Title

Interrelationship Between Cognitive Control, Anxiety, and Restricted and Repetitive Behaviors in Children with 22q11.2 Deletion Syndrome.

Journal

Autism Research, 12(12)

Authors

Uljarević, Mirko
McCabe, Kathryn
Angkustsiri, Kathleen
et al.

Publication Date

2019-12-01

DOI

10.1002/aur.2194

Peer reviewed

HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Autism Res. 2019 December ; 12(12): 1737–1744. doi:10.1002/aur.2194.

Interrelationship Between Cognitive Control, Anxiety, and Restricted and Repetitive Behaviors in Children with 22q11.2 Deletion Syndrome

Mirko Uljarević, **Kathryn L. McCabe**, **Kathleen Angkustsiri**, **Tony J. Simon**, **Antonio Y. Hardan**

Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California (M.U., A.Y.H.); Melbourne School of Psychological Sciences, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia (M.U.); Department of Psychiatry and Behavioral Sciences, University of California, Davis, California (K.L.M., T.J.S.); MIND (Medical Investigation of Neurodevelopmental Disorders) Institute, University of California, Davis, California (K.L.M., K.A., T.J.S.); Department of Pediatrics, University of California, Davis, Sacramento, California (K.A.)

Abstract

Restricted and repetitive behaviors (RRB) are common in individuals with 22q11.2 microdeletion syndrome (22q11.2DS), yet the underlying mechanisms of these behaviors remain poorly characterized. In the present pilot investigation, we aimed to further our understanding of RRB in 22q11.2DS by exploring their relationship with cognitive control and anxiety as well as with sex, chronological age, and full-scale IQ. Parents of 38 children with 22q11.2DS (17 females; M_{age} = 11.15 years, SD = 2.46) completed the Social Communication Questionnaire as a measure of RRB and social and communication (SC) problems and the Behavioral Assessment System for Children-2 as a measure of anxiety and cognitive control. Higher RRB scores were significantly associated with higher anxiety levels (r = 0.44, P = 0.006), more impairments in cognitive control (r = 0.56, P < 0.001), and higher SC scores (r = 0.43, P = 0.011). In the first step of the hierarchical regression model, anxiety accounted for 24.5% of variance (F = 10.05, P = 0.003); cognitive control accounted for an additional 18.1% of variance ($Fchange$ = 11.15, P < 0.001) in the second step; SC score accounted for only 0.8% of additional variance in the third step ($Fchange$ = 0.40, P = 0.53). The final model explained 43.4% of variance (F = 7.42, P = 0.001), with cognitive control as a unique independent predictor of RRB score (t = 2.52, P = 0.01). The current study provides the first exploration of the cognitive control—anxiety—RRB link in individuals with 22q11.2DS and points to cognitive control as a potentially viable target for treatments aimed at reducing RRB.

Lay Summary:

Address for correspondence and reprints: Mirko Uljarević, Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305-5719. mirkoulj@stanford.edu.

Conflict of Interest

The authors declare that they have no conflict of interests to declare.

People with 22q11.2 deletion syndrome show high levels of repetitive behaviors, however, the previous research has not explored why people with this syndrome exhibit high rates of repetitive behaviors. Understanding the reasons for the high levels of repetitive behaviors is important given that these behaviors can be highly impairing. Our study found that repetitive behaviors were associated with impaired ability to self-regulate and high levels of anxiety. These findings need to be further replicated; however, they are important as they suggest potentially promising ways of reducing these behaviors.

Keywords

22q11.2DS; repetitive behaviors; anxiety; cognitive control

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS) results from a microdeletion of a segment of chromosome 22 at the q11.2 band, which affects approximately 40–50 genes [Shapiro, Tassone, Choudhary, & Simon, 2014]. 22q11.2DS occurs in approximately one in every 3,000–6,000 live births [Grati et al., 2015]. The phenotype of 22q11.2 is highly variable encompassing physical, metabolic, and endocrine as well as behavioral and cognitive features. Physical phenotype of 22q11.2DS is characterized by a wide range of features including congenital heart, palatal and pharyngeal abnormalities, mild facial dysmorphism, skeletal anomalies, immune deficiency, and hypoparathyroidism with resultant hypocalcemia [Shprintzen, 2008]. At least 40% of individuals with 22q11.2DS are diagnosed with a neurodevelopmental and/or neuropsychiatric disorders, with schizophrenia, anxiety disorders, attention-deficit hyperactivity disorder, autism spectrum disorder (ASD), and obsessive–compulsive disorder being the most common [Schneider et al., 2014]. Importantly, even when symptom presentations and severity do not reach the diagnostic threshold, they can still significantly impair functioning [Esterberg, Ousley, Cubells, & Walker, 2013; Kates et al., 2007; Tang et al., 2014]. Therefore, over-reliance on the diagnostic categories can lead to clinically meaningful symptoms being discounted. In addition, individuals classified under separate diagnostic categories can exhibit a range of shared symptoms, while those diagnosed with the same disorder can exhibit different deficits [Antshel et al., 2006; Kates, Tang, Antshel, & Fremont, 2015; Niklasson, Rasmussen, Oskarsdóttir, & Gillberg, 2009]. In line with the current dimensional psychopathology frameworks such as the Research Domain Criteria [RDoC; Insel et al., 2010], it has been suggested that focusing on symptom domains that cut across different categorically defined disorders and their underlying mechanisms is one potentially fruitful approach for better understanding of the diverse and variable phenotypic manifestations that characterize 22q11.2DS [Baker & Vorstman, 2012; Biswas & Furniss, 2016]. In this investigation, we focus on one such symptom domain—restricted and repetitive behaviors (RRB) that has been reported to be common in 22q11.2DS population, irrespective of the primary diagnosis [Kates et al., 2007; Ousley et al., 2017; Serur et al., 2019], yet remains poorly characterized in terms of underlying mechanisms.

RRB are one of the core diagnostic features of ASD, however, they are not specific to ASD but are also prevalent across a range of other disorders and genetic syndromes [Moss, Oliver, Arron, Burbridge, & Berg, 2009] where they cannot be fully accounted for by either the potential presence of ASD or intellectual disability [Janes, Riby, & Rodgers, 2013; Rodgers, Riby, Janes, Connolly, & McConachie, 2012; Waite et al., 2015]. Importantly, RRB also occur in young typically developing children [Arnott et al., 2010; Evans et al., 1997; Leekam et al., 2007; Uljarević et al., 2017]. Emergence, increase and decrease of RRB during normative development, is paralleled by the trajectory of normative fears and anxieties [Brooker et al., 2014; Evans, Gray, & Leckman, 1999; Gullone, 2000] suggesting that certain RRB serve to constrain the unpredictability of the environment and to ward off fears and anxieties [Evans et al., 1999; Gesell, Ames, & Ilg, 1974; Leekam, Prior, & Uljarević, 2011; Zohar & Felz, 2001]. The developmental period when both RRB and normative fears/anxieties start to reduce in frequency and severity corresponds to the development of different facets of cognitive control such as attentional control, inhibition of dominant and activation of subdominant responses and the ability to shift between multiple tasks and/or mental sets. Cognitive control develops gradually, becoming progressively more advanced and complex from early toddlerhood to the school years and beyond [Bridgett, Oddi, Laake, Murdock, & Bachmann, 2013; Zelazo et al., 2003; Zhou, Chen, & Main, 2011]. Based on these developmental trends, it was suggested [Evans, Lewis, & Iobst, 2004; Uljarević & Evans, 2017; Uljarević, Richdale, Cai, Evans, & Leekam, 2017] that as self-regulation capacities develop, children rely less on RRB behaviors for managing fears. On the other hand, in disorders such as ASD, where delays in impairments in cognitive control are well established [Hill, 2004; Poljac & Bekkering, 2012; Solomon, Ozonoff, Cummings, & Carter, 2008], RRB continue to persist, but given their inflexible nature they are ineffective in reducing anxiety and might lead to its worsening. Indeed, in ASD, (a) anxiety is highly prevalent across the life-span [Lever & Geurts, 2016; van Steensel, Bogels, & Perrin, 2011; Uljarević et al., 2019; White, Oswald, Ollendick, & Scahill, 2009] and associated with elevated RRB levels [Lidstone et al., 2014; Rodgers et al., 2012], (b) poor cognitive control is separately associated with both elevated anxiety [Hollocks et al., 2014; Schwartz et al., 2009; Wallace et al., 2016] and RRB [Boyd, McBee, Holtzclaw, Baranek, & Bodfish, 2009; Lopez, Lincoln, Ozonoff, & Lai, 2005; Mostert-Kerckhoffs, Staal, Houben, & de Jonge, 2015; South et al., 2007], and (c) a recent study by Uljarević, et al. [2017] found that the relationship between RRB and anxiety is mediated by poor cognitive control.

Given that both anxiety and cognitive control are transdiagnostic processes that vary across both normative and clinical populations and have been explicitly described within the RDoC framework, their role in relation to RRB is unlikely to be constrained or specific to ASD but rather to be generalizable to other disorders that exhibit impairments across these two domains. Anxiety is highly prevalent in 22q11.2DS with at least 35% of children and adolescents and around 30% of adults having a clinical diagnosis and an additional percentage of individuals showing elevated symptoms [Schneider et al., 2014; see Kates et al., 2015 for recent overview]. It has been reported that individuals with 22q11.2DS consistently perform more poorly than typically developing controls on a range of tasks taping into different aspects of cognitive control [Antshel et al., 2010; Campbell et al., 2010; McCabe et al., 2014; Shapiro et al., 2014; Maeder et al., 2016] and these impairments have

been found to be predictive of poor social skills, adaptive functioning, positive symptoms of psychosis, and externalizing problems [Albert, Abu-Ramadan, Kates, Fremont, & Anthsel, 2018; Kiley-Brabeck & Sobin, 2006]. Surprisingly, to our knowledge, no studies to date have investigated the relationship between cognitive control and anxiety with RRB in 22q11.2DS. Therefore, our study aimed to characterize this interrelationship and further explore whether cognitive control and anxiety predict RRB levels over and above the influence of IQ and the presence of social and communication deficits.

Methods

Participants

Thirty-eight individuals with molecularly confirmed 22q11.2DS and their parents took part in the study (17 females; M_{age} = 11.15 years, SD = 2.46). Participants were recruited through the UC Davis MIND Institute, postings on online discussion groups, foundation newsletters, and by word of mouth. Twenty-nine participants completed the Wechsler Intelligence Scale for Children—4th edition [Wechsler, 2003] and four completed the Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999]. This research study was approved by the Institutional Review Board at the UC Davis. The parents of all participants provided written informed consent. See Table 1 for the descriptive statistics of the sample.

Procedures and Measures

The social communication questionnaire.—The social communication questionnaire [SCQ; Rutter, Bailey, & Lord, 2003] is a 40-item parent-report questionnaire designed to index the severity of impairments in social, communication, and repetitive behavior domains. It was originally suggested [Berument, Rutter, Lord, Pickles, & Bailey, 1999] that a cutoff score of 15 represents an optimal balance between sensitivity (0.85) and specificity (0.75) when screening for ASD, however, a recent meta-analysis by Chesnut, Wei, Barnard-Brak, and Richman [2017] suggests a cutoff score of 11 as more optimal (area under the curve = 0.885). Both the cutoff of 11 and 15 were used in this article.

The behavioral assessment system for children-2 (BASC-2; Reynolds & Kamphaus, 2004).—The behavioral assessment system for children-2 (BASC-2) is a parent report measure that provides an assessment of clinical and adaptive aspects of behavior. The clinically relevant items are grouped into the following eight specific clinical scales: aggression, anxiety, attention problems, atypicality, depression, hyperactivity, somatization, withdrawal, and the following three overarching clinical composite scores: externalizing problems, internalizing problems, and behavioral symptoms index. Adaptive items are grouped into activities of daily living, adaptability, functional communication, and social skills scales, which jointly constitute adaptive skills composite scale. For clinical scales, T scores between 60 and 69 are considered “at-risk” and scores ≥70 as “clinically significant.” Here, we focused on the anxiety scale and the executive functioning scale which assesses the ability to control behavior by planning, anticipating, inhibiting, or maintaining goal-directed activity as measures of anxiety and cognitive control, respectively [Karr & Garcia-Barrera, 2017].

Analysis Plan

Statistical analyses were conducted using the statistical package for the social sciences (SPSS v. 25.0, New York, NY). Pearson *r* and point bi-serial correlations were used to explore the associations between SCQ RRB scale with chronological age (CA), sex, FSIQ, BASC-2 anxiety and cognitive control scores, and SCQ Social and Communication score. Variables significantly associated with SCQ RRB score were then entered into the hierarchical regression model.

Results

Twenty-six percent of participants had SCQ total scores above the cutoff of 15 and 47.4% above the cutoff of 11. Thirty-four percent of participants had BASC-2 anxiety *T* scores in "at-risk" and a further 23.7% were in the "clinically significant" range. The RRB domains score of the SCQ were significantly associated with BASC-2 anxiety ($r = 0.44$, $P = 0.006$) and executive functioning ($r = 0.56$, $P < 0.001$) scores and with SCQ social and communication score ($r = 0.43$, $P = 0.011$). No significant association between SCQ RRB scores and CA, gender, and FSIQ was found. SCQ social and communication score was significantly associated with BASC-2 anxiety ($r = 0.37$, $P = 0.027$) and executive functioning ($r = 0.53$, $P = 0.001$). Table 2 shows the pattern of associations described above.

Before conducting regression, we looked for evidence of multicollinearity. The highest correlation was 0.56, significantly lower than the 0.7 suggested as the threshold by Tabachnick and Fidell [2014]. In addition, the highest Variance Inflation Factor value in the regression model was 1.53, significantly lower than suggested cutoffs of 5 [Sheather, 2009] or 10 [Kutner, Neter, Nachtsheim, & Li, 2004], further suggesting that multicollinearity was not a concern. Table 3 summarizes the hierarchical regression model exploring the predictors of SCQ RRB score. In the first step, BASC-2 anxiety score accounted for 24.5% of variance ($F = 10.05$, $P = 0.003$). In the second step, BASC-2 executive functioning score accounted for an additional 18.1% of variance ($Fchange = 11.15$, $P < 0.001$). Although anxiety was a significant predictor in step 1 ($t = 3.17$, $P = 0.003$), it was no longer an independent predictor in step 2 ($t = 1.75$, $P = 0.091$) after executive functioning was added ($t = 3.08$, $P = 0.004$). In the third step, SCQ social and communication score accounted for only 0.8% of additional variance ($Fchange = 0.40$, $P = 0.53$). The final model accounted for 43.4% of variance ($F = 7.42$, $P = 0.001$), with executive functioning as a unique independent predictor of SCQ RRB score ($t = 2.52$, $P = 0.01$).

Given that SCQ SC score was also associated with BASC-2 anxiety and depression, we conducted a follow-up regression model to explore the % of variance accounted by these variables. BASC-2 executive functioning and anxiety explained 29.4% of variance ($F = 5.13$, $P = 006$) with executive functioning providing unique significant contribution ($t = 2.49$, $P = 0.019$), however, once SCQ RRB score was entered in the regression model BASC-2 executive functioning score was no longer a significant predictor ($t = 1.83$, $P = 0.076$).

Discussion

This study aimed to further our understanding of RRB in 22q11.2DS by exploring their relationship with cognitive control and anxiety as well as with sex, CA, and full-scale IQ (FSIQ) in a sample of children and adolescents with this syndrome.

We first considered the relationship between the RRB and sex, CA and FSIQ and found no significant associations. Across both ASD and normative literature findings on the relationship between sex and RRB have been mixed, with no differences [Evans et al., 1997; Hus, Pickles, Cook, Risi, & Lord, 2007; Joseph, Thurm, Farmer, & Shumway, 2013; Lam, Bodfish, & Piven, 2008], higher levels in males [Arnott et al., 2010; Çevikaslan, Evans, Dedeoğlu, Kalaça, & Yazgan, 2014; Frazier & Hardan, 2017] or in females [Kim & Lord, 2010] being reported. When considering the lack of age and FSIQ effects on RRB two aspects are important to note. First, despite the lack of long-term longitudinal studies, existing findings suggest that the major of RRB age-related changes in ASD occur during early childhood when RRB steadily increase and then remain somewhat stable during later childhood and adolescence [Esbensen, Seltzer, Lam, & Bodfish, 2009; Richler, Huerta, Bishop, & Lord, 2010; South, Ozonoff, & McMahon, 2005]. Therefore, given that our sample included children aged 7–15, the lack of a significant association between CA and RRB is not surprising. Second, SCQ provides total RRB scores rather than separate ascertainment of the insistence on sameness and repetitive motor behavior domains, which have been shown to have a distinct pattern of associations with CA and FSIQ [Bishop et al., 2013; Cannon et al., 2010; Cuccaro et al., 2003]. Therefore, total score could have potentially masked some of these effects. Previous studies on RRB in 22q11.2DS have not explored the impact of sex, age, or FSIQ on RRB, and therefore it will be important for future research to further replicate findings reported here.

Consistent with the literature on RRB in ASD and other disorders [Lidstone et al., 2014; Janes et al., 2013; Rodgers et al., 2012; South et al., 2007], higher levels of anxiety and poor cognitive control were predictive of higher RRB scores. For example, individual variation in cognitive control has been linked with RRB across both normative [Pietrefesa & Evans, 2007; Peleg-Popko & Dar, 2003; Tregay, Gilmour, & Charman, 2009] and ASD samples [Mostert-Kerckhoffs et al., 2015; South et al., 2007] and with anxiety across both normative and clinical groups, including ASD [Eisenberg et al., 2009; Hollocks et al., 2014; Hughes & Ensor, 2011; Murray & Kochanska, 2002; Wallace et al., 2016]. Anxiety has been previously reported to be associated with RRB in typically developing individuals [Evans et al., 1999] as well as in individuals with Down Syndrome [Uljarević & Evans, 2017], ASD [Lidstone et al., 2014; Wigham, Rodgers, South, McConachie, & Freeston, 2015], and Williams Syndrome [Rodgers et al., 2012]. Finally, the only study to date to explore joint effects of cognitive control and anxiety on RRB in ASD [Uljarević et al., 2017] has found a similar pattern of findings as reported here. Importantly, although both anxiety and executive functioning deficits were also association with social and communication deficits as measured by the SCQ, the comparison between regression models indicated that anxiety and executive functioning accounted for significantly more variance in RRB than social and communicative impairments (42.6% vs. 29.4%).

Several study limitations are important to note. Although 22q11.2DS has relatively low prevalence and all analyses were supplemented with bootstrapped confidence intervals, findings reported here should be treated as preliminary given the small sample size. The SCQ is a well-validated screening measure for ASD sampling both social and communication impairments as well as the presence of RRB. However, as noted above, the SCQ only provides overall RRB score and does not allow for a more fine-grained sampling of different RRB domains such as repetitive motor behaviors and insistence on sameness that might have distinct underlying mechanisms [Langen, Durston, Kas, Van Engeland, & Staal, 2011; Leekam et al., 2011] nor for capturing of more subtle symptom expressions. This study was further limited by the cross-sectional design. Therefore, it is necessary to extend findings reported here and further characterize the dynamics of the cognitive control-anxiety-RRB interrelationship using the longitudinal designs and comprehensive and sensitive measures of RRB such as, for example, the Repetitive Behavior Scale-Revised [Bodfish, Symons, Parker, & Lewis, 2000] or the Repetitive Behavior Questionnaire-2 [Leekam et al., 2007; Barrett et al., 2015; Barrett, Uljarević, Jones, & Leekam, 2018] as well as multimodal assessments of cognitive control.

Despite the limitations, our pilot study provides a significant contribution by establishing for the first time the link between RRB with impaired cognitive control and anxiety in individuals with 22q11.2DS. It has been suggested [see Leekam et al., 2011; Uljarević, Richdale, et al., 2017 for an overview] that insistence on sameness behaviors, which serve as adaptive way of controlling the environment and warding of anxiety earlier in the development, if persistent, can limit exposure to new environments both directly and indirectly (through reinforcing anxiety) and thus deprive an individual from valuable learning opportunities that are necessary for the acquisition of a range of skills and adaptive strategies necessary for functioning across social, education, and vocational contexts. Therefore, the ability to reduce the insistence on sameness and to increase flexibility can have highly beneficial effects for improving daily life functioning of affected individuals. Given that effective treatment approaches targeting RRB across neurodevelopmental disorders are currently lacking [Grahame et al., 2015; NICE, 2013], findings reported in this study point to the centrality of the cognitive control domain as a candidate mechanism behind the RRB and therefore as a potentially viable target for treatments aimed at reducing these behaviors.

Acknowledgments

We would like to thank the study participants and their parents. The research reported in this article was supported by Grant R01HD042974 (Simon) by the National Institute of Health. Dr. Mirko Uljarević is currently supported by the Discovery Early Career Researcher Award from the Australian Research Council (DE180100632).

References

Albert AB, Abu-Ramadan T, Kates WR, Fremont W, & Anthsel KM (2018). Childhood executive functioning predicts young adult outcomes in 22q11.2 deletion syndrome. Journal of the International Neuropsychological Society, 24 (9), 905–916. [PubMed: 30375321]

Antshel KM, Aneja A, Strunge L, Peebles J, Fremont WP, Stallone K, … Kates WR (2006). Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). Journal of Autism and Developmental Disorders, 37(9), 1776–1786. [PubMed: 17180713]

Antshel KM, Shprintzen R, Fremont W, Higgins AM, Faraone SV, & Kates WR (2010). Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: A 3-year follow-up study. Journal of American Academy of Child and Adolescent Psychiatry, 49(4), 333–344.

Arnott B, McConachie H, Meins E, Fernyhough C, Le Couteur A, Turner M, … Leekam S (2010). The frequency of restricted and repetitive behaviors in a community sample of 15-month old infants. Journal of Developmental and Behavioral Pediatrics, 31, 223–229. [PubMed: 20375735]

Baker K, & Vorstman JA (2012). Is there a core neuropsychiatric phenotype in 22q11.2 deletion syndrome? Current Opinion in Neurology, 25(2), 131–137. [PubMed: 22395003]

Barrett SL, Uljarević M, Baker EK, Richdale AL, Jones CRG, & Leekam SR (2015). The Adult Repetitive Behaviours Questionnaire-2 (RBQ-2A): A self-report measure of restricted and repetitive behaviours. Journal of Autism and Developmental Disorders, 45(11), 3680–3692. [PubMed: 26155763]

Barrett SL, Uljarević M, Jones CRG, & Leekam SR (2018). Assessing the two subtypes of the Adult Repetitive Behaviour Questionnaire – 2 in autistic adults. Molecular Autism, 9(1), 58. [PubMed: 30505424]

Berument SK, Rutter M, Lord C, Pickles A, & Bailey A (1999). Autism screening questionnaire: Diagnostic validity. British Journal of Psychiatry, 175, 444–451. [PubMed: 10789276]

Bishop SL, Hus V, Duncan A, Huerta M, Gotham K, Pickles A, … Lord C (2013). Subcategories of restricted and repetitive behaviors in children with autism spectrum disorders. Journal of Autism and Developmental Disorders, 43(6), 1287–1297. [PubMed: 23065116]

Biswas AB, & Furniss F (2016). Cognitive phenotype and psychiatric disorder in 22q11.2 deletion syndrome: A review. Research in Developmental Disabilities, 53-54, 242–257.

Bodfish JW, Symons FJ, Parker DE, & Lewis MH (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. Journal of Autism and Developmental Disorders, 30, 237–243. [PubMed: 11055459]

Boyd BA, McBee M, Holtzclaw T, Baranek GT, & Bodfish JW (2009). Relationships among repetitive behaviors, sensory features, and executive functions in high functioning autism. Research in Autism Spectrum Disorders, 3(4), 959–966. [PubMed: 21475640]

Bridgett DJ, Oddi KB, Laake LM, Murdock KW, & Bachmann MN (2013). Integrating and differentiating aspects of self-regulation: Effortful control, executive functioning, and links to negative affectivity. Emotion, 13, 47–63. [PubMed: 22906086]

Brooker RJ, Buss KA, Lemery-Chalfant K, Aksan N, Davidson RJ, & Goldsmith HH (2014). The development of stranger fear in infancy and toddlerhood: Normative development, individual differences, antecedents, and outcomes. Developmental Science, 16, 864–878.

Campbell LE, Azuma R, Ambery F, Stevens A, Smith A, Morris RG, … Murphy KC (2010). Executive functions and memory abilities in children with 22q11.2 deletion syndrome. Australian and New Zealand Journal of Psychiatry, 44 (4), 364–371. [PubMed: 20307169]

Cannon DS, Miller JS, Robinson RJ, Villalobos ME, Wahmhoff NK, Allen-Brady K, … Coon H (2010). Genome-wide linkage analyses of two repetitive behaviors phenotypes in Utah pedigrees with autism spectrum disorders. Molecular Autism, 1(3), 1–13. [PubMed: 20678244]

Çevikaslan A, Evans DW, Dedeoğlu C, Kalaça S, & Yazgan Y (2014). A cross-sectional survey of repetitive behaviors and restricted interests in a typically developing Turkish child population. Child Psychiatry & Human Development, 45(4), 472–482. [PubMed: 24242356]

Chesnut SR, Wei T, Barnard-Brak L, & Richman DM (2017). A meta-analysis of the social communication questionnaire: Screening for autism spectrum disorder. Autism, 21(8), 920–928. [PubMed: 27503464]

Cuccaro ML, Shao YJ, Grubber J, Slifer M, Wolpert CM, Donnelly SL, … Pericak-Vance MA (2003). Factor analysis of restricted and repetitive behaviors in autism using the autism diagnostic interview-R. Child Psychiatry & Human Development, 34, 3–17. [PubMed: 14518620]

Eisenberg N, Valiente C, Spinrad TL, Cumberland AJ, Liew J, Reiser M, & Cumberland AJ (2009). Longitudinal relations of children's effortful control, impulsivity, and negative emotionality to their externalizing, internalizing, and co-occurring behavior problems. Developmental Psychology, 45(4), 988–1008. [PubMed: 19586175]

Esbensen AJ, Seltzer M, Lam K, & Bodfish JW (2009). Age-related differences in restricted repetitive behaviors in autism spectrum disorders. Journal of Autism and Developmental Disorders, 39, 57–66. [PubMed: 18566881]

Esterberg ML, Ousley OY, Cubells JF, & Walker EF (2013). Prodromal and autistic symptoms in schizotypal personality disorder and 22q11.2 deletion syndrome. Journal of Abnormal Psychology, 122(1), 238–249. [PubMed: 22686870]

Evans DW, Gray FL, & Leckman JF (1999). The rituals, fear and phobias of young children: Insights from development, psychopathology and neurobiology. Child Psychiatry and Human Development, 29, 261–276. [PubMed: 10422351]

Evans DW, Leckman JF, Carter A, Reznick JS, Henshaw D, King RA, & Pauls D (1997). Ritual, habit and perfectionism: The prevalence and development of compulsive-like behavior in normal young children. Child Development, 68, 58–68. [PubMed: 9084125]

Evans DW, Lewis MD, & Iobst E (2004). The role of the orbitofrontal cortex in normally developing compulsive-like behaviors and obsessive–compulsive disorder. Brain and Cognition, 55(1), 220–234. [PubMed: 15134855]

Frazier TW, & Hardan AY (2017). Equivalence of symptom dimensions in females and males with autism. Autism, 21(6), 749–759. [PubMed: 27503465]

Grahame V, Brett D, Dixon L, McConachie H, Lowry J, Rodgers J, & LeCouteur A (2015). Managing repetitive behaviours in young children with autism spectrum disorder (ASD): Pilot randomised controlled trial of a new parent group intervention. Journal of Autism and Developmental Disorders, 45(10), 3168–3182. [PubMed: 26036646]

Gesell A, Ames LB, & Ilg FL (1974). Infant and the child in culture today. New York, NY: Harper and Row.

Grati FR, Molina Gomes D, Ferreira JC, Dupont C, Alesi V, Gouas L, … Vialard F (2015). Prevalence of recurrent pathogenic microdeletions and microdup lications in over 9500 pregnancies. Prenatal Diagnosis, 35, 801–809. [PubMed: 25962607]

Gullone E (2000). The development of normal fear: A century of research. Clinical Psychology Review, 20, 429–451. [PubMed: 10832548]

Hill EL (2004). Evaluating the theory of executive dysfunction in autism. Developmental Reviews, 24(2), 189–233.

Hollocks M, Jones C, Pickles A, Baird G, Happe F, & Simonoff E (2014). The association between social cognition and executive functioning and symptoms of anxiety and depression in adolescents with autism spectrum disorders. Autism Research, 7(2), 216–228. [PubMed: 24737743]

Hughes C, & Ensor R (2011). Individual differences in growth in executive function across the transition to school predict externalizing and internalizing behaviors and children's self-perceived academic success at age 6. Journal of Experimental Child Psychology, 108, 663–676. [PubMed: 20673580]

Hus V, Pickles A, Cook EH, Risi S, & Lord C (2007). Using the Autism Diagnostic Interview–Revised to increase phenotypic homogeneity in genetic studies of autism. Biological Psychiatry, 61, 438–448. [PubMed: 17276746]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, … Wang P (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. American Journal of Psychiatry, 167(7), 748–751. [PubMed: 20595427]

Janes E, Riby DM, & Rodgers J (2013). Exploring the prevalence and phenomenology of repetitive behaviours and abnormal sensory processing in children with Williams Syndrome. Journal of Intellectual Disability Research, 58(8), 746–757. [PubMed: 23962322]

Joseph L, Thurm A, Farmer C, & Shumway S (2013). Repetitive behavior and restricted interests in young children with autism: Comparisons with controls and stability over two years. Autism Research, 6(6), 584–595. [PubMed: 23868881]

Karr JE, & Garcia-Barrera MA (2017). The assessment of executive functions using the BASC-2. Psychological Assessment, 29(9), 1182–1187. [PubMed: 27831727]

Kates WR, Antshel KM, Fremont WP, Shprintzen RJ, Strunge LA, Burnette CP, & Higgins AM (2007). Comparing phenotypes in patients with idiopathic autism to patients with velocardiofacial

syndrome (22q11 DS) with and without autism. American Journal of Medical Genetics A, 143A(22), 2642–2650.

Kates WR, Tang KL, Antshel KM, & Fremont WP (2015). Behavioral and psychiatric phenotypes in 22q11.2 deletion syndrome. Journal of Developmental and Behavioral Pediatrics, 36(8), 639–650. [PubMed: 26372046]

Kiley-Brabeck K, & Sobin C (2006). Social skills and executive function deficits in children with the 22q11 Deletion Syndrome. Applied Neuropsychology, 13(4), 258–268. [PubMed: 17362146]

Kim SH, & Lord C (2010). Restricted and repetitive behaviors in toddlers and preschoolers with autism spectrum disorders based on the autism diagnostic observation schedule (ADOS). Autism Research, 3, 162–173. [PubMed: 20589716]

Kutner MH, Neter J, Nachtsheim CJ, & Li W (2004). Applied linear statistical models (5th ed.). Boston: McGraw-Hill Irwin.

Lam KSL, Bodfish JW, & Piven J (2008). Evidence for three subtypes of repetitive behavior in autism that differ in familiality and association with other symptoms. Journal of Child Psychology and Psychiatry, 49, 1193–1200. [PubMed: 19017031]

Langen M, Durston S, Kas MJH, Van Engeland H, & Staal WG (2011). The neurobiology of repetitive behavior and men. Neuroscience and Biobehavioral Reviews, 35, 356–365. [PubMed: 20153769]

Leekam S, Tandos J, McConachie H, Meins E, Parkinson K, Wright C, … Couteur AL (2007). Repetitive behaviors in typically developing 2-year-olds. Journal of Child Psychology and Psychiatry, 48(11), 1131–1138. [PubMed: 17995489]

Leekam SR, Prior MR, & Uljarević M (2011). Restricted and repetitive behaviors in autism spectrum disorders: A review of research in the last decade. Psychological Bulletin, 137(4), 562–593. [PubMed: 21574682]

Lever A, & Geurts HM (2016). Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. Journal of Autism and Developmental Disorders, 46(6), 1916–1930. [PubMed: 26861713]

Lidstone J, Uljarević M, Sullivan J, Rodgers J, McConachie H, Freeston M, … Leekam S (2014). Relations among restricted and repetitive behaviours, anxiety and sensory symptoms in individuals with autism spectrum disorders. Research in Autism Spectrum Disorders, 8(2), 82–92.

Lopez BR, Lincoln AJ, Ozonoff S, & Lai Z (2005). Examining the relationship between executive functions and restricted, repetitive symptoms of autistic disorder. Journal of Autism and Developmental Disorders, 35(4), 445–460. [PubMed: 16134030]

Maeder J, Schneider M, Bostelmann M, Debbané M, Glaser B, Menghetti S, … Eliez S (2016). Developmental trajectories of executive functions in 22q11.2 deletion syndrome. Journal of Neurodevelopmental Disorders, 8, 10. [PubMed: 27018204]

McCabe KL, Atkinson RJ, Cooper G, Melville JL, Haris J, Schall U, … Campbell LE (2014). Pre-pulse inhibition and antisaccade performance indicate impaired attention modulation of cognitive inhibition in 22q11.2 deletion syndrome (22q11DS). Journal of Neurodevelopmental Disorders, 6(1), 38. [PubMed: 25279014]

Moss J, Oliver C, Arron K, Burbridge C, & Berg K (2009). The prevalence and phenomenology of repetitive behavior in genetic syndromes. Journal of Autism and Developmental Disorders, 39, 572–588. [PubMed: 19037716]

Mostert-Kerckhoffs MAL, Staal WG, Houben RH, & de Jonge MV (2015). Stop and change: Inhibition and flexibility skills are related to repetitive behavior in children and young adults with autism spectrum disorders. Journal of Autism and Developmental Disorders, 45(10), 3148–3588. [PubMed: 26043846]

Murray KT, & Kochanska G (2002). Effortful control: Relation to externalizing and internalizing behaviors and factor structure. Journal of Abnormal Child Psychology, 30, 503–514. [PubMed: 12403153]

National Institute for Health and Care Excellence. (2013). Autism: The management and support of children and young people on the autism spectrum. (Clinicalguidelines 170.)

Niklasson L, Rasmussen P, Oskarsdóttir S, & Gillberg C (2009). Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. Research in Developmental Disabilities, 30(4), 763–773. [PubMed: 19070990]

Ousley O, Evans AN, Fernandez-Cariba A, Smearman EL, Rockers K, Morrier MJ, … Cubells J (2017). Examining the overlap between autism spectrum disorder and 22q11.2 deletion syndrome. International Journal of Molecular Sciences, 18(5), 1071.

Peleg-Popko O, & Dar R (2003). Ritual behavior in children and mothers' perceptions of family patterns. Journal of Anxiety Disorders, 17(6), 667–681. [PubMed: 14624817]

Pietrefesa A, & Evans DW (2007). Affective and neuropsychological correlates of children's rituals and compulsive-like behaviors: Continuities and discontinuities with obsessive–compulsive disorder. Brain and Cognition, 65, 36–46. [PubMed: 17630062]

Poljac E, & Bekkering K (2012). A review of intentional and cognitive control in autism. Frontiers in Psychology, 5(3), 436.

Reynolds CR, & Kamphaus RW (2004). The behavioral assessment system for children (2nd ed.). Circle Pines, MN: American Guidance Service.

Richler J, Huerta M, Bishop SL, & Lord C (2010). Developmental trajectories of restricted and repetitive behaviors in children with autism spectrum disorders. Development and Psychopathology, 22, 55–69. [PubMed: 20102647]

Rodgers J, Riby DM, Janes E, Connolly B, & McConachie H (2012). Anxiety and repetitive behaviours in autism spectrum disorders and Williams syndrome: A cross-syndrome comparison. Journal of Autism and Developmental Disorders, 42, 175–180. [PubMed: 21424863]

Rutter M, Bailey A, & Lord C (2003). Social communication questionnaire (SCQ). Los Angeles: Western Psychological Services.

Schneider M, Debbané M, Bassett AS, Chow EW, Fung WL, van den Bree M, … International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: Results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. American Journal of Psychiatry, 171(6), 627–639. [PubMed: 24577245]

Schwartz CB, Henderson HA, Inge AP, Zahka NE, Coman DC, Kojkowski NM, … Mundy PC (2009). Temperament as a predictor of symptomatology and adaptive functioning in adolescents with high-functioning autism. Journal of Autism and Developmental Disorders, 39, 842–855. [PubMed: 19165586]

Serur Y, Frumer DS, Daon K, Sobol-Havia D, Weinberger R, Shulman C, & Gothelf D (2019). Psychiatric disorders and autism in young children with 22q11.2 deletion syndrome compared to children with idiopathic autism. European Psychiatry, 55, 116–121. [PubMed: 30453155]

Shapiro HM, Tassone F, Choudhary NS, & Simon TJ (2014). The development of cognitive control in children with chromosome 22q11.2 deletion syndrome. Frontiers in Psychology, 5, 566. [PubMed: 24959159]

Sheather S (2009). A modern approach to regression with R. New York: Springer Science & Business Media.

Shprintzen RJ (2008). Velo-cardio-facial syndrome: 30 years of study. Developmental Disabilities Research Reviews, 14(1), 3–10. [PubMed: 18636631]

Solomon M, Ozonoff SJ, Cummings N, & Carter CS (2008). Cognitive control in autism spectrum disorders. International Journal of Developmental Neuroscience, 26(2), 239–247. [PubMed: 18093787]

South M, Ozonoff S, & McMahon WM (2005). Repetitive behaviour profiles in Asperger syndrome and high-functioning autism. Journal of Autism and Developmental Disorders, 35, 145–158. [PubMed: 15909401]

South M, Ozonoff S, & McMahon WW (2007). The relationship between executive functioning, central coherence, and repetitive behaviors in the high-functioning autism spectrum. Autism, 11(5), 437–451. [PubMed: 17942457]

Tabachnick BG, & Fidell LS (2014). Using multivariate statistics (6th ed.). London: Pearson.

Tang SX, Yi JJ, Moore TM, Kohler CG, Whinna DA, Souders MC, … Gur RE (2014). Subthreshold psychotic symptoms in 22q11.2 deletion syndrome. Journal of American Academy of Child and Adolescent Psychiatry, 53(9), 991–1000.

Tregay J, Gilmour J, & Charman T (2009). Childhood rituals and executive functions. British Journal of Developmental Psychology, 27(2), 283–296. [PubMed: 19998532]

Uljarević M, Arnott B, Carrington SJ, Meins E, Fernyhough C, McConachie H, … Leekam SR (2017). Development of restricted and repetitive behaviors from 15 to 77 months: Stability of two distinct subtypes? Developmental Psychology, 53(10), 1859–1868. [PubMed: 28758781]

Uljarević M, & Evans DW (2017). Relationship between repetitive behaviours and fears across normative development, autism spectrum disorder and Down syndrome. Autism Research, 10(3), 502–507. [PubMed: 27459229]

Uljarević M, Nuske H, & Vivanti G (2016). Anxiety in autism spectrum disorder In Mazzone L & Vitiello B (Eds.), Psychiatric symptoms and comorbidities in autism spectrum disorder (pp. 21–38). Cham: Springer International Publishing.

Uljarević M, Richdale A, Cai RY, Evans DW, & Leekam SR (2017). Inter-relationship between insistence on sameness, effortful control and anxiety in adolescents and young adults with autism spectrum disorder (ASD). Molecular Autism, 8, 36. [PubMed: 28736608]

Uljarević M, Hedley D, Rose-Foley K, Magiati I, Cai R-Y, Dissanayake C, Richdale A, & Trollor J (2019). Anxiety and Depression from Adolescence to Old Age in Autism Spectrum Disorder. Journal of Autism and Developmental Disorders. 10.1007/s10803-019-04084-z

van Steensel FJ, Bogels SM, & Perrin S (2011). Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis. Clinical Child and Family Psychology, 14, 302–317.

Waite J, Moss J, Beck S, Richards C, Nelson L, Arron K, … Oliver C (2015). Repetitive behaviour in Rubinstein Taybi syndrome: Parallels with autism spectrum phenomenology. Journal of Autism and Development Disorders, 45, 1238–1253.

Wallace GL, Kenworthy L, Pugliese CE, Popal HS, White EI, Brodsky E, & Martin A (2016). Real-world executive functions in adults with autism spectrum disorder: profiles of impairment and associations with adaptive functioning and co-morbid anxiety and depression. Journal of Autism and Developmental Disorders, 46(3), 1071–1083. [PubMed: 26572659]

Wechsler D (1999). Wechsler abbreviated scale of intelligence (WASI). San Antonio, TX: Psychological Corporation.

Wechsler D (2003). Wechsler intelligence scale for children (4th ed.). San Antonia, TX: Psychological Corporation.

White SW, Oswald D, Ollendick T, & Scahill L (2009). Anxiety in children and adolescents with autism spectrum disorders. Clinical Psychology Review, 29, 216–229. [PubMed: 19223098]

Wigham S, Rodgers J, South M, McConachie H, & Freeston M (2015). The interplay between sensory processing abnormalities, intolerance of uncertainty, anxiety and restricted and repetitive behaviours in autism spectrum disorder. Journal of Autism and Development Disorders, 45 (4), 943–952.

Zelazo PD, Muller U, Frye D, Marcovitch S, Argitis S, Boseovski J, … Sutherland A (2003). The development of executive function in early childhood. Monographs of the Society for Research in Child Development, 68(3), vii–137.

Zhou Q, Chen SH, & Main A (2011). Commonalities and differences in the research on children's effortful control and executive function: A call for an integrated model of self-regulation. Child Development Perspectives, 6(2), 112–121.

Zohar AH, & Felz L (2001). Ritualistic behaviour in young children. Journal of Abnormal Child Psychology, 29, 121–128. [PubMed: 11321627]

Table 1.

Participant Characteristics

	Mean	*SD*
Age (years)	11.15	2.46
FSIQ*	68.50	16.86
SCQ total	10.31	7.50
SCQ RRB	2.26	2.11
SCQ SC	7.65	6.41
BASC-2 anxiety	61.16	14.98
BASC-2 executive functioning	66.11	10.60

Note.

*data available for *N* = 33 participants; BASC-2: The Behavioral Assessment System for Children-2; FSIQ: Full-Scale IQ; RRB: restricted and repetitive behaviors; SC: Social and Communication; SCQ: Social Communication Questionnaire.

Table 2.

Correlations Between Variables of Interest

	SCQ RRB	CA	Sex	SCQ SC
SCQ RRB	1	−0.22	−0.06	0.43 *
FSIQ	0.02	−0.04	0.15	−0.12
BASC-2 executive functioning	0.56 **	−0.40 *	−0.007	0.53 **
BASC-2 anxiety	0.44 **	−0.13	0.07	0.37 *

Note.

* $P < 0.05$;

** $P < 0.01$; BASC-2: The Behavioral Assessment System for Children-2; CA: Chronological Age; FSIQ: Full-scale IQ; RRB: restricted and repetitive behaviors; SC: Social and Communication; SCQ: Social Communication Questionnaire.

Table 3.

Hierarchical Regression

	R2Δ	R2Δ change	*B*	SEB	*β*	BCa 95% CI
Step 1	0.245**					
Constant			−1.98	1.35		
BASC-2 Anxiety			0.067	0.021	0.495	0.024; 0.110
Step 2	0.426**	0.181**				
Constant			−5.967	1.762		
BASC-2 anxiety			0.037	0.021	0.272	−0.006; 0.080
BASC-2 executive functioning			0.089	0.029	0.481	0.030; 0.148
Step 3	0.434**	0.008				
Constant			−5.446	1.962		
BASC-2 anxiety			0.033	0.022	0.245	−0.012; 0.078
BASC-2 executive functioning			0.081	0.032	0.436	0.015; 0.146
SCQ SC			0.036	0.056	0.108	−0.080; 0.151

Note.

*$P < 0.05$;

**$P < 0.01$; BASC-2: The Behavioral Assessment System for Children-2; FSIQ: Full-scale IQ; RRB: restricted and repetitive behaviors; SC: Social and Communication; SCQ: Social Communication Questionnaire.