddlers with FXS (see Figure 3).

<insert Figure 3 about here>

Because this difference may suggest an effect for DS but not FXS in terms of fine motor predicting receptive communication, we tested this model with FXS as the reference group to address this consideration. These results indicated that fine motor was indeed a significant predictor for children with FXS (b = 0.62; p < .001).

Results from models testing fine motor as a predictor of expressive communication showed a significant effect for children with DS (b=1.17; p<.001), such that each additional raw

score point in fine motor predicted a 1-point increase in expressive communication raw scores. Accounting for fine motor, there was no still no significant difference between groups on expressive communication (b = -3.04; p = .068). Additionally, there was no difference in the effect of fine motor on expressive communication between children with DS and those with FXS (b = -0.02; p = .954), indicating fine motor also significantly predicted expressive communication for children with FXS.

Discussion

This study characterized early developmental profiles of motor and communication skills and examined potential phenotypic specificity across these domains for two distinct neurogenetic disorders – DS and FXS. Our findings illustrated nuanced differences in motor and communication profiles across each condition, with gross motor and communication identified as specific areas of phenotypic difference between these groups. Further, our results yielded important evidence that gross and fine motor serve prominent roles in expressive as well as receptive communication for both children with DS and those with FXS. In general, the role of motor in communication abilities was found to be relatively comparable across conditions; however, the effect of fine motor on receptive communication was identified as an area of phenotypic specificity with a significantly stronger association for children with DS relative to those with FXS. Collectively, our findings have important implications for early development and targeted intervention in each of these neurogenetic conditions.

Gross Motor

We found gross motor to be a specific area of phenotypic difference between DS and FXS, with infants and young children with DS showing significantly lower gross motor abilities based on the magnitude of mean difference effect sizes. It may be anticipated that poorer gross motor

abilities would relate to poorer communication abilities, particularly in the expressive domain, given the strong association between these areas in TD infants (Iverson, 2010; Walle & Campos, 2014). Upon initial examination, our findings indicated no differential association between gross motor and receptive or expressive communication across groups, despite more severe gross motor impairments in the DS group. However, when accounting for gross motor abilities between groups, differences in both receptive and expressive communication emerged. This more nuanced finding suggests that gross motor appears to play role in communication for each of these groups, but also that additional developmental factors may influence these outcomes. It may be the case that a phenotype-specific pattern may emerge when examining the role of isolated motor milestones (e.g., achieving independent sitting or walking) in communication abilities, or when examining additional developmental factors that may account for communication differences beyond the role of gross motor.

Collectively, these results suggest that gross motor may serve a key role for both receptive and expressive communication for children with neurogenetic conditions. Our findings are consistent with prior work on neurodevelopmental disorders – specifically autism spectrum disorder (ASD; Bedford et al., 2016; see also Leonard et al., 2015). For children with ASD, broad gross motor skills, in addition to the isolated milestone of walking, were found to predict the rate of both receptive and expressive communication (Bedford et al., 2015). This specific effect was found to be greater than merely the onset of walking alone, which, as previously discussed, has a strong connection to communication for typically developing populations (Adolph & Franchek, 2017; Libertus & Violo, 2016). This evidence indicates that a constellation of gross motor skills – sitting, reaching, and walking – supports the overall development of both types of communication, rather than just an association between walking

and expressive communication alone (Bedford et al., 2015). This developmental link occurs as these gross motor skills afford critical new learning opportunities that allow infants to acquire knowledge about new objects, elicit communicative input around these objects, and match actions with words and sounds (Iverson, 2010; LeBarton & Iverson, 2013; Libertus & Violi 2016). Our results indicate this is likely also true for children with DS and those with FXS. A lack of phenotype-specific association despite more pervasive delays in independent walking characteristic to children with DS provides further support for the notion that a constellation of gross motor skills contributes to receptive and expressive communication in DS and FXS. Because walking is such a salient gross motor milestone, it may become a specific point of therapeutic emphasis when delayed, as it is in FXS and even more so in DS. Our findings, as well as prior work suggesting that collective gross motor skills are significantly associated with communication provide rationale for focusing intervention efforts across a variety of gross motor skills in addition to emphasizing delayed walking. Targeting gross motor skills broadly via intervention for children with DS or FXS may in turn accelerate communication skills given that an increase in these motor skills is likely to create new communicative learning opportunities through enhanced exploration and social experiences.

Fine Motor

Fine motor skills were also identified as a significant predictor of expressive and receptive communication for both children with DS and those with FXS. These findings are consistent with, and also extend, existing work in other high-risk populations where fine motor was identified as a significant support for the development of expressive communication in infant siblings of children with ASD (Lebarton & Iverson, 2013). These infants at high-risk for ASD demonstrated significant delays in fine motor skills at 12 and 24 months, and their fine

motor skills were found to predict expressive communication outcomes at 36-months (LeBarton & Iverson, 2013). Although a cross-sectional demonstration of this link between fine motor and expressive skills, the present study provides additional evidence for the role of fine motor skills in expressive communication, as well as receptive communication, and more specifically within neurogenetic conditions.

In addition to the general significance of association between fine motor for receptive and expressive communication, our findings offer evidence of a syndrome-specific pattern. Specifically, the association between fine motor and receptive communication was identified as significantly stronger for children with DS compared to those with FXS. The lack of group differences in fine motor abilities and the small magnitude of differences on receptive communication suggests additional phenotypic features may contribute to the stronger association in these domains identified for children with DS. In considering what additional factors may contribute to this syndrome specific pattern, it is important to note that fine motor abilities facilitate unique learning opportunities through the manipulation of objects (LeBarton & Iverson, 2013; Libertus & Violo, 2016) – a context that provides a platform for elicited communicative input from caregivers (Mason, Goldstein, & Schwade, 2019). The ability to flexibly shift attention between objects and social partners and, more complexly, have joint attention (i.e., coordinated attention between a child, caregiver, and object or event) are central to this learning opportunity (Bruyneel, Demurie, Warreyn, & Roeyers, 2019). Children with DS and FXS demonstrate markedly different patterns of joint attention abilities, where young children with DS show joint attention commensurate with developmental level (Fidler, 2005; Hahn et al., 2018), and children with FXS show greater difficulty depending on the complexity of the specific joint attention skill (Hahn et al., 2017). These attentional phenotypic differences

may be a potential contributing factor for the difference in magnitude of association between fine motor and receptive communication for children with DS identified in the present study.

Additional phenotypic considerations

There are several other areas of phenotypic distinction between DS and FXS that may contribute to the current study findings. Importantly, social motivation is well documented in DS. Children with DS have strong social reciprocity (Fidler et al., 2005) and make social overtures, but often at the expense of important object-related learning opportunities (Kasari et al., 2001). This robust social feature of the DS phenotype is not shared across FXS, as FXS is well characterized by social avoidance (Roberts et al., 2019) and impaired social communication (Roberts, Tonnsen et al., 2016). In addition, the differential rates of estimated comorbid ASD across DS and FXS (Diguiseppi et al., 2010; Klusek et al., 2014) may further affect social behavior in a way that has implications for specific opportunities that facilitate object-related learning and communication skills through motor experiences. While the social phenotype may be somewhat overestimated as a strength in DS (Whishart, 2007), it may indeed serve as a protective factor against developmental constraints that considerable motor delays may impose in catalyzing communicative development (LeBarton & Iverson, 2013). Conversely, the social difficulties evident in the FXS phenotype may serve as an impediment for communicative learning opportunities afforded through motor experiences. Although children with FXS experience less severe impairments in gross motor, and comparable abilities in fine motor to children with DS, the mechanisms through which motor relates to communication for these groups may indeed differ. While these questions are beyond the scope of the present study, future work should aim to further delineate the role of social mechanisms in the association

between motor and communication in neurogenetic conditions to elucidate possible mechanisms and viable intervention targets.

Our findings offer important considerations for early intervention in these neurogenetic groups. It is unequivocally established that early and comprehensive developmental interventions in high dosages are optimal for improving developmental outcomes (Dawson et al., 2010). However, rather than having readily available access to comprehensive developmental interventions (Thurm, Farmer, Salzman, Lord, & Bishop, 2019; Will & Hepburn, 2015), children with DS or FXS typically receive very specific intervention approaches (e.g., physical therapy, occupational therapy, or speech therapy) at relatively low doses (e.g., once per week or twice per month). A different combination of therapies and/or a different dosage depending on access and timing of genetic diagnosis may differentially influence developmental outcomes for children with DS or FXS. The direct association between developmental domains like motor and communication identified in the present study suggests comprehensive developmental interventions may be of particular benefit for children with neurogenetic conditions. Furthermore, evidence demonstrates that higher doses of intervention are also more beneficial than lower doses in improving communication outcomes for young children with DS (Yoder, Woynaroski, Fey, & Warren, 2014), suggesting greater intensity of intervention than typically is provided to children with DS or FXS may be of benefit. Interestingly, phenotype-specific features have been found to influence intervention efficacy, even when delivered in high doses (Yoder et al., 2014). Specifically, children with DS receiving a high dosage intervention showed decelerated growth in communication outcomes as a function of their diminished interest and engagement with objects (Yoder et al., 2014), a phenotypic characteristic unique to DS (Fidler et al., 2005). These considerations warrant further advancement in the development of intensive

comprehensive developmental interventions for children with neurogenetic disorders such as DS or FXS (Thurm et al., 2019; Will & Hepburn, 2015). There is encouraging evidence of the utility of these approaches for some children with FXS (Vismara, McCormick, Shields, & Hessl, 2019); however, further progress is needed to understand how these approaches may directly contribute to improved motor and communication outcomes for children with DS or FXS, and to what extent such approaches should account for phenotypic differences to optimize outcomes.

Limitations and Future Directions

Our study is the first to examine the associations between motor and communication and how they may differ between children with DS or FXS in early development. However, the current study has some limitations. Notably, the measures provide a broad picture of motor and communication but are somewhat limited in providing a precise index of motor or communication abilities. As such, an even stronger association between motor and communication may exist but require more fine-grained measures, such as postural stability, motor planning, or prelinguistic communication. Findings are also somewhat limited by the cross-sectional nature of the study. While our results provide useful insight on concurrent importance of motor and communication skills in DS and FXS, longitudinal work could elucidate greater cross-syndrome differences or yield better insight into developmental changes in the association between motor and communication in children with DS or FXS. Finally, examining potential sources of within-syndrome variability, such as ASD symptomatology or a more detailed examination of sex effects, in the association between motor and communication were beyond the scope of the present study due to aims of the study and ages of many participants (i.e., <18 months). Investigating these additional factors may further elucidate unique developmental processes occurring both within and across these genetic groups and

important developmental influences on the connection between early motor and communication abilities.

Summary and Conclusions

The present study is among the first to characterize the early developmental association between motor and communication and how this may differ as a function of genetic etiology across children with DS or FXS. We identified unique phenotypic profiles across motor, language and communication abilities between infants and young children with DS and those with FXS, contributing to the broader understanding on phenotypic differences between these syndromes. Our findings also establish an important link between both fine and gross motor abilities and both receptive and expressive communication, regardless of inherent profile differences between children with DS or FXS in these domains. These results, along with our finding of a significantly stronger association between fine motor and receptive communication for young children with DS, highlight the importance of considering targeted intervention strategies that may enhance development across distal developmental domains, and also potentially the importance of considering etiologically specific treatment approaches.

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Table 1. Group Differences by Etiology and Sex

		DS				FXS			
	d *	Whole Group *M (SD)*	Males *M (SD)*	Females *M (SD)*	*d* †	Whole Group *M (SD)*	Males *M (SD)*	Females *M (SD)*	*d* †
MSEL Gross Motor	0.51	14.86 (4.63)	14.96 (4.48)	14.64 (5.18)	0.07	17.46 (5.54)	16.50 (5.02)	19.73 (6.28)	0.58
MSEL Fine Motor	0.01	15.32 (3.97)	15.04 (3.93)	16.00 (4.15)	0.23	15.24 (4.70)	14.65 (4.74)	16.64 (4.50)	0.44
MSEL Receptive Language	0.21	12.51 (3.85)	11.27 (3.79)	12.64 (3.64)	0.37	11.62 (4.44)	11.08 (3.90)	12.91 (5.52)	0.38
MSEL Expressive Language	0.51	11.70 (3.96)	12.46 (4.00)	12.73 (4.36)	0.07	9.59 (4.32)	8.46 (3.74)	12.27 (4.58)	0.91
VABS Gross Motor	0.23	24.73 (14.47)	24.96 (14.43)	24.18 (15.26)	0.05	29.89 (15.15)	27.96 (14.56)	34.45 (16.23)	0.42
VABS Fine Motor	0.07	14.54 (3.80)	14.42 (4.13)	14.82 (3.03)	0.11	14.22 (5.67)	13.38 (5.69)	16.18 (5.36)	0.51
VABS Receptive Communication	0.26	12.08 (6.22)	11.54 (5.80)	13.36 (7.24)	0.13	10.57 (5.28)	9.42 (4.51)	13.27 (6.18)	0.71
VABS Expressive Communication	0.37	18.84 (7.01)	17.69 (6.42)	21.55 (7.92)	0.54	15.70 (9.89)	13.50 (7.59)	20.91 (12.88)	0.70
Chronological Age	0.12	20.38 (8.17)	20.58 (8.76)	19.91 (6.93)	0.10	19.51 (8.00)	19.65 (8.29)	19.18 (7.63)	0.06
Mental Age	0.01	13.19 (3.71)	13.00 (3.82)	13.64 (3.59)	0.17	13.16 (4.34)	12.38 (4.30)	15.00 (4.02)	0.63
Visual Reception	0.10	15.81 (3.49)	15.85 (3.62)	15.73 (3.35)	0.03	15.43 (4.37)	14.50 (4.23)	17.64 (4.06)	0.76

MSEL = Mullen Scales of Early Learning (raw scores)
VABS = Vineland Adaptive Behavior Scales (raw scores)
**Mean difference effect size between whole group DS v. FXS*
†*Mean difference effect size between males and females within genetic group*

Table 2. Moderated Regression Models

	Receptive Communication					Expressive Communication				
				95% CI					95% CI	
	b	SE(b)	p	lower	upper	b	SE(b)	p	lower	Upper
Intercept	13.61	0.80	<.001	12.02	15.19	20.60	1.16	<.001	18.29	22.92
FXS	-3.54	1.09	.002	-5.72	-1.36	-5.89	1.60	.001	-9.07	-2.70
Gross Motor	0.88	0.16	<.001	0.56	1.20	1.02	0.24	<.001	0.54	1.50
Gross Motor x FXS	-0.30	0.21	.162	-0.72	0.12	0.13	0.31	.682	-0.49	0.75
Adjusted R^2=0.39						*Adjusted R^2=0.42*				
				95% CI					95% CI	
	b	SE(b)	p	lower	upper	b	SE(b)	p	lower	upper
Intercept	12.03	0.70	<.001	10.62	13.43	18.79	1.16	<.001	16.47	21.10
FXS	-1.44	0.99	.153	-3.42	0.55	-3.04	1.64	.068	-6.31	0.23
Fine Motor	1.19	0.18	<.001	0.84	1.55	1.17	0.30	<.001	0.56	1.77
Fine Motor x FXS	-0.57	0.24	.017	-1.04	-0.10	-0.02	0.39	.954	-0.80	0.75
Adjusted R^2=0.45						*Adjusted R^2=0.34*				

**Note: Models are estimated with Down syndrome as the reference group*

***Note: Gross and Fine Motor are centered at the mean*

Figure

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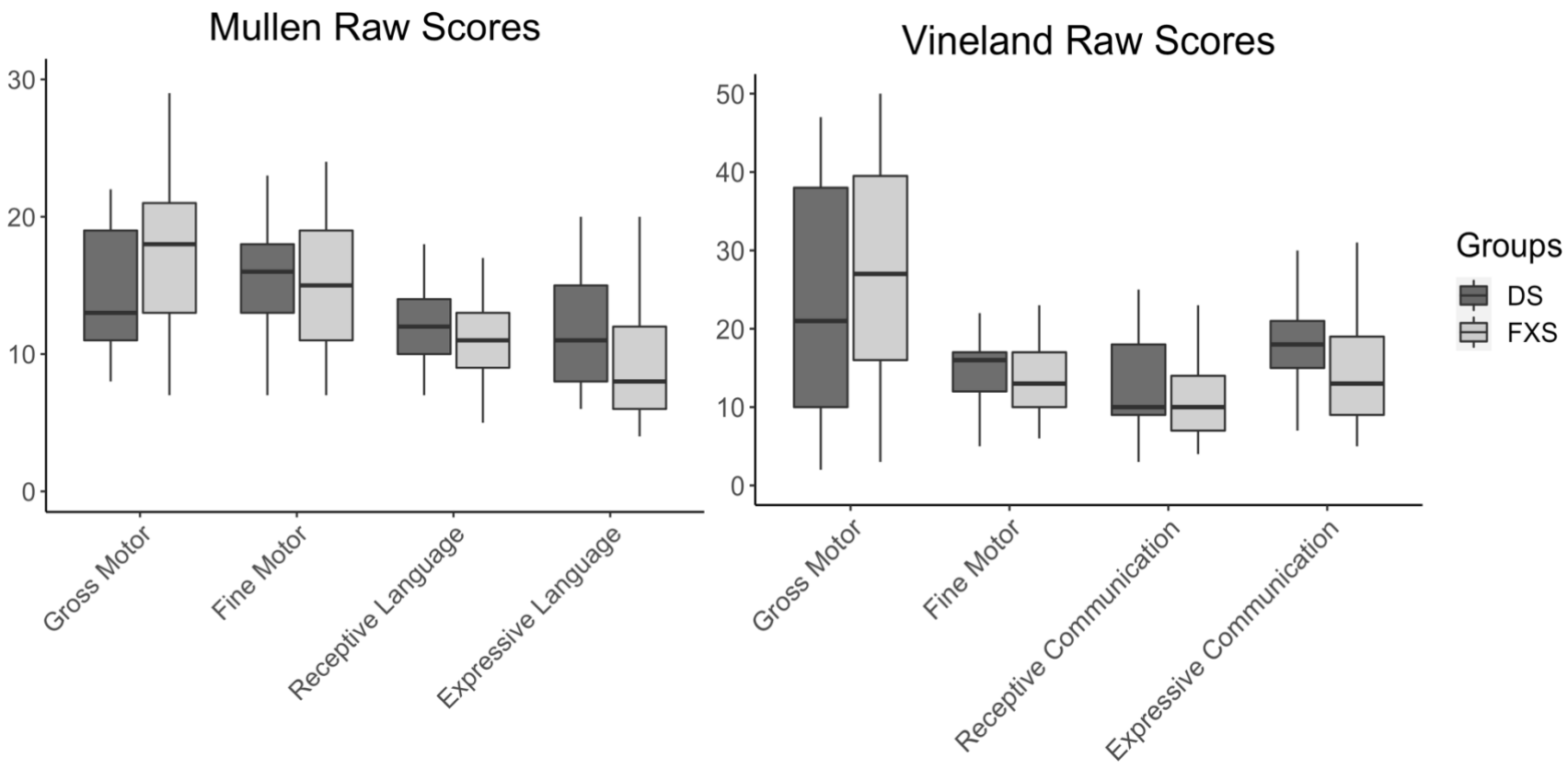

Figure 1. Performance Profiles by Etiology

Figure

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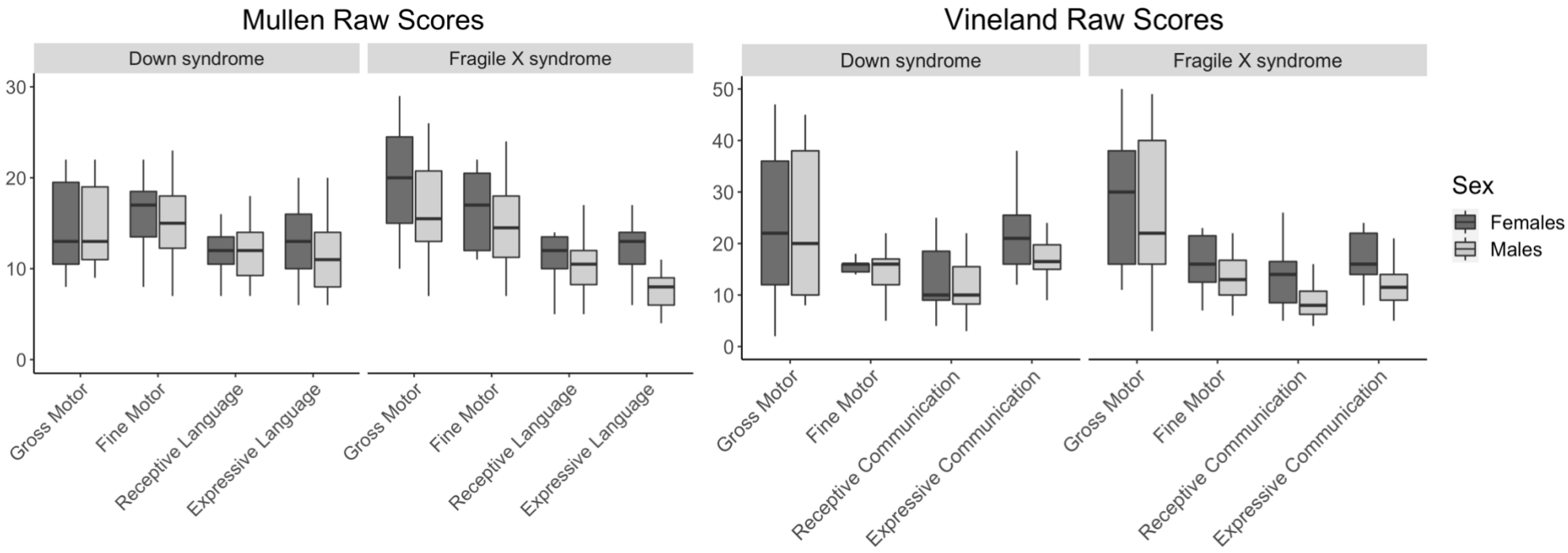

Figure 2. Performance Profiles by Etiology and Sex

Figure

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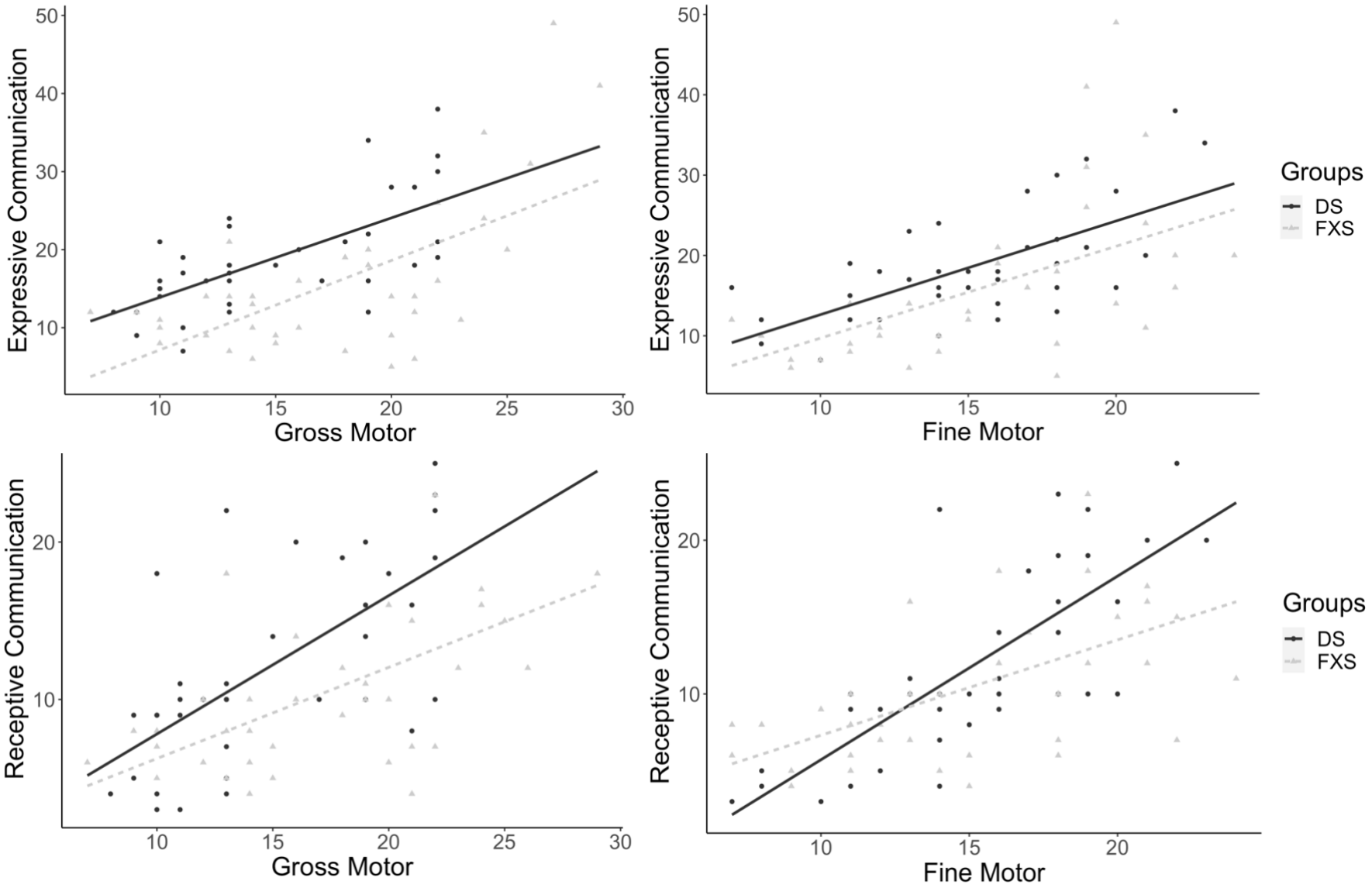

Figure 3. Moderated Regression Models