Title: Deconstructing the repetitive behaviour phenotype in Autism Spectrum Disorder through a large population-based analysis

Abbreviated Title: Repetitive Behaviours in Autism

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Conflict of Interest: None.

Word Count: 6063

Abstract

Objective: Restricted and repetitive pattern of behaviours (RRB) are a cardinal feature of autism spectrum disorder (ASD), but there remains uncertainty about how these diverse behaviours vary according to individual characteristics. This study provided the largest exploration to date of the relationship between Repetitive Motor Behaviours, Rigidity/Insistence on Sameness and Circumscribed Interests with other individual characteristics in newly diagnosed individuals with ASD.

Method: Participants (N= 3647; 17.7% females; Mage= 6.6 years [SD= 4.7]) were part of the Western Australian (WA) Register for ASD, an independent, prospective collection of demographic and diagnostic data of newly diagnosed cases of ASD in WA. Diagnosticians rated each of the DSM-IV-TR criteria on a 4-point Likert severity scale and here we focused on the Repetitive Motor Behaviours, Insistence on Sameness and Circumscribed Interests symptoms.

Results: The associations between RRB domains, indexed by Kendall's Tau, were weak, ranging from non-significant 0.003 for both Circumscribed Interests and Repetitive Motor Behaviours to significant 0.20 for Insistence on Sameness and Repetitive Motor Behaviours. Older age at diagnosis was significantly associated with lower Circumscribed Interests and significantly associated with higher Insistence on Sameness and Repetitive Motor Behaviours. Male sex was significantly associated with higher Repetitive Motor Behaviours but not Insistence on Sameness or Circumscribed Interests. Higher social impairments were a significant predictor of higher severity of only Circumscribed Interests but did not significantly predict other two domains.

Conclusion: The pattern of associations identified in this study provides suggestive evidence for the distinctiveness of Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests, suggesting the potential utility of RRB domains for stratifying the

larger ASD population into smaller, more phenotypically homogeneous subgroups that can help to facilitate efforts to understand diverse ASD etiology and inform design of future interventions.

Key Words: repetitive behaviours; autism; social and communication impairments.

Introduction

Restricted and repetitive pattern of behaviours and interests (RRB) are among the earliest infant predictors of later ASD diagnosis (Kim & Lord, 2010; Ozonoff et al., 2008), present a major barrier to subsequent learning and adaptation, and are associated with parental stress (Harrop, McBee, & Boyd, 2016; South, Ozonoff, & McMahon, 2005). Therefore, RRB constitute an important intervention target (Boyd, McDonough, & Bodfish, 2012). Nevertheless, relative to the substantial literature investigating the social and communication deficits associated with ASD, RRB have received considerably less empirical research, resulting in a limited understanding of this class of behaviours. In particular, although it is accepted that RRB reflect a multi-dimensional construct encompassing several related but distinct behavioural categories (Leekam, Prior, & Uljarević, 2011), it remains unclear how best to define and operationalize RRB domains. Clarity in conceptualizing RRB and parceling them into distinct, meaningful domains is necessary for robust identification of the underlying neurobiological mechanisms that, to date, remain elusive. Despite the noted clinical significance of RRB, there is a paucity of available effective interventions (Grahame et al., 2015; Harrop, 2015; Leekam et al., 2011). Therefore, clarifying which of the RRB subdomains are relatively independent in terms of their trajectories, mechanisms and relationship with other aspects of core ASD phenotype and co-occurring symptoms is a crucial step for the informing the development of targeted interventions and for intervention planning.

A number of factor analytical studies conducted on clinical interview methods such as the Autism Diagnostic Interview-Revised (ADI-R) (Cuccaro et al., 2003; Bishop et al., 2013) and questionnaire measures including the Repetitive Behaviour Questionnaire-2, the Repetitive Behaviours Scale-Revised and the Childhood Routines Inventory-Revised (Barrett et al., 2015; Barrett et al., 2018; Evans et al., 2017; Georgiades et al., 2010; Lidstone,

Uljarević et al., 2014) have most consistently identified two factor structure encompassing Repetitive Motor Behaviours (RMB) and Insistence on Sameness (IS). RMB and Insistence on Sameness domains map well onto 'lower-order' and 'higher-order' domains proposed by Prior and Macmillan (1973) and later Turner (1999) based on clinical observations and a developmental approach. It has been pointed out, however, that these domains, in particular Insistence on Sameness, might be too broad, potentially masking the existence of other distinct RRB domains (Leekam et al., 2011). Indeed, several studies have identified the existence of a factor labeled as restricted or circumscribed interests (CI) (Bishop et al., 2013; Honey et al., 2008; Lam et al., 2008). Repetitive Motor Behaviours, IS, and Circumscribed Interests factors largely align with the RRB categories of adherence to routines, resistance to change, repetitive movements, and intense and restrictive interests suggested by international classification systems.

An alternative method to factor analytic approaches in establishing valid, clinically meaningful, and independent RRB domains is to explore how these symptoms may vary according to social and communication aspects of ASD phenotype and factors such as chronological age (CA), sex, cognitive ability, executive functioning and/or co-occurring conditions (Leekam et al., 2011). Despite the lack of long-term longitudinal studies, preliminary findings suggest that while the Repetitive Motor Behaviours domain is more prevalent and intense during early years, with subsequent waning throughout childhood (Richler et al., 2010; Esbensen et al., 2009; Harrop et al., 2014), in contrast, Circumscribed Interests and Insistence on Sameness domains, rarely observed at 2 years of age, increase gradually throughout early childhood, and remain relatively stable during later childhood and adolescence (Richler et al., 2010; South et al., 2005). Cross-sectional correlational studies have yielded inconsistent results. While the Repetitive Motor Behaviours domain has been reported to be negatively correlated with CA and IQ (Bishop et al., 2013; Cuccaro et al.,

2003), and the Insistence on Sameness and Circumscribed Interests domains positively associated with CA and IQ (Bishop, Richler, & Lord, 2006; Bishop et al., 2013) other studies did not report significant links (Hus et al., 2007; Lam et al., 2008; South et al., 2005). Similarly inconsistent findings have been reported in terms of associations between RRB domains with sex and social and communication impairments. Kim and Lord (2010) found higher RMB levels in females, and several studies reported higher Circumscribed Interests among males (Frazer & Hardan,2017; Hiller, Young, & Weber, 2014; Knutsen et al., 2019), however, other studies suggested no sex differences for Repetitive Motor Behaviours, Insistence on Sameness, or Circumscribed Interests domains (Hus et al., 2007; Lam et al., 2008; Sutherland et al., 2017). Frequency and severity of both Repetitive Motor Behaviours (Hus et al., 2007; Lam et al., 2008; Szatmari et al., 2008) and Insistence on Sameness (Canon et al., 2010; Lam et al., 2008; Richler et al., 2010) factors have been found to be associated with more frequent and severe social and communication impairments, but non-significant (Harrop et al., 2014) and even negative relationships (Hus et al., 2007; Richler et al., 2010) have also been reported.

As can be seen from the overview presented above, it has proven difficult to establish whether Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests factors are indeed related to other phenotypic aspects of ASD in a distinct way. It might then be suggested that these domains are neither valid nor functionally distinct. However, this conclusion would be premature, as inconsistent findings can also be ascribed to a number of methodological limitations of previous studies. Firstly, the majority of studies that combined factor analysis with exploring the pattern of association with other variables had small sample sizes (majority had $N < 340$). This is a significant issue given the vast heterogeneity of ASD, and given that studies differed widely in terms of characteristics of participants, with some studies focusing on very young children and other studies including individuals with a very

wide chronological age range and also variable IQ level. Secondly, previous studies have not considered in great detail how the presence of co-morbidities influenced the results. In particular, it has been reported that co-occurrence of attention hyperactivity disorder (ADHD) and ASD is associated with more severe impairments in executive functioning (Craig et al., 2016) and reward processing (Dichter et al., 2012) each of which have been associated with IS and Circumscribed Interests respectively (Uljarević et al., 2017a; Kohls et al., 2018).

Firm findings in large, well characterized, heterogeneous cohorts are essential in order to advance the ASD research agenda (Amaral et al., 2017). Therefore, the current study aimed to enhance our understanding of RRB by utilizing a unique repository of clinical data from the Western Australian (WA) Register for Autism Spectrum Disorders (WA ASD)—a long-term prospective, state-wide register of newly diagnosed cases of ASD. The WA ASD Register contains data on the severity of the ASD DSM criteria, therefore collection of information on the Repetitive Motor Behaviours, Insistence on Sameness and Circumscribed Interests RRB domains that have been, as reviewed above, identified most consistently across the factor analyses as the main RRB subtypes. The WA ASD register also collects data on IQ, and co-morbidities. Importantly, all the data are standardized to the time of diagnosis. These features, combined with a very large sample size, offer a unique opportunity to arrive at a more comprehensive understanding of how Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests RRB domains are related to other individual characteristics such as sex, CA, IQ, social-communicative impairments and the presence of ADHD, at the time of diagnosis. Given mixed findings across the above reviewed studies and specific nature of this sample (data collected at the time of the diagnosis), it was difficult to form firm hypotheses. However, we expected positive relationship between Insistence on Sameness with CA and FSIQ and the opposite pattern for Repetitive Motor Behaviors. It was further expected that male gender would be associated with higher levels of RRB.

Methods

Autism assessments and diagnoses in WA

In WA, eligibility for ASD-specific services is dependent on a joint diagnosis by a team of three clinicians (paediatrician, clinical psychologist and a speech pathologist) (Glasson et al 2008). This has enabled a uniform and consistent approach to the diagnostic decisions, service eligibility, reporting requirements and assessor training for ASD assessments and services to children throughout WA over a number of decades. In cases where children are younger than 12 years of age, the diagnostic assessments are performed by a team of paediatrician or psychiatrist, psychologist, and speech-language pathologist. For adolescents and adults, assessments are performed by a clinical psychologist, a paediatrician (for adolescents) and/or a psychiatrist, as well as a speech-language pathologist as needed (Glasson et al., 2008).

Sample

Data for this study were sourced from the WA ASD Register (established in 1999), an independent, prospective collection of demographic and diagnostic information of individuals newly diagnosed with ASD across WA in both government and private settings (Glasson et al., 2019; Whitehouse et al., 2017). At the time of diagnosis, the diagnosing clinicians voluntarily submit demographic and diagnostic information directly to the Register including the severity of individual criteria used for the diagnosis, cognitive assessments, language abilities, adaptive behaviour and the presence of comorbid conditions such as anxiety and ADHD (for more detail please see Glasson, 2002). The collection of data for the Register involved active recapture of any missed cases between 1999-2006 and hence this period of data collection is considered complete. However, from 2007 recapture of missed cases was not performed due to changes in governance associated with service provision, and so this period will not be complete as it solely relied on voluntary notifications. It is not possible to

provide percentages or statistics to quantify the completeness as the Register itself is the only comprehensive source of data collection in WA for diagnoses occurring during the childhood period and hence no other comparative statistics exist from which to measure its completeness.

Data collection has ethical approval from the Perth Children's Hospital Human Research Ethics Committee (294EP).

Diagnostic and behavioural characteristics

In addition to the information on age at diagnosis and sex, diagnosing clinicians were asked to rate each of the DSM-IV-TR items on a 4 point Likert severity scale (0 "Criteria Definitely NOT met", 1 "Criterion questionable/partially met", 2 "Clearly meets criterion (to mild or moderate degree)" and 3 "Clearly meets criterion (to an extreme degree)"). For each of the 12 DSM-IV assessment scales, in order for a criterion to be considered to be met (in accordance with the DSM's descriptions) a severity rating of at least 2 must be given. This rating scale is not a part of the formal DSM diagnostic process but represents a clinically based construct devised and adopted by Western Australian clinicians (Glasson et al., 2008). All Western Australian ASD diagnosticians are encouraged to attend a cross-service meeting, occurring at quarterly intervals, to discuss diagnostic issues, including standardisation of the severity ratings. While attendance at these meetings was encouraged, it was not mandatory. Descriptive statistics for social, communication, and RRB items are presented in Table 1.

In this paper, we focus on the presence and severity of the following RRB domains: stereotyped and restricted patterns of interests (hereafter Circumscribed Interests), inflexible and rigid adherence to specific routines (hereafter Insistence on Sameness) repetitive motor mannerisms (hereafter Repetitive Motor Behaviours). This decision was guided by the fact that these three behavioural types map onto the corresponding factors that have consistently emerged across factor analytic studies that have explored the structure of RRB domain.

Overall scores were generated for the social and communication subscales by taking the mean of the individual scores within that subscale. In addition, diagnosticians reported FSIQ (Mean FSIQ= 85.65; SD=21.27) derived from standardized tests including the Bayley Scales of Infant Development, Stanford Binet Intelligence Scale, Mullen Scales of Early Learning, Wechsler Preschool and Primary Scale of Intelligence, or Wechsler Intelligence Scale for Children.

Insert Table 1 Here

Statistical Analysis

The analyses were broadly descriptive and exploratory in an effort to characterize the relationship between measures; descriptive statistics are presented as mean (standard deviation) or N (percentage). The two primary variables of interest were the RRB rating (Circumscribed Interests, Insistence on Sameness, and Repetitive Motor Behaviours) and Full-Scale IQ (FSIQ) score, with an additional interest in how these two variables were associated. FSIQ data were available for 42.6% of participants. Cohort characteristics are presented for the full cohort, the subgroup with FSIQ data, and the subgroup without FSIQ. Importantly, there were no significant differences between subgroups with and without FSIQ information. The lack of FSIQ of data is largely due to variation in the assessment protocol used across cases and centers.

Kendall's tau coefficient was used to assess the correlation between ordered categorical variables and to characterise the concordance of the RRB ratings with both the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) RRB ratings. Ordinal logistic regression was used to analyze each RRB rating (0,1,2,3) as an outcome, with Odds Ratios (OR) and 95% Confidence Intervals (95% CI) reported. FSIQ was analyzed both as a continuous outcome measure and as a dichotomous 'Low IQ' outcome measure

(defined as a FSIQ score <70); these were analyzed via linear regression (with unstandardized coefficients and 95% CIs reported) and logistic regression (with OR and 95% CIs reported) respectively; an alpha of 0.05 was used to determine statistical significance. Age of autism diagnosis, year of autism diagnosis, sex, and comorbid ADHD were entered into the model as both potential confounders and variables of interest.

Exploratory analysis involved stratification based on sex and/or age of Autism diagnosis. Age of Autism diagnosis groups were defined based on the following groupings 0-3, 4-6, 7-12, and 13+ years. It is important to note however that there are no long-term longitudinal studies charting the developmental trajectory of distinct RRB domains across both normative and atypical development. We have based the initial age brackets on two longitudinal studies by Richler et al. (2010) and Uljarević et al. (2017b) which have explored the change in RRB in ASD and normative development, respectively, that have shown opposite age related patterns of IS and RMB domains in both samples, and the 0-3 and 4-6 brackets as being periods when the most significant changes occur and to smaller extent between ages 7 and 12 with patterns flattening after that. This has informed our initial age groupings. A range of relevant data plots (including heatmaps with summary statistics and violin distribution plots, locally weighted scatterplot smoothing [LOESS], and splined linear-regression lines) were generated and inspected to guide stratification prior to model fitting. Analysis were carried out, and graphics were produced, using R.

Results

Data were available for 3647 participants, all diagnosed with ASD. Mean age at ASD diagnosis was 6.6 years (SD = 4.7), 82.3% were male, and 11.0% had comorbid ADHD (Table 1). Full-Scale IQ data was available for 1554 participants, 451 (28.8%) had low IQ (a score <70, 357 (27.8%) males and 91 (33.2%) females).

Inter-relationship between RRB domains

For each of the RRB, the most common rating was 2, observed for 38.9% of participants for Insistence on Sameness and 50.4% of participants for both CI and Repetitive Motor Behaviours; the least common rating was 3 (ranging 3.5% o5 3.3%; Table 1). The correlation between RRB ratings, as measured by Kendall's Tau, was weak, ranging in magnitude from 0.00 for 'Circumscribed Interests and Repetitive Motor Behaviours (female) to 0.20 for 'Insistence on Sameness and Repetitive Motor Behaviours (male) (Figure 1). Repetitive Motor Behaviours and Insistence on Sameness, independently, were not associated with Circumscribed Interests (Supplementary Table S1). A 1 unit increase in Repetitive Motor Behaviours was significantly associated with a higher Insistence on Sameness rating (OR 1.59; 95% CI 1.47,1.72), and, a 1 unit increase in Insistence on Sameness was significantly associated with a higher Repetitive Motor Behaviours rating (OR 1.53; 95% CI 1.43,1.65). Effect size estimates for these associations did not significantly differ when each of the two RRB were entered into the model, together, to predict the third. The correlation between the clinician RRB ratings of interest and the ADI-R (N= 596; 16.34% of the total sample) and ADOS (N= 211; 5.78% of the total sample; all individuals with ADOS also had ADI-R data available)scores ranged 0.18 to 0.31 and 0.10 to 0.23 in magnitude, respectively.

Insert Figure 1 Here

Relationship between RRB domains and age, sex, IQ and ADHD

An older age at ASD diagnosis was significantly associated with a lower rating for Circumscribed Interests (OR 0.96; 95% CI 0.94,0.97) but a higher rating for Insistence on Sameness (OR 1.06; 95% CI 1.05,1.08) and Repetitive Motor Behaviours (OR 1.07; 95% CI 1.06,1.09), Supplementary Table S1. Comorbid ADHD was significantly associated with a higher rating for Insistence on Sameness (OR 1.38; 95% CI 1.13,1.69) and Repetitive Motor Behaviours (OR 1.27; 95% CI 1.03,1.58) but not Circumscribed Interests. In the full cohort analysis, a significant association was observed between male sex and a higher rating for

Repetitive Motor Behaviours (OR 1.81; 95% CI 1.54,2.12), but not for Insistence on Sameness (OR 1.01; 95% CI 0.86, 1.18) or Circumscribed Interests (OR 0.93; 95% CI 0.79 1.09). Distribution of Circumscribed Interests for females and males across different age groups for the entire sample is shown in Table 2a. Tables 2b and 2c show distribution of Circumscribed Interests ratings for females and males across different age groups separately for individuals without intellectual disability and with intellectual disability respectively.

The linear nature of the relationship between each RRB and FSIQ, by sex, was examined and validated graphically (Figure 2). An increase of one unit in Circumscribed Interests rating, for males, was significantly associated with a lower FSIQ score (unstandardized coefficient -3.74; 95% CI -5.11,-2.38) and an increased odds (OR 1.52; 95% CI 1.31,1.77) of having a low IQ (Supplementary Table S2). Effect sizes were smaller and not statistically significant for females, however, they were in the same direction. An increase of one unit in Insistence on Sameness rating, for males, was significantly associated with a higher FSIQ score (unstandardized coefficient 3.61; 95% CI 2.23,4.99) and a decreased odds (OR 0.72; 95% CI 0.62,0.83) of having a low IQ (Supplementary Table S2); these effect sizes were also significant and larger in magnitude within females, unstandardized coefficient 5.95 (95% CI 3.20,8.69) and OR 0.56 (95% CI 0.41,0.75) respectively. Observations for Repetitive Motor Behaviours were similar to those of Insistence on Sameness, with the effect sizes being attenuated. The relationship between each RRB and age was examined visually using a LOESS non-parametric regression line. A clear change in the relationship occurred around the age of eight 8 years, hence, a linear spline model was hit with a knot at 8 years (Figure 3). This showed a significant increase in both Insistence on Sameness and Repetitive Motor Behaviours (0.11 and 0.08 units per year of age, respectively) and a decrease in Circumscribed Interests (-0.05 units per year of age) prior to age 8, which contrasted to a less rapid change after 8 years (-0.001, 0.001, -0.012 units per year of age, for Insistence on

Sameness, Repetitive Motor Behaviours, and CI respectively; not significant with the exception of CI).

Insert Figure 2 Here

Insert Figure 3 Here

Following a visual inspection of FSIQ scores by each RRB for sex and age (Figure 4), regression models stratified by age were fitted. Circumscribed Interests and Repetitive Motor Behaviours appeared to be best explained within a two-level cohort structure (0-12, 13+ years), whereas the relationship with Insistence on Sameness was less clear so was modeled within a four-level cohort structure (Supplementary Table S3). The magnitude of the decrease in IQ for males, for each unit increase in Circumscribed Interests, was significant in both cohorts but larger in magnitude (-6.5 units; 95% CI -10.1,-2.9) among those diagnosed with ASD after age 13 years than those diagnosed prior (-3.3 units; 95% CI -4.7,1.9); this difference was not observed for females. For Repetitive Motor Behaviours in males, a one unit increase in Repetitive Motor Behaviours was significantly associated with an increase (3.3 units; 95% CI 1.8,4.8) in IQ among those diagnosed with ASD prior to age 13 years, with a decline (not significant) observed for those diagnosed after age 13 years; this pattern differed in females where an increase was observed for both groups, albeit not significant for those diagnosed after age 13 years. The magnitude of the relationship between Insistence on Sameness and FSIQ was smallest in magnitude and not significant within the cohort aged 7 to 12 years at the time of ASD diagnosis for both sexes; the increase in FSIQ for each unit increase in Insistence on Sameness was largest in magnitude and significant among those diagnosed between ages 4 and 6 years for females (8.6 units; 95% CI 4.4,12.8), and those diagnosed between ages 0 and 3 years for males (5.3 units; 95% CI 2.5,8.1).

Insert Figure 4 Here

Analysis of RRB and social and communication scales

The rate of meeting any two of the DSM-IV-TR (in pairs) criteria are presented as the percentage of the total sample that met both criteria as opposed to the conditional percentage. This rate varied (Supplementary Figure S1), ranging from as low as 21.0% (Insistence on Sameness and Repetitive Motor Behaviours, females) and 21.3% (Insistence on Sameness and Repetitive Motor Behaviours, males) to 72.1% (Social/emotional reciprocity and Conversation initiation and sustaining, females) and 71.4% (Social/emotional reciprocity and Conversation initiation and sustaining, males). The mean score for the DSM-IV social scale was a significant predictor of Circumscribed Interests with an OR of 1.65 (95% CI 1.46,1.88) for receiving a higher RRB rating, but was not significant for Insistence on Sameness and RMB (Supplementary Table S4). The mean score for the DSM-IV communication scale was a significant predictor only for an increase in Circumscribed Interests (OR 1.25) and a decrease in Insistence on Sameness (OR 0.78) and Repetitive Motor Behaviours (OR 0.86). These effects were adjusted for age of diagnosis, sex, and calendar year. When the DSM-IV predictors were entered into the model together, the results were broadly similar, with the relationship between the social scale and both Insistence on Sameness and Repetitive Motor Behaviours increasing in magnitude and becoming significant.

Discussion

This study utilized an internationally unique prospective, state-wide cohort to provide the most comprehensive exploration to date of whether Repetitive Motor Behaviours, Insistence on Sameness and Circumscribed Interests RRB domains can be distinguished based on their patterns of associations with other individual characteristics. Exploration of the relationships between the RRB domains showed weak associations ranging from non-significant .00 for the associations of Circumscribed Interests with Insistence on Sameness and Repetitive Motor Behaviours to significant .20 for the IS-Repetitive Motor Behaviours relationship. Male sex was significantly associated with higher ratings for Repetitive Motor

Behaviours, with small effect sizes and a lack of statistical significance observed for both Insistence on Sameness and Circumscribed Interests. The lack of significant relationship between sex and Circumscribed Interests is particularly interesting to consider given that this RRB domain can be atypical in terms of content, focus and intensity and focusing on only one of these aspects can result on either over- or under-estimation of sex differences. A study by Sutherland et al. (2017) is particularly informative in this regard given that while they did not find sex differences in terms of Circumscribed Interests frequency, which is consistent with findings reported here, differences were present in terms of Circumscribed Interests content. Therefore, future research with comprehensive assessment of Circumscribed Interests domain are needed to further clarify and characterize this RRB domain.

Associations with CA, FSIQ and ADHD suggested somewhat distinctive patterns—while Insistence on Sameness and Repetitive Motor Behaviours ratings were significantly related to older age and higher FSIQ, the opposite was the case for Circumscribed Interests. Comorbid ADHD was significantly associated with a higher rating for Insistence on Sameness and Repetitive Motor Behaviours but was not significantly related to Circumscribed Interests. We further conducted a series of exploratory analyses to provide a more detailed understanding of the relationship between FSIQ and RRB domains across different age periods. For Circumscribed Interests, the magnitude of the significant negative association between CA and FSIQ was larger for the individuals aged 13 years and older than for the younger group. The relationship between Insistence on Sameness and FSIQ across ages was more complex, with both females and males showing the magnitude of the effect for the Insistence on Sameness-FSIQ relationship being smallest and not significant in the 7 to 12 year-old cohort for females and 13+ cohort for males, and largest in magnitude and significant in the 4-6 year-old females and the 0-3 year-old males.

The positive significant association identified in this study between Insistence on Sameness with age and FSIQ aligns with the conceptualization of this RRB domain as higher order domain and with findings from both longitudinal and cross-sectional studies (Bishop et al., 2006; Richler et al., 2010). Based on the fact that during normative development, occurrence and rise in Insistence on Sameness tend to be concomitant with the occurrence of normative fears (Evans et al., 1999) it has been suggested that Insistence on Sameness serves as an early form of self-regulation by exerting control, constraining the environment thus limiting unpredictability, and reducing normative fears (Uljarević et al., 2017a; Uljarević & Evans, 2017; Uljarević et al., 2019). Normative fears occur at earlier stages of typical development, and, unlike clinical anxiety, are transitory in nature (Gullone, 2000). Therefore, it is not surprising that in our study, the magnitude of the effect between FSIQ and Insistence on Sameness changed across different age groups. Contrary to our findings, Richler et al. (2010) reported no evidence of an IQ-Insistence on Sameness association at age 2 nor the influence of IQ on subsequent change in Insistence on Sameness scores over time, however, this study focused on only effects of non-verbal IQ (NVIQ) and therefore did not tap into more symbolic levels of development.

Although empirical findings thus far have been largely inconsistent, with studies showing both negative (Bishop et al., 2006; Esbensen et al., 2009) and non-significant associations (Hus et al., 2007; South et al., 2005) of Repetitive Motor Behaviours with CA and FSIQ; no studies to date have reported significant positive association. Compared to Insistence on Sameness and Repetitive Motor Behaviours, the Circumscribed Interests domain has been under-researched, with studies reporting both a positive (Bishop et al., 2013) and the lack (Lam et al., 2008; South et al., 2005) relationship of Circumscribed Interests with CA and IQ. To our knowledge, no studies have reported a significant negative relationship. However, it is important to have in mind the nature of the WA ASD Register

dataset. More specifically, this study is rare in the sense that it records age at diagnosis and data is standardised to the time of diagnosis. Therefore, some of the inconsistencies, when compared to previous studies, could be related to presenting factors at the age of diagnosis. For example, children tend to be diagnosed earlier due to language delay and social-communication difficulties, rather than specific concerns with regard to RRB, and these issues might override other signs. Therefore, it is possible that, for the children who are diagnosed earlier in life, the relationship between RRB and FSIQ noted at the time of diagnosis will change when they are older. For instance, it is possible that children who are referred to diagnostic evaluation at younger age might exhibit Circumscribed Interests that are either more unusual in terms of their content or more intense (or both) and that children who are referred later (and have higher FSIQ) exhibit Circumscribed Interests that are either less unusual in their content or their intensity or have learned to camouflage them in particular contexts.

Our findings suggest that the severity of communication deficits provided stronger prediction for Circumscribed Interests as opposed to Insistence on Sameness and Repetitive Motor Behaviours. The severity of social impairments was a significant predictor of all three RRB domains. While several studies have indicated a positive relationship between the degree of social and communication impairments, and frequency and severity of both Repetitive Motor Behaviours (Hus et al., 2007; Lam et al., 2008; Szatmari et al., 2006) and Insistence on Sameness (Cannon et al., 2010; Lam et al., 2008), other studies have found either no association (Harrop et al., 2014) or even a negative relationship (Richler et al., 2010). The Circumscribed Interests factor was not related to other core ASD traits in a study by Lam and colleagues (2008).

When considering what mechanisms account for the association of RRB domains with social and communication impairments, it is important to take into account

developmental trajectory and the functions of RRB domains during normative development. Normative Repetitive Motor Behaviours and Insistence on Sameness are suggested to play adaptive roles during development with Repetitive Motor Behaviours being associated with neuromuscular development (Thelen, 1979; Uljarević et al., 2017c) and Insistence on Sameness, as already noted, acting as a means of limiting unpredictability and reducing ensuing fears (Laing et al., 2009; Leekam et al., 2011; Uljarević et al., 2017a; Uljarević et al., 2019). Although Repetitive Motor Behaviours and Insistence on Sameness are adaptive during early development, if they persist, they may negatively influence subsequent development (Larkin et al., 2017; Leekam et al., 2011). For instance, Insistence on Sameness serve to regulate and reduce stress via constraining the unpredictability of environment, however, if elevated and persistent, they may also reduce exposure to situations conducive to learning and socio-emotional development (Leekam et al., 2011; Uljarević et al., 2017a). Similarly, intensity and inability to inhibit Circumscribed Interests can limit child's involvement in other activities, and interfere with learning and the formation of social relationships. This is supported by our findings that both Insistence on Sameness and Circumscribed Interests were related to greater social problems and that Circumscribed Interests was related to greater communication problems. When considering the dynamics of the relationships between RRB and social and communication impairments, two additional scenarios are also possible. Firstly, children with more severe levels of social and communicative impairments have a lower likelihood of being exposed to novel situations that are conducive to the development of flexible patterns of behaviours and interests. Secondly, it may also be the case that lower social motivation and lower social engagement lead individuals to be more focused on internal stimuli and stimulation, be more rigid and insistent on sameness, and prefer Circumscribed Interests to other forms of engagement, or it might be

a combination of both processes. Future longitudinal research is needed to address questions raised above as they have direct implications for the conceptualization of ASD as a disorder.

Our study focused on using a large, well-characterized sample of individuals with ASD to explore evidence for Repetitive Motor Behaviours, Insistence on Sameness and Circumscribed Interests as distinct RRB domains. However, despite the strengths of the sample, it is important to acknowledge the limitations and limited range of the RRB assessment utilized in this study. While attempts have been made to standardise severity ratings amongst diagnosticians within Western Australia (through quarterly standardisation meetings), it is possible that inter-rater variability influenced the findings. RRB clinician ratings utilized in this project were associated with RRB scores from ADOS and ADI-R. However, the strength of associations was small to moderate which can be explained by the lack of variability in both clinician ratings and ADOS RRB score, as well as by the fact that both ADOS and ADI-R provided total, rather than more fine-grained subscale scores. Further, numbers of participants with ADI-R and ADOS data was small. The range for each of the items and the conclusions are further limited by the very nature of the sample. More specifically, the cohort examined here consisted of individuals diagnosed with ASD, therefore, majority of them would have exhibited symptoms within at least one of the RRB domain, and therefore further restricting the *variability* in RRB scores. Despite this limitation, varied relationships both with RRB measures and with RRB measures and other outcomes were observed; nevertheless, this limitation needs to be considered when interpreting the pattern of findings reported here. Due to the design of the data collection from clinicians, long data collection period (1999-2014) and large number of clinicians involved, it was not possible to formally explore the presence of systematic differences in clinicians' ratings, a limitation that is important to consider. ASD diagnosticians are encouraged to attend quarterly meetings to discuss diagnostic issues and recommendations

for diagnostic practices, including standarisation of the severity ratings, however, the rates of diagnosticians that attend these meetings is not available. It is important however to emphasize that while attendance at meetings is variable, the diagnostic process and pathways to services in WA is modelled on the formal recommendations of the group on behalf of all ASD diagnosticians and must be adhered to by those conducting diagnostic assessments. Finally, this study was restricted to the ratings of the DSM-IV-TR criteria. Repetitive Motor Behaviours, Insistence on Sameness and Circumscribed Interests RRB subdomains have remained unchanged across DSM-IV-TR and DSM-5 diagnostic systems, however, DSM-5 criteria explicitly requires the presence of RRB for the ASD diagnosis which was not the case in DSM-IV-TR. Given that the data reported here were collected at the time of diagnosis, it will be important to further explore whether the inter-relationship between RRB subdomains with social and communication aspects of ASD phenotype might to some extent differ for individuals diagnosed across these two incarnations of the international diagnostic systems.

Regardless of the measurement limitations, findings reported here provide further support to the proposal about the potential utility of RRB domains for stratifying the larger ASD population into smaller, more phenotypically homogenous subgroups that can help to facilitate efforts to understand diverse ASD etiology and inform the design of future interventions. Development of targeted and effective interventions of RRB is a particular priority given that certain RRB can have negative impact on certain aspects of functioning and the current lack of dedicated treatment options (Harrop, 2015; Grahame et al., 2015). However, it is also important to point out that not all RRB require treatment. Indeed recent papers utilizing focus group format suggest that individuals with ASD perceive that certain RRB can serve a range of important functions including reducing external stimuli and coping with stress (Joyce, Honey, Leekam, Barrett, & Rodgers, 2017; .Kapp et al., 2019; Manor-Binyamini & Schreiber-Divon, 2019). The pattern of associations identified in this study

provides tentative evidence for the distinctiveness of Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests and lends support to the notion that interventions should target specific RRB. This is further supported by the relatively recent small scale, pilot Randomised Controlled Trial of a parent group intervention by Grahame and colleagues (2015) which reported that for instance targeting Circumscribed Interests had a positive impact on that particular RRB domain but not on Repetitive Motor Behaviours. Further, as noted, existing evidence suggests that elevated anxiety and impaired cognitive control are related to IS but not Repetitive Motor Behaviours (Lidstone, Uljarević et al., 2014; Uljarević et al., 2017a; Uljarević et al., 2019) indicating that targeting anxiety and impaired self-regulation might be a viable mechanisms for reducing Insistence on Sameness but not Repetitive Motor Behaviours. Since RRB represent dimensional traits that intersect a wide range of neurodevelopmental and neuropsychiatric disorders and extend well into the general population (Evans et al., 2017; Leekam et al., 2011; Uljarević et al., 2017b; Uljarević et al., 2019) it will be important for future studies to explore evidence for the distinctiveness of RRB domains across both typical development and disorders using sensitive and comprehensive RRB measures such as the Repetitive Behaviour Questionnaire-2 (RBQ-2; Barrett et al., 2015) and the Childhood Routines Inventory-Revised (Evans et al., 2017).

Key Points:

- Restricted and repetitive pattern of behaviours (RRB) are a cardinal feature of autism spectrum disorder (ASD), but there remains uncertainty about how these diverse behaviours vary according to individual characteristics.
- This study utilized an internationally unique prospective state-wide cohort to provide the most comprehensive exploration to date of whether Repetitive Motor Behaviours , Insistence on Sameness and Circumscribed Interests RRB domains can be distinguished based on their patterns of associations with other individual characteristics.
- When considering the pattern of associations of RRB with other subject characteristics identified in this study, there was suggestive evidence that Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests were differently related to sex, CA, FSIQ, social and communication deficits and ADHD.
- The pattern of associations identified in this study provides suggestive evidence for the distinctiveness of Repetitive Motor Behaviours, Insistence on Sameness, and Circumscribed Interests, suggesting the potential utility of RRB domains for stratifying the larger ASD population into smaller, more phenotypically homogeneous subgroups that can help to facilitate efforts to understand diverse ASD etiology and inform design of future interventions.

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Acknowledgments: Research reported in this study was supported by the National Health and Medical Research Council Senior Research Fellowship to author AJOW (APP1077966). MU is currently supported by the Discovery Early Career Researcher Award from the Australian Research Council (DE180100632).

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Table 1. Overview of cohort characteristics

Variable	All participants* (n=3647)	Participants with IQ data* (n=1554)	Participants without IQ data (n=2093)
Age diagnosed	6.56 (4.7)	7.06 (4.4)	6.20 (4.9)
Comorbid ADHD	406 (11.0%)	231 (14.8%)	175 (8.3%)
Full-Scale IQ*		82.70 (22.2)	
Low IQ**		451 (28.8%)	
Sex (Male)	3007 (82.3%)	1282 (82.4%)	1725 (82.2%)
Year diagnosed	2007 (4.0)	2006 (3.5)	2008 (4.2)
CI			
0	829 (22.5%)	427 (27.3%)	402 (19.0%)
1	907 (24.6%)	412 (26.3%)	495 (23.4%)
2	1855 (50.4%)	691 (44.2%)	1164 (55.0%)
3	89 (2.4%)	34 (2.2%)	55 (2.6%)
IS			
0	1161 (31.5%)	435 (27.8%)	726 (34.3%)
1	994 (27.0%)	386 (24.7%)	608 (28.7%)
2	1431 (38.9%)	697 (44.6%)	734 (34.7%)
3	94 (2.6%)	46 (2.9%)	48 (2.3%)
RMB			
0	684 (18.6%)	293 (18.7%)	391 (18.5%)
1	1020 (27.7%)	378 (24.2%)	642 (30.3%)
2	1853 (50.4%)	820 (52.4%)	1033 (48.8%)
3	123 (3.3%)	73 (4.7%)	50 (2.4%)

Note: * Full-Scale IQ data was only available for a sub-group of the study's cohort; ** Defined as a FSIQ score <70; ADHD: Attention deficit hyperactivity disorder; CI, Circumscribed Interests; IS, Insistence on Sameness; RMB, Repetitive Motor Behaviours.

Table 2a. Circumscribed Interests severity ratings for ASD diagnoses by age and sex.

	Ratings	0-3 Years	4-6 Years	7-12 Years	13+ years
Female	**0**	18.36%	23.04%	23.95%	20.78%
	1	22.22%	24.08%	31.14%	24.68%
	2	54.11%	49.21%	41.92%	53.25%
	3	5.31%	3.66%	2.99%	1.30%
Male	**0**	15.61%	23.20%	26.64%	31.65%
	1	23.58%	26.29%	23.81%	22.30%
	2	57.34%	48.76%	48.30%	43.88%
	3	3.47%	1.75%	1.25%	2.16%

Table 2b. Circumscribed Interests severity ratings for ASD diagnoses (without intellectual disability) by age and sex.

	Ratings	0-6 Years	6-12 Years	13+ years
Female	**0**	26.09%	26.56%	24.0%
	1	29.35%	31.25%	28.0%
	2	39.13%	34.38%	48.0%
	3	5.43%	7.81%	0%
Male	**0**	30.13%	31.48%	37.39%
	1	29.02%	26.74%	20.87%
	2	38.84%	40.67%	38.26%
	3	2.01%	1.11%	3.48%

Table 2c. Circumscribed Interests severity ratings for ASD diagnoses (with intellectual disability) by age and sex.

	Ratings	0-6 Years	6-12 Years	13+ years
Female	**0**	23.19%	14.29%	12.50%
	1	23.19%	35.71%	37.50%
	2	50.72%	50.0%	37.50%
	3	2.90%	0%	12.50%
Male	**0**	16.67%	25.0%	21.21%
	1	24.24%	15.0%	18.18%
	2	58.71%	56.67%	57.78%
	3	0.38%	3.33%	3.03%

Figure 1: Heat map of RRB rating concordance, for each RRB pair by sex.

Note: Concordance between RRB ratings is characterized by Kendall's tau coefficient; CI: Circumscribed Interests; IS: Insistence on Sameness; RMB: Repetitive Motor Behaviours; RRB: Restricted and Repetitive behaviours.

Figure 2: Violin plot showing the distribution of Full Scale IQ for each RRB by sex

Note: CI: Circumscribed Interests; IS: Insistence on Sameness; RMB: Repetitive Motor Behaviours; RRB: Restricted and Repetitive behaviours.

Figure 3: Plot showing regression line (from a two-stage spline fit) for RRB score against age at Autism diagnosis

Note: CI: Circumscribed Interests; IS: Insistence on Sameness; RMB: Repetitive Motor Behaviours; RRB: Restricted and Repetitive behaviours. Lines are generated from a two-stage linear spline model, with a split at age 8 years; grey bands represent 95% confidence interval; truncated beyond age 30 years to due to sparse data.

Figure 4: Plot showing the distribution of Full Scale IQ against each RRB by sex and age of diagnosis category

Note: CI: Circumscribed Interests; IS: Insistence on Sameness; RMB: Repetitive Motor Behaviours; RRB: Restricted and Repetitive behaviours.