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Manuscript Title: Relationship between early motor milestones and severity of restricted and repetitive behaviours in children and adolescents with Autism Spectrum Disorder (ASD)

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Lay Abstract

The present study aimed to explore the relationship between the attainment of early motor milestones, as well as current motor atypicalities indexed by toe walking, and the severity of restricted and repetitive behaviours (RRBs) in individuals with autism spectrum disorder (ASD). Parents of 147 children and adolescents with ASD completed an early developmental milestones questionnaire and the Social Responsiveness Scale as a measure of Insistence on Sameness (IS) and Repetitive Mannerisms (RM) subtypes of RRBs. Two hierarchical regression analyses were conducted to test whether RM and IS behaviours were predicted by age of attainment of early motor milestones or current toe walking. RM behaviours were predicted by toe walking while IS behaviours were predicted by a combination of a delay in motor milestones and the presence of toe walking. Similarly, a combination of toe walking and early motor milestones predicted RRBs on an observational autism assessment. Our study replicates previous findings on the relationship between concurrent motor impairments and RRBs and provides the first evidence for the association between RRBs and later age of achievement of early motor milestones.

Scientific Abstract

This study explored the relationships between the later age of achievement of early motor milestones, current motor atypicalities (toe walking), and the severity of restricted and repetitive behaviours (RRBs) in individuals with autism spectrum disorder (ASD). Parents of 147 children and adolescents with ASD (M_{age} = 8.09 years, SD = 4.28; 119 males) completed an early developmental milestones questionnaire and the Social Responsiveness Scale as a measure of Insistence on Sameness (IS) and Repetitive Mannerisms (RM). Two hierarchical regression analyses were conducted to test whether RM and IS behaviours were predicted by early motor milestones, or current toe walking. The final model predicting RM accounted for 15% of the variance (F = 3.02, p = .009), with toe walking as a unique and independent predictor of RM scores (t = 3.568, p = .001). The final model predicting IS accounted for 19.1% of variance in IS scores (F = 4.045, p = .001), with CA (t = 2.92, p = .004), with age when first standing (t = 2.09, p = .038), and toe walking (t = 2.53, p = .013) as unique independent predictors. Toe walking (t = 2.4, p = .018) and age when first sitting (t = 2.08, p = .04) predicted the severity of RRBs on the Autism Diagnostic Observation Schedule (F = 2.334, p = .036). Our study replicates previous findings on the relationship between concurrent motor impairments and RRBs, and provides the first evidence for the association between RRBs and age of attainment of early motor milestones.

Key words: Repetitive Behaviour, Motor Milestones, Atypical Gait, Autism

Introduction

Current diagnostic criteria (DSM-5; APA, 2013) does not consider delays and atypicalities in motor development as a core symptom of Autism Spectrum Disorder (ASD). However, from the original clinical descriptions provided by Leo Kanner (Kanner, 1943) to the most recent empirical work (for comprehensive overviews see Goven & Hamilton, 2013; Hannant, Tavassoli, & Cassidy, 2016; Leonard & Hill, 2014), it is clear that a range of motor problems are frequently reported among individuals with ASD. Estimated frequency and type of motor atypicalities vary between studies, but it is estimated that at least 80% of individuals with ASD present with some form of motor impairment (Green et al., 2009; Ming, Brimacombe, & Wagner, 2007; Miyahara et al., 1997; Whyatt, & Craig, 2012). Motor delays can negatively impact on the development and severity of social and communicative symptoms (Goven & Hamilton, 2013; Leonard & Hill, 2014), and on restricted and repetitive behaviours (RRBs; Bodfish et al., 2001; Lewis & Kim, 2009). Studies have shown that early motor atypicalities are predictive of a subsequent ASD diagnosis (Brian et al., 2008; Nickel et al., 2013), and the severity of social and communication problems (Leonard et al., 2007); however, the relationship with RRBs is yet to be systematically explored. The aim of this study was to explore the relationship between age of attainment of early motor milestones, current motor atypicalities, and severity of concurrent RRBs.

RRBs is an umbrella term encompassing a wide range of behaviours that are usually grouped into Repetitive Sensory-Motor (RSM), and Insistence on Sameness (IS) behaviours (Leekam, Prior, & Uljarević, 2011; Prior & Macmillan, 1973). Anxiety, problems with executive functions, self-regulation, and sensory modulation problems have all been linked to the occurrence and persistence of RRBs. However, the mechanisms underlying the occurrence and persistence of RRBs are currently not well characterized (for a comprehensive review see Leekam et al., 2011).

RRBs have been previously linked to motor impairments and underlying impairments in basal ganglia (Bodfish et al., 2001; Lewis & Kim, 2009; Radanovich, Fournier, & Hass, 2013). Bodfish et al. (2001) found that impairments in motor control were associated with increased rates of motor RRBs in a sample of individuals with intellectual disability. Furthermore, Radanovich et al. (2013) found that, in addition to motor RRBs, impairments in motor control, measured by postural sway, were associated with higher rates of rigidity and insistence on sameness in children and adolescents with ASD (all with non-verbal IQ >70). In further support of a potential relationship between the basal ganglia and motor abnormalities in ASD, atypicalities in basal ganglia have been found to be associated with levels of both repetitive motor and insistence on sameness behaviours (Estes et al., 2011; Hollander et al., 2005; see Langen et al., 2011 for a comprehensive overview). Numerous studies using questionnaires/interviews, observation protocols and experimental procedures suggest that individuals with ASD, irrespective of age, show a wide range of motor abnormalities and control deficits including atypicalities in gait, toe walking, posture, coordination, and fine and gross motor skills (Barrow, Jaworski, & Accardo, 2011; Ghaziuddin & Butler, 1998; Glazebrook, Elliott, & Lyons, 2006; Manjiviona & Prior, 1995; Minshew, Sung, Jones, & Furman, 2004; Rinehart et al., 2006).

In summary, although previous research suggests an association between the severity of RRBs and concurrent motor impairments (Radanovich et al., 2013), a potential relationship with delays in achieving early motor milestones has not previously been explored. Our paper is the first to explore this relationship in a cross-sectional sample of children and adolescents with ASD. In addition, we explored the relationship between concurrent motor atypicalities, indexed by toe walking, one of the most commonly reported disturbances in gait in ASD, and levels of RRBs. We hypothesized that age of attainment of early motor milestones and atypical gait would be associated with higher levels of RRBs.

Methods

Participants

The sample consists of 147 children with ASD (M_{age} = 8.09 years, *SD* = 4.28, range, 2.08–17.8; 119 males) who were part of the Western Australian Autism Biological Registry (WAABR) study. All children had a community based diagnostic assessment conducted by a multidisciplinary team comprising a paediatrician, clinical psychologist, and speech pathologist, leading to a best-estimate clinical diagnosis of an ASD (82.7% Autism, 8.3% Asperger Syndrome, 9% PDD-NOS). Diagnosis was verified using the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord, Rutter, & DiLavore, & Risi, 2000) administered by a research-reliable assessor at the Telethon Kids Institute in Perth, Western Australia, as part of the study. Very preterm infants (≤ 32 weeks of gestation) and children with co-morbid intellectual disability, cerebral palsy, or any organic motor or neurological impairment were excluded.

Procedures and measures

The study was approved by the Princess Margaret Hospital Human Research Ethics Committee, and all participants provided written informed consent. Parents completed an *early developmental milestones questionnaire* and the *Social Responsiveness Scale Second Edition (SRS-2;* Constantino & Gruber, 2012) as part of the WAABR study. The SRS-2 is a parent report measure designed to index autism trait severity. Factor analysis indicated a five factor structure, including three scales (Emotion Recognition, Social Avoidance, Interpersonal Relatedness) related to social and communication impairments and two scales (Insistence on Sameness, IS; Repetitive Mannerisms, RM) related to RRBs (Frazier et al., 2014). Here we report on the IS and RM scales only.

Results

Descriptive statistics are presented in Table 1. There was a wide range in ages of attainment of early motor milestones. As early milestone variables were skewed, all of the subsequent analyses were conducted using bootstrapping with 1000 resamples in order to generate more reliable, robust statistics. Reported results are for bootstrapped analyses. The parents of 51% of children indicated that their child had never toe walked, 33.8% that their child had in the past but no longer does, and 15.2% that their child currently toe walks.

Two hierarchical regression analyses were conducted to explore the predictors of RM (analysis 1) and IS (analysis 2) behaviours. In both models chronological age (CA) was entered in the first step, age of the attainment of early motor milestones in the second step, and toe walking in the third step (for a summary of the models see Table 2).

SRS-2 Repetitive Mannerism (RM) Scores: In the first step, CA accounted for 1.5% of the variance in RM scores (p = .197). In the second step, early motor milestones accounted for an additional 2.9% of the variance (p = .53). The final step accounted for an additional 10.5% of variance, with the whole model accounting for 15% of variance (F = 3.02, p = .009), with toe walking identified as a unique and independent predictor of scores (t = 3.568, p = .001).

SRS-2 Insistence on Sameness (IS) Scores: CA accounted for 9.2% of variance in the first step (p = .001), early motor milestones and toe walking accounted for an additional 4.9% (p = .007) and 5% of the variance (p = .001) in the second and third steps, respectively. The whole model accounted for 19.1% of variance in IS scores (F = 4.045, p = .001), with CA (t = 2.92, p = .004), age when first standing (t = 2.09, p = .038) and toe walking (t = 2.53, p = .013) identified as unique independent predictors.

The analysis was repeated using ADOS-G RRBs calibrated severity scores (following Hus, Gotham, & Lord, 2014). The model explained 11.8% of variance (F = 2.334, p = .036),

with age at sitting (t = 2.08, p = .04) and toe walking (t = 2.4, p = .018) as unique independent predictors.

Discussion

While it has been proposed that delays in achieving early motor milestones might be associated with RRBs (Bodfish et al., 2001; Lewis & Kim, 2009), this relationship has not been previously explored. In the present study we found that in children and adolescents with ASD, later attainment of early motor milestones was predictive of higher levels of SRS-2 IS scores, and also ADOS RRB calibrated severity scores. Furthermore, concurrent motor atypicalities assessed via atypical gait (toe walking) were predictive of SRS-2 IS and RM behaviours as well as ADOS RRB calibrated severity scores. An association between atypical gait and RRBs is consistent with two previous studies that explored the relationship between motor impairments and RRBs (Bodfish et al., 2001; Radanovich et al., 2013).

Links between motor delays and atypicalities and RRBs can be explained in several ways. Dynamic system (Thelen & Smith, 1994) and developmental cascade (Masten & Cicchetti, 2010) frameworks emphasize that in development, different abilities are organized in a hierarchical manner; consequently, a delay or disruption in one of these skills can have a cascading effect on the development of subsequent skills and abilities. Therefore, later attainment of motor milestones, in particular the ability to stand and walk, may impact a child's ability to explore and interact with their environment in an increasingly complex and flexible way, reducing opportunities for learning. Reduced learning opportunities can lead to increased insistence on sameness and behavioural rigidity both directly, or through the impact on the development of self-regulation skills. In support of this hypothesis, in non-ASD populations, variability in early motor milestones has been associated with self-regulation and cognitive abilities indexed by executive functions (Murray et al., 2006) and effortful control (De Santis et al., 2013). Furthermore, a recent study by St John et al. (2016) indicated that in

a sample of children subsequently diagnosed with ASD, fine and gross motor skills when children were 12 and 24 months old were associated with later executive functions, measured by a reversal learning task. Links between impairments in self-regulation and RRBs, in particular IS, in both ASD and non-ASD populations are well established (see Leekam et al., 2011; Evans et al, 2014 for comprehensive overviews). Another explanation for the associations reported here relates to a common underlying neural basis, as overlapping brain regions including the cerebellum, fronto-striatal and basal ganglia, in particular the caudate nucleus, have been found to subserve motor control and executive functions in non-ASD populations (Ridler et al., 2006). Moreover, impairments in these circuits among individuals with ASD have been associated with RRBs (Langen et al., 2011), executive dysfunction (Yerys et al., 2015) and motor abnormalities (Mosconi et al., 2015; Mostofsky et al., 2009; Rinehart et al., 2006; Qiu et al., 2010).

Both retrospective (Baranek, 1999; Esposito & Venuti, 2008; Teitelbaum et al., 1998; Teitelbaum, 2004) and prospective (Bryson et al., 2007; Landa & Garrett-Mayer, 2006; Nickel et al., 2013) studies indicate that children later diagnosed with ASD show delays in attaining early motor milestones and present with other atypicalities, such as asymmetrical postures, that are detectable even before social and communication deficits arise (Flanagan et al., 2012; Macdonald, Lord, & Ulrich, 2013). The fact that motor delays seem to be one of the earliest risk markers for ASD and relate to the subsequent severity of social and communication deficits (Brian et al., 2008; Bhat, Galloway, & Landa, 2012; Leonard et al., 2007), has led to suggestions that motor skills should be targeted as part of early autism interventions (Macdonald, Lord, & Ulrich, 2013). With this in mind, our findings of the relationship between delays in motor development and concurrent motor atypicalities and IS behaviours suggests that motor skills interventions might be a potential way of reducing RRBs. However, it is first important to note several limitations of our study.

Our study only included individuals without a co-morbid diagnosis of intellectual disability; however, we relied on parent report and did not have a dedicated measure of cognitive level. Although early studies indicated that motor impairments may be related to lower developmental level (e. g. Ghaziuddin & Butler, 1998), subsequent studies suggest that the severity and/or frequency of motor impairments is either independent of IQ (Jansiewicz et al., 2006; Radanovich et al., 2013), or may even be higher in individuals with ASD (Green et al., 2002). As an additional limitation, assessment of motor atypicalities and motor milestones relied on parental reports and, in the case of early motor milestones, the report was retrospective. However, previous reports have demonstrated moderate to good reliability of parental recall for the age of attainment of early motor milestones (Majnemer & Rosenblatt, 1994), and high correlations between parental reports of their children's current motor functioning and clinical and laboratory assessments in both ASD and non-ASD samples (Gudmundsson & Gretarsson, 1994; 2013; Leonard et al., 2014; Loyd, MacDonald, & Lord, 2011). Finally, although SRS provides adequate sampling of RSM and IS behaviours, it does not allow for a more fine grained exploration that is afforded by the use of dedicated RRBs measures such as the Repetitive Behaviour Questionnaire-2 (RBQ-2; Leekam et al., 2007; Barrett et al., 2015), the Childhood Routines Inventory-Revised (Evans et al., 2016) or the Repetitive Behaviour Scale-Revised (Bodfish, Symons, & Lewis, 1997).

It will be necessary to replicate these findings using a combination of parental reports, observational and experimental measures sampling a wide range of motor impairments as well as enabling comprehensive sampling and fine grained approach to RRBs, and taking cognitive/developmental level into account. In addition to disentangling the nature of the relationship between motor impairments and RRBs, and considering the potential for a bi-directional relationship with ASD, a longitudinal design is needed. Finally, it will be

important to determine how the unfolding of these factors during early development map onto developing neural substrates.

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Table 1. Descriptive Statistics

	Mean (SD)	Range	Shapiro-Wilk Test (sig)
Sitting	6.44 (1.70)	2-12	p <.001
Crawling	8.33 (2.22)	3-15	p = .003
Standing	10.9 (2.49)	4-20	p = .001
Walking	13.18 (3.12)	5-30	p < .001
SRS-2 IS score	47.26 (10.49)	22-70	p = .189
SRS-2 RM score	20.47 (5.8)	8-34	p = .146

Note: motor milestones are expressed in months

Table 2. Regression Models

	R2Δ	R2Δ Change	B	SEB	β		R2Δ	R2Δ Change	B	SEB	β
SRS-2 Repetitive Mannerisms						**SRS Insistence on Sameness**					
Step 1	.015					**Step 1**	.092**				
constant			19.592	1.222		constant			2.354	.112	
CA			.014	.011	.124	Verbal DQ			.003	.001	.303**
Step 2	.05	.029				**Step 2**	.14**	.049			
constant			22.192	3.269		constant			2.761	.268	
CA			.011	.011	.097	CA			.003	.001	.286**
Sitting			.269	.394	.079	Sitting			.022	.01	.066
Crawling			.018	.336	.007	Crawling			.003	.03	.012
Standing			.395	.367	.170	Standing			.065	.029	.292*
Walking			.294	.293	.160	Walking			.016	.024	.09
Step 3	.15**	.105**				**Step 3**	.191**	.05*			
constant			17.941	3.299		constant			2.477	.285	
CA			.008	.01	.068	CA			.003	.001	.266**
Sitting			.354	.380	.104	Sitting			.016	.01	.049

Crawling	.081	.346	.030	Crawling	.007	.03	.029
Standing	.342	.363	.148	Standing	.062	.028	.276*
Walking	.219	.268	.119	Walking	.011	.023	.062
Toe Walking	5.249	1.339	.330**	Toe Walking	.351	.137	.229*