

# Co-occurring trajectories of anxiety and insistence on sameness behaviour in autism spectrum disorder

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## Background

Children with autism spectrum disorder (ASD) have increased susceptibility to anxiety disorders. Variation in a common ASD symptom, insistence on sameness behaviour, may predict future anxiety symptoms.

## Aims

To describe the joint heterogeneous longitudinal trajectories of insistence on sameness and anxiety in children with ASD and to characterise subgroups at higher risk for anxiety.

## Method

In a longitudinal ASD cohort ( $n = 421$ ), insistence on sameness behaviour was measured using the Autism Diagnostic Interview-Revised at approximately ages 3, 6 and 11 years. Anxiety was quantified at 8 time points between ages 3 and 11 years using the Child Behavior Checklist (CBCL) (parent report). Clusters of participants following similar trajectories were identified using group-based and joint trajectory modelling.

## Results

Three insistence on sameness trajectories were identified: (a) 'low-stable' (41.7% of participants), (b) 'moderate-increasing' (52.0%) and (c) 'high-peaking' (i.e. increasing then stabilising/decreasing behaviour) (6.3%). Four anxiety trajectories were

identified: (a) 'low-increasing' (51.0%), (b) 'moderate-decreasing' (16.2%), (c) 'moderate-increasing' (19.6%) and (d) 'high-stable' (13.1%). Of those assigned to the 'high-peaking' insistence on sameness trajectory, 95% jointly followed an anxiety trajectory that surpassed the threshold for clinical concern ( $T$ -score  $>65$ ) by middle childhood (anxiety trajectories 3 or 4). Insistence on sameness and anxiety trajectories were similar in severity and direction for 64% of the sample; for 36%, incongruous patterns were seen (e.g. decreasing anxiety and increasing insistence on sameness).

## Conclusions

The concurrent assessment of insistence on sameness behaviour and anxiety in ASD may help in understanding current symptom profiles and anticipating future trajectories. High pre-school insistence on sameness in particular may be associated with elevated current or future anxiety symptoms.

## Keywords

Autism spectrum disorder; anxiety disorders; comorbidity; epidemiology; developmental disorders.

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Autism spectrum disorder (ASD) is a neurodevelopmental condition that occurs in 1–2% of children. The core symptoms include social communication deficits and restricted/repetitive patterns of behaviour. Anxiety disorders often co-occur with ASD in childhood, with prevalence estimates between 20 and 40%.<sup>1,2</sup> Anxiety significantly contributes to difficulties in social and adaptive functioning and is associated with reduced quality of life for individuals with ASD.<sup>3</sup> Data suggest that, although anxiety is a separate construct that occurs independently of ASD severity,<sup>4</sup> anxiety and core ASD symptoms may overlap to some extent in very young children.<sup>5</sup> Anxiety can be especially challenging to identify in ASD, given non-traditional anxiety symptoms (e.g. unusual specific phobias), diagnostic overshadowing by other ASD symptoms, and variation in cognitive and language abilities in ASD.<sup>6</sup> With respect to risk factors, older age, lower family income, female gender and higher cognitive or adaptive abilities have all emerged as potential correlates of anxiety in select ASD studies; however, these variables explain little of the variance in anxiety symptoms.<sup>2,7–9</sup> Regarding treatment, although cognitive-behavioural therapy (CBT) adapted for ASD is effective for anxiety disorders in school-aged children and youth with ASD without intellectual disabilities,<sup>10</sup> there is an absence of evidence with respect to other anxiety treatments or prevention strategies in this population.<sup>11</sup> ASD is also a highly heterogeneous condition in terms of both individual symptom profiles and longitudinal course, which necessitates individualised and adaptable treatment approaches. Data from

typically developing samples suggest that there are likely heterogeneous trajectories of anxiety symptoms over childhood (e.g. 'pre-school limited,' 'moderate and increasing' or 'persistently high' anxiety<sup>12,13</sup>). Given the high prevalence of anxiety disorders in ASD, knowledge about risk factors, early clinical presentations and heterogeneous longitudinal trajectories of anxiety in this population is greatly needed,<sup>11</sup> to inform the development of prevention programmes and early intervention initiatives.

## Association between anxiety and insistence on sameness

Emerging evidence suggests a relationship between the rigid, repetitive and routinised patterns of behaviour that are core to the diagnosis of ASD and the severity of anxiety symptoms in this population. Restricted and repetitive behaviour is routinely and reliably quantified as part of a diagnostic evaluation for ASD, even in very young children. It is comprised of two subtypes: repetitive motor behaviour (e.g. hand-flapping) and insistence on sameness behaviour (e.g. rigid adherence to rituals and routines, difficulties with transitions).<sup>14</sup> A large body of cross-sectional work has shown that anxiety and restricted/repetitive behaviour are correlated.<sup>15–19</sup> The relationship with anxiety may be specific to insistence on sameness behaviour in particular (more so than repetitive movements).<sup>16–19</sup> Despite this correlation, anxiety and insistence on sameness behaviour have been shown to function as distinct

constructs.<sup>16</sup> Emerging data suggest that there may be a longitudinal relationship between early insistence on sameness behaviour and future anxiety as well.<sup>20,21</sup> Similar to anxiety, distinct subgroups of children also appear to follow different courses of insistence on sameness behaviour over childhood in ASD.<sup>22</sup> Insistence on sameness behaviour as a possible early predictor of future anxiety in ASD (e.g.<sup>21</sup>) merits further study, while also taking into account the likely longitudinal heterogeneity in the trajectories of both symptoms.

## Aims

The overall goal of this study was to elucidate the longitudinal relationship between insistence on sameness behaviour and anxiety symptoms in children with ASD. The specific objective was to delineate and characterise subgroups of preschool children at higher risk for future anxiety symptoms in order to guide subsequent prevention and treatment initiatives. Using data from a large longitudinal cohort of children with ASD followed between 3 and 11 years of age, we examined the patterns of association between developmental trajectories of insistence on sameness behaviour and anxiety.

## Method

### Study design and participants

Data were collected through the Pathways in ASD study, a large ( $n = 421$ ) longitudinal inception cohort study of children with ASD and their families that began in 2005. Details of the study methodology are described elsewhere.<sup>8</sup> Participants were recruited between ages 2 years and 5 years, across five community and academic Canadian sites, within 4 months of receiving an ASD diagnosis (sites in Halifax, Nova Scotia; Montreal, Quebec; Hamilton, Ontario; Edmonton, Alberta; and Vancouver, British Columbia). Participants were then followed longitudinally through a variety of standardised assessment and report measures, using an accelerated design (i.e. staggered entry age, then synchronisation of assessment time points at age 6). The current study focused on the first eight assessment time points:  $T_1$  (mean age 3.3 years) through  $T_8$  (mean age 10.7 years).

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were initially approved at McMaster University by the Hamilton Integrated Research Ethics Board (REB) (project number 04-353) and subsequently by REBs at each participating site. Written informed consent was obtained from all participating families.

### Behavioural assessments

Severity of insistence on sameness behaviour was measured using the Autism Diagnostic Interview-Revised (ADI-R).<sup>23</sup> The ADI-R is a semi-structured validated parent interview; clinicians quantify current and past behaviour on a scale of 0–3, with 3 representing an ASD-associated behaviour that causes severe impairment. The ADI-R has a widely used 12-item subscale capturing ‘stereotyped and repetitive interests and behaviours’. Factor analysis has been used repeatedly to confirm that items on this subscale reliably load onto one of two underlying constructs: insistence on sameness behaviour and repetitive motor behaviour.<sup>14,24,25</sup> For this study, we used the total raw current ADI-R Insistence on sameness (ADI-R-IS) subscale scores (6 items, total possible range 0–18, actual range 0–12) collected at  $T_1$ ,  $T_4$  and  $T_8$ .

Anxiety symptoms were measured using the DSM-oriented Anxiety Problems subscale of the Child Behavior Checklist

(CBCL),<sup>26</sup> which was completed by parents at each study time point ( $T_1$  through  $T_8$ ). There are two versions of the CBCL: one for school-aged (6–18 years) and one for preschool-aged (1.5–5 years) children. The CBCL proprietary software provides age- and gender-normed standardised scores (T-scores) across a range of common childhood psychiatric disorders and symptom profiles, with T-scores above 65 considered to indicate a clinical concern because of elevated symptomatology.<sup>26</sup> The CBCL Anxiety subscale appears to have adequate sensitivity (0.83) and moderate specificity (0.52) as a screening tool to detect anxiety disorders in children with ASD (AUC = 0.71).<sup>27</sup>

Other baseline ( $T_1$ ) measures used to characterise the sample and the different trajectory groups were: age (in months), gender, family income on an 11-point scale from <Can\$5000 to >Can\$80 000 per year; parenting stress levels on the Parenting Stress Index-Short Form (PSI-SF) (total stress score);<sup>28</sup> Adaptive Behavior Composite score from the Vineland Adaptive Behavior Scales Second Edition (VABS-II);<sup>29</sup> IQ on the Developmental Index of the Merrill–Palmer–Revised Scales of Development (M-P-R);<sup>30</sup> and language abilities on the Preschool Language Scale Fourth Edition (PLS-4).<sup>31</sup>

### Analyses

Analyses were conducted in SAS (version 9.5 for Windows). Preliminary analyses using exploratory factor analysis (EFA) were initially used to examine the extent to which symptoms on both measures separated into distinct constructs at each study time point.

Clusters of participants following similar longitudinal trajectories over time were then identified using a well-established finite-mixture modelling procedure (PROC TRAJ).<sup>32,33</sup> This method is useful to examine heterogeneity and describe multiple distinct patterns of change over time in a population.<sup>34</sup>

Multigroup trajectories were estimated for the continuous ADI-R insistence on sameness subscale raw total scores (at  $T_1$ ,  $T_4$  and  $T_8$ ) and the CBCL anxiety subscale T-scores (at  $T_1$  through  $T_8$ ). For the anxiety trajectories, T-scores (as opposed to raw scores) were used to facilitate clinically interpretable modelling of anxiety across both versions of the CBCL (preschool and school-age). Specifically, as the raw scores and number of items from the two versions are incongruous, and since many anxiety symptoms (e.g. separation anxiety) are expected or normative at younger ages, analyses using T-scores were chosen to examine anxiety symptoms in ASD relative to typically developing norms. We also subsequently examined anxiety trajectories using mean item raw scores as a sensitivity analysis. Note that the CBCL proprietary software truncates CBCL T-scores at 50. To preserve maximum heterogeneity in the data, at each study time point we imputed anxiety T-scores for participants who had initially been assigned a T-score of 50, based on their age, gender and raw score, in keeping with the CBCL scoring procedures. Multiple imputation was considered for this step.

All trajectories of insistence on sameness and anxiety were first modelled using quadratic growth curves. The optimal number of trajectory groups was selected on the basis of inspection of the Akaike information criterion (AIC), Bayesian information criterion (BIC) and log-likelihood values, while considering parsimony, group sizes and previous literature. Once the optimal number of groups was identified, the polynomial order was varied (e.g. linear, cubic) and model fit statistics were further compared. Model adequacy was assessed by considering the odds of correct classification (target  $\geq 5$ ) and the average posterior probability of assignment (APPA) (target  $> 0.70$ ) for each group.

Descriptive characteristics at  $T_1$  were compared between assigned trajectory groups. As an exploratory analysis, we also examined  $T_1$  measures as predictors of group assignment.<sup>35</sup>

Trajectory group assignment was treated as a probabilistic ordinal outcome, and the odds of transitioning to a higher-severity trajectory group relative to the reference low-severity group was estimated for time-stable baseline covariates, while accounting for uncertainty in group assignment.<sup>36</sup>

A joint trajectory model of insistence on sameness and anxiety was subsequently estimated to allow examination of these simultaneous developmental paths. We estimated: (a) the probability of belonging to each anxiety trajectory, conditioned on the insistence on sameness trajectory assignments; (b) the probability of belonging to each insistence on sameness trajectory, conditioned on the anxiety trajectory assignments; and (c) the joint probabilities of belonging simultaneously to all combinations of anxiety–insistence on sameness trajectories.<sup>37</sup> Three select joint trajectory groups of interest with unique anxiety profiles to which >10% of the study sample were assigned and a low-risk reference group were compared in terms of descriptive characteristics.

With respect to missing data, PROC TRAJ uses the maximum likelihood method to estimate parameters from all available data and therefore permits inclusion of participants with missing information, provided that it is missing at random (MAR).<sup>34</sup> We conducted preliminary analyses to explore patterns and correlates of missingness. We then conducted sensitivity analyses, including restricting group comparisons to participants with APPA  $\geq 0.90$ , to account for potential misclassification. We also repeated the unidimensional trajectory analyses by (a) excluding participants with high proportions of missing data (i.e. missing >1 of 3 ADI-R time points, or >3 of 8 CBCL time points) and (b) imputing missing outcome data through predictive mean matching using the following auxiliary variables: age at diagnosis, gender, baseline VABS-II and PSI-SF scores. We also estimated the trajectories while accounting for the possibility that participant attrition is group dependent.<sup>38</sup>

## Results

### Preliminary analyses and demographic characteristics

Preliminary analyses confirmed that insistence on sameness and anxiety on these measures generally separated into distinct constructs (supplementary Table 1, available at <https://doi.org/10.1192/bjp.2020.127>), with some overlap at  $T_1$  (baseline assessment, mean age 3.3 years). Descriptive characteristics at  $T_1$  are presented in Table 1 and data from all time points are shown in supplementary Table 2. Sites were fairly balanced with respect to participant recruitment ( $n = 57, 134, 68, 92$  and  $70$ ) as well as clinical characteristics, including age and gender (data available on request).

Imputation extended the range of CBCL anxiety T-scores below 50 (range = 41–92). Imputed CBCL T-scores and raw scores were very highly correlated ( $r^2 = 0.94$ – $0.99$ ) (supplementary Table 2 and supplementary Fig. 1) and results of the trajectory analyses did not change with multiple rounds of imputation (data available on request), and we therefore present data from a single round of T-score imputation only.

### Missing data

Of 421 recruited participants, 409 had ADI-R data at one or more time points ( $T_1 = 404$ ;  $T_4 = 324$ ; and  $T_8 = 188$ ) and 378 had CBCL data at one or more time points ( $T_1 = 365$ ;  $T_2 = 327$ ;  $T_3 = 301$ ;  $T_4 = 250$ ;  $T_5 = 197$ ;  $T_6 = 206$ ,  $T_7 = 151$ ; and  $T_8 = 158$ ). Further information about missing data, and their correlates, is presented in supplementary Tables 2–4. Overall, data patterns were felt to be sufficient to meet the (untestable) assumption of MAR.

### Separate insistence on sameness and anxiety trajectories

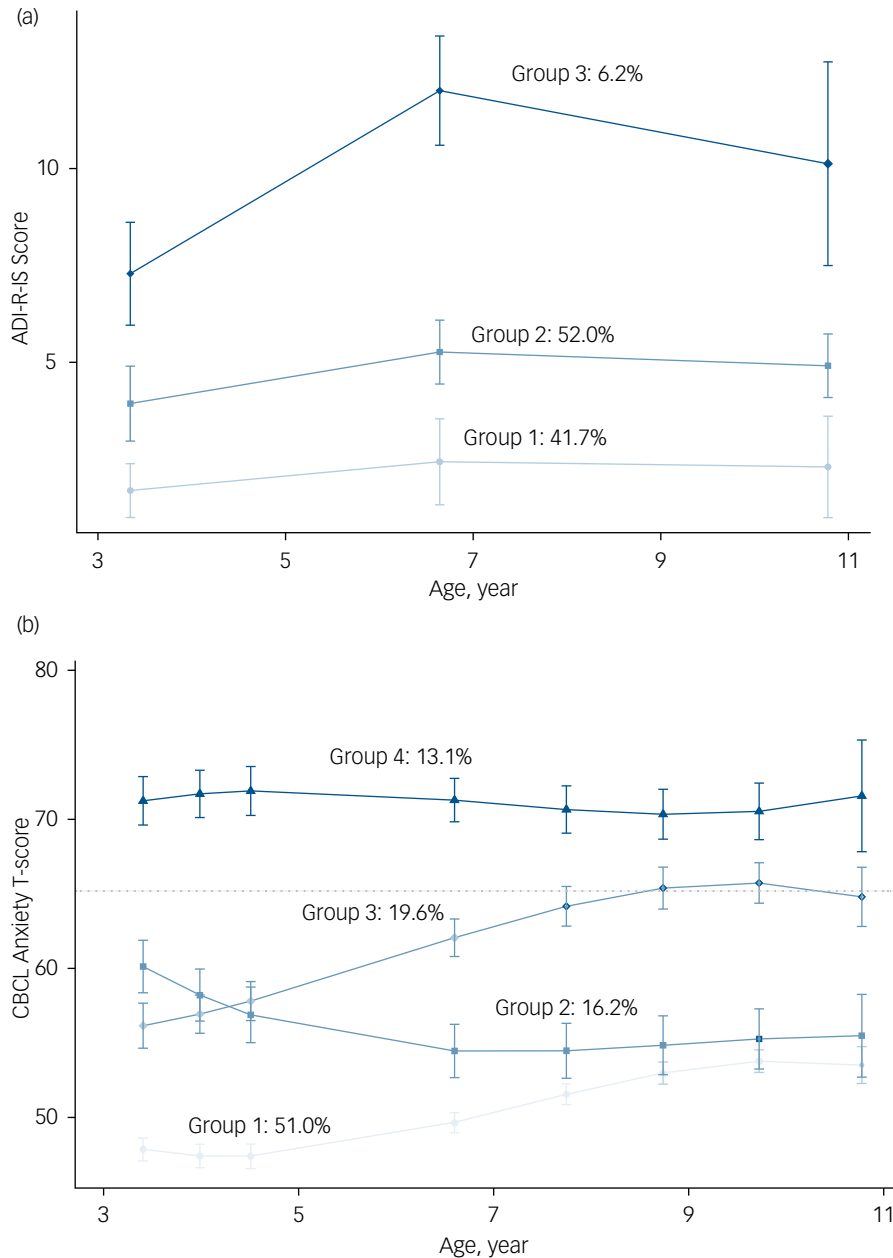
Model fit and adequacy parameters for the multigroup trajectories were considered acceptable (supplementary Table 5). For insistence on sameness, a three-group solution was selected, which identified a low-stable group (group 1; assigned to 41.7% of participants), a moderate-increasing group (group 2; 52.0%) and a high-peaking group (group 3; 6.3%) (Fig. 1(a)). For the anxiety trajectories, a four-group solution best fit the data (Fig. 1(b)). This identified a low-increasing group (group 1; 51.0%), a moderate-decreasing group (group 2; 16.2%), a moderate-increasing group (group 3; 19.6%) and a high-stable group (group 4; 13.1%). Note that anxiety groups 3 and 4 (32.7% combined) had ‘elevated’ CBCL anxiety subscale T-scores, surpassing the threshold for concern (T-score >65) at one or more time points. Anxiety trajectories were similar using mean item scores instead of T-scores (supplementary Fig. 2). All data points for anxiety and insistence on sameness trajectories are shown in supplementary Figs 3 and 4 respectively.

Baseline differences between the assigned unidimensional trajectory groups are presented in Table 2. Sensitivity analyses restricting group comparisons to participants with APPA  $\geq 0.90$  (supplementary Table 6) and exploratory analyses treating trajectory group assignment as an ordinal outcome (supplementary Table 7) yielded largely similar conclusions with respect to significant predictors. Specifically, for the insistence on sameness trajectories, higher  $T_1$  anxiety, lower income, higher parenting stress, lower adaptive functioning, and language impairment were

**Table 1** Baseline ( $T_1$ ) demographic and missing data for cohort ( $n = 421$ )

Variable	Original data-set ( $n = 421$ ) <sup>a</sup>	Missing, $n$ (%)
Descriptive characteristics at $T_1$		
Age at diagnosis, months: median (IQR)	37.5 (31.5–44.0)	0 (0)
Gender, female: $n$ (%)	65 (15.4)	0 (0)
Family income, Can\$: median (IQR)	70 000 (40 000 to >80 000)	51 (12.1)
M-P-R standard score (IQ), median (IQR)	58.00 (43.0–72.0)	54 (12.8)
PSI total score (range 0–180), mean (s.d.)	89.5 (21.5)	62 (14.7)
VABS-II composite standard score, median (IQR)	72.0 (65.0–79.0)	22 (5.2)
PLS-4 total standard score, median (IQR)	57.0 (50.0–74.0)	62 (14.7)
Study variables of interest at $T_1$		
CBCL anxiety T-score, <sup>b</sup> median (IQR)	54.0 (50.0–63.0)	56 (13.3)
CBCL anxiety raw total score (range 0–17), mean (s.d.)	4.5 (3.3)	56 (13.3)
ADI-R-IS items sum (range 0–12), mean (s.d.)	3.4 (2.8)	17 (4.0)

a. Means are presented for data that approximated a normal distribution; medians are presented for non-normally distributed data; proportions are presented for categorical data. Of the entire sample ( $n = 421$ ), 409 had ADI-R data at one or more time points, 378 had CBCL anxiety data at one or more time points, and 376 had data on both measures at one or more time points.  
b. Non-imputed, T-score range 50–92.  
IQR, interquartile range; M-P-R, Merrill–Palmer–Revised Scales of Development; PSI, Parenting Stress Index; VABS-II, Vineland Adaptive Behavior Scales, Second Edition; PLS-4, Preschool Language Scale Fourth Edition; CBCL anxiety, Child Behavior Checklist Anxiety subscale; ADI-R-IS, Autism Diagnostic Interview-Revised Insistence on sameness subscale.



**Fig. 1** (a) The three-group solution with respect to insistence on sameness ( $n = 409$  total): group 1, low-stable (41.7%); group 2, moderate-increasing (52.0%); group 3, high-peaking group (6.2%). (b) The four-group solution regarding trajectories of anxiety symptoms in autism spectrum disorder ( $n = 378$  total): group 1, low-increasing (51.0%); group 2, moderate-decreasing (16.2%); group 3, moderate-increasing (19.6%); group 4, high-stable (13.1%). Error bars with solid circles depict the predicted mean scores for each trajectory; error bars with solid triangles show the 95% CI for the mean predicted scores at each study time point. ADI-R-IS, Autism Diagnostic Interview-Revised Insistence on sameness subscale; CBCL, Child Behavior Checklist Anxiety subscale.

associated with membership of a higher-severity insistence on sameness trajectory on one or more analyses. For the anxiety trajectories, baseline insistence on sameness, parenting stress and female gender were significant predictors or differed between groups.

Sensitivity analyses examining the impact of missing data did not significantly alter results. Group size estimates were nearly identical (within 3%) after excluding participants with high proportions of missing data. Concurrently modelling the probability of drop out resulted in similar group sizes for both the anxiety trajectories (within 3%) and the insistence on sameness trajectories (groups 1 and 2 within 4.5% and group 3 within 1.1%). Imputation of missing outcome data yielded consistent

group sizes (within 1–3% of original estimates) as well (data available on request).

### Joint trajectories of insistence on sameness and anxiety

When conditioning on insistence on sameness group assignment (Table 3, top), 11.0% of children assigned to the low-stable insistence on sameness group (group 1), 41.3% of those assigned to the moderate-increasing insistence on sameness group (group 2) and 94.7% of children assigned to the high-peaking insistence on sameness group (group 3) were jointly assigned to an ‘elevated’ anxiety trajectory (i.e. anxiety group 3 or 4). Conversely, when conditioned



**Table 2** Demographic and developmental differences at T<sub>1</sub> between assigned insistence on sameness (top panel) and anxiety trajectory groups (bottom panel)<sup>a</sup>

Variable	Insistence on sameness (IS) trajectories			P
	IS group 1 (low-stable)	IS group 2 (moderate-increasing)	IS group 3 (high-peaking)	
Total N	166	221	22	
Age, months: mean (s.d.)	37.0 (8.3) <sup>b</sup>	39.0 (8.9) <sup>b</sup>	39.0 (9.6)	<b>0.04</b>
Female, n (%)	30 (18.1)	31 (14.0)	3 (13.6)	0.55
Family income, Can\$1000: median (IQR)	75 (50 to >80)	70 (40 to >80)	85 (50 to >80)	0.07
M-P-R IQ, mean (s.d.)	59.2 (24.1)	58.2 (24.7)	66.7 (33.8)	0.36
PSI, mean (s.d.)	86.3 (21.0) <sup>b</sup>	90.8 (21.8)	102.0 (17.8) <sup>b</sup>	<b>0.007</b>
VABS-II, mean (s.d.)	74.6 (9.7) <sup>b</sup>	71.5 (10.0) <sup>b</sup>	71.0 (12.5)	<b>0.007</b>
PLS-4, median (IQR)	58.5 (50.0–75.0)	56.0 (50.0–71.0)	59.0 (50.0–84.0)	0.46
CBCL anxiety T-score, median (IQR)	51.0 (50.0–57.0) <sup>b,c</sup>	54.0 (50.0–63.0) <sup>b</sup>	60.0 (57.0–63.0) <sup>c</sup>	<b>&lt;0.001</b>
CBCL anxiety imputed T-score, median (IQR)	51.0 (45.4–57.0) <sup>b,c</sup>	54.0 (48.4–63) <sup>b</sup>	60.0 (57.0–63.0) <sup>c</sup>	<b>&lt;0.001</b>
CBCL anxiety raw score (s.d.)	3.4 (2.9) <sup>b,c</sup>	5.1 (3.5) <sup>b</sup>	6.7 (2.8) <sup>c</sup>	<b>&lt;0.001</b>

Variable	Anxiety trajectories				P
	Anxiety group 1 (low-increasing)	Anxiety group 2 (moderate-decreasing)	Anxiety group 3 (moderate-increasing)	Anxiety group 4 (high-stable)	
Total N	201	61	69	47	
Age months, mean (s.d.)	37.9 (8.8)	37.3 (7.9)	40.1 (8.3)	39.7 (9.6)	0.15
Female, n (%)	32 (15.9)	9 (14.8)	8 (11.6)	12 (25.5)	0.24
Family income, Can\$1000: median (IQR)	70 (50 to >80)	65 (40 to >80)	70 (40 to >80)	60 (40 to >80)	0.07
M-P-R IQ, mean (s.d.)	57.7 (24.0)	59.3 (20.0)	63.6 (23.6)	64.2 (34.0)	0.26
PSI, mean (s.d.)	81.4 (19.7) <sup>b,c,d</sup>	94.5 (18.0) <sup>b</sup>	95.3 (18.9) <sup>c</sup>	103.8 (21.3) <sup>d</sup>	<b>&lt;0.001</b>
VABS-II, mean (s.d.)	73.7 (9.8)	71.0 (9.8)	73.7 (10.6)	71.6 (11.8)	0.24
PLS-4, median (IQR)	55.5 (50.0–69.0)	57.0 (50.0–74.0)	62.5 (50.0–86.0)	59.0 (50.0–83.0)	0.21
ADI-R IS, mean (s.d.)	2.5 (2.2) <sup>b,c,d</sup>	3.8 (2.9) <sup>b</sup>	4.1 (2.9) <sup>c</sup>	4.9 (3.1) <sup>d</sup>	<b>&lt;0.001</b>

IQR, interquartile range; M-P-R, Merrill–Palmer–Revised Scales of Development; PSI, Parenting Stress Index; VABS-II, Vineland Adaptive Behavior Scales, Second Edition; PLS-4, Preschool Language Scale Fourth Edition; CBCL, Child Behavior Checklist Anxiety subscale; ADI-R-IS, Autism Diagnostic Interview-Revised Insistence on sameness subscale.  
a. Means are presented for data that approximated a normal distribution; medians are presented for non-normally distributed data; proportions are presented for categorical data.  
Demographic characteristics and baseline behavioural measures at T<sub>1</sub> were compared between participants across assigned trajectory groups using analysis of variance (ANOVA) for continuous normally distributed data, the Kruskal–Wallis test for non-normally distributed data, and a chi-squared or Fisher’s exact probability test for categorical data. P-values in **bold** are significant.  
b–d. Groups that differed from each other at P < 0.05 for the specified test.

**Table 3** Joint trajectories of anxiety and insistence on sameness<sup>a</sup>

Estimated anxiety trajectory group proportions conditioned on insistence on sameness group assignment			
	Insistence on sameness groups		
	1 (low-stable)	2 (moderate-increasing)	3 (high-peaking)
Anxiety			
1 (low-increasing)	81.8%	31.0%	5.2%
2 (moderate-decreasing)	7.3%	27.6%	0.0%
3 (moderate-increasing)	9.5%	21.1%	59.5%
4 (high-stable)	1.5%	20.2%	35.2%
Total	100%	100%	100%

Estimated insistence on sameness trajectory group proportions conditioned on anxiety group assignment				
	Insistence on Sameness Groups			Total
	1 (low-stable)	2 (moderate-increasing)	3 (high-peaking)	
Anxiety				
1 (low-increasing) (n = 195)	68.6%	30.7%	0.8%	100%
2 (moderate-decreasing) (n = 68)	18.3%	81.7%	0.0%	100%
3 (moderate-increasing) (n = 64)	21.2%	55.9%	22.0%	100%
4 (high-stable) (n = 49)	4.7%	76.0%	19.3%	100%

Joint anxiety–insistence on sameness trajectories (all cells total 100%)			
	Insistence on sameness groups		
	1 (low-stable)	2 (moderate-increasing)	3 (high-peaking)
Anxiety			
1 (low-increasing)	<b>34.8%</b> <sup>b</sup>	15.6% <sup>b</sup>	0.4% <sup>c</sup>
2 (moderate-decreasing)	3.1% <sup>c</sup>	<b>13.8%</b> <sup>c</sup>	0.0%
3 (moderate-increasing)	4.0% <sup>c</sup>	<b>10.6%</b> <sup>b</sup>	4.3% <sup>c</sup>
4 (high-stable)	0.6% <sup>c</sup>	<b>10.1%</b> <sup>c</sup>	2.6% <sup>b</sup>

a. The top panel shows the estimated proportion of participants in each anxiety trajectory group, conditioned on the insistence on sameness group assignment (i.e. columns total 100%). The middle panel shows the estimated insistence on sameness group membership proportions conditioned on anxiety group membership (i.e. rows total 100%). The bottom panel shows the estimated joint trajectory membership assignments across both symptom domains (i.e. all cells total 100%). The joint trajectory estimates included participants who had data available at one or more time points on both measures (n = 376).  
b. Congruent symptom trajectories.  
c. Incongruent symptom trajectories. Values in **bold** represent groups for whom descriptive characteristics are compared in supplementary Table 8. Specifically, the joint anxiety:insistence on sameness groups 2:2, 3:2 and 4:2 were selected for comparison to the reference group 1:1, as they represent >10% of the study sample and differed from the reference group with respect to their anxiety trajectory.

on anxiety group assignment (Table 3, middle), of the 113 children assigned to an 'elevated' anxiety trajectory, 22.0 and 19.3% respectively were jointly assigned to the high-peaking insistence on sameness group 3. On the other hand, of those in insistence on sameness group 2 (moderate-increasing insistence on sameness), anxiety group assignments were relatively equally distributed across the four trajectories.

Unconditioned joint trajectory assignments are presented at the bottom of Table 3. Descriptive characteristics for four selected unconditioned joint trajectory groups are presented in supplementary Table 8. The most common profile (34.8%) involved low-stable insistence on sameness (insistence on sameness group 1) and low-increasing anxiety symptoms (anxiety group 1). Participants assigned to this 'low-risk' reference group had higher adaptive functioning, higher family income and lower parenting stress than other groups. A second group (13.8%) had 'incongruent' joint trajectories, specifically moderate-increasing insistence on sameness (insistence on sameness group 2) and moderate-decreasing anxiety (anxiety group 2). A third joint trajectory profile (10.6%) showed 'congruent' moderate-increasing symptoms across both domains. This group did not significantly differ from the incongruent group with respect to pairwise comparisons of demographic characteristics. A final 'persistently anxious' group (10.1%) with moderate-increasing insistence on sameness behaviour and persistently elevated anxiety symptoms had the highest parenting stress and proportionately more female children (27.9 v. <18% for other groups).

Overall, 63.6% of the sample was jointly assigned to insistence on sameness and anxiety trajectories with generally congruent symptom patterns over time (i.e. low-stable insistence on sameness and low-increasing anxiety (34.8%), moderate-increasing insistence on sameness with either low-increasing (15.6%) or moderate-increasing (10.6%) anxiety, or high-peaking insistence on sameness with high-stable anxiety (2.6%)). Conversely, for the remaining 36.3%, joint trajectories were incongruous across symptom domains (Table 3, bottom).

## Discussion

Overall, this study revealed that developmental trajectories of insistence on sameness and anxiety in ASD over childhood are heterogeneous and associated; for most participants, the association was congruous but for approximately 1 in 3, trajectories were incongruous.

### Anxiety trajectories in ASD

Our results shed light on the natural history of anxiety symptoms in children with ASD, for whom longitudinal data have previously been scarce. Most children in our sample were matched to a trajectory with low yet increasing anxiety over childhood; this contrasts with typically developing cohorts, where most have been found to have low and stable anxiety symptoms.<sup>12,13</sup> One-third (32.7%) of our participants were assigned to an 'elevated' anxiety trajectory, where symptoms surpassed a threshold for concern on the CBCL (T-score >65) at one or more time points (i.e. anxiety group 3 or 4). This reflects estimates of the high prevalence of anxiety disorders in children with ASD from meta-analyses, which range from 20 to 40%.<sup>1,2</sup> Of the 138 participants in our study with 'elevated' anxiety, 40% were assigned to the persistently high and stable anxiety group. Most (60%) were assigned to the moderate-increasing anxiety trajectory; their symptoms gradually increased between ages 3 and 10 years, presenting an opportunity for prevention.

### Characterising anxiety trajectory subgroups and anxiety predictors

Overall, clusters of preschool children following elevated anxiety trajectories included not only those with high baseline anxiety symptoms, but also those with high insistence on sameness behaviour. Conversely, low insistence on sameness behaviour appeared to be protective with respect to anxiety outcomes. For children with moderate preschool anxiety, the presence of notably high or low insistence on sameness may help stratify them clinically with respect to increasing or decreasing anxiety prognoses. Trajectories are less clear, however, for children with moderate symptoms across both domains in the preschool period. That said, children with 'higher-risk' anxiety profiles may benefit from early anxiety interventions, even before meeting full criteria for an anxiety disorder. Emerging data suggest that brief parent-focused programmes may be helpful for anxiety prevention in 'high-risk' typically developing preschoolers<sup>39</sup> and that CBT adapted for ASD is an effective treatment for school-aged children (e.g. >8 years of age);<sup>10</sup> evidenced-based anxiety prevention studies targeting younger children with ASD (e.g.<sup>40</sup>) are now needed.

Regarding other anxiety predictors, elevated baseline parenting stress was consistently a significant predictor of assignment to a non-'low-risk' anxiety group. The degree to which parenting stress may reflect shared informant bias, other forms of adversity/early childhood risk or may be in the causal path towards anxiety (e.g. mediating the insistence on sameness-anxiety relationship) is an active area of future inquiry. Causal models exploring how early family and child characteristics lead to different mental health outcomes in ASD (e.g.<sup>5</sup>) are needed and such work is underway. Across joint trajectory and sensitivity analyses, female gender and lower family income also emerged as potential predictors of elevated anxiety, in keeping with some previous literature.<sup>1,7,8</sup> IQ scores did not significantly differ between groups on any analyses. Therefore, in addition to severity of insistence on sameness behaviour, contextual and family factors may play a role in mediating or moderating vulnerability to anxiety in ASD.

### Patterns of associations across symptom domains

Approximately one-third of the sample was assigned to joint trajectories with symptom domains that were incongruous over childhood. For some, symptom trajectories appeared to have an inverse relationship (e.g. 13.8% in the moderate-decreasing anxiety and moderate-increasing insistence on sameness group). This could reflect some degree of heterotypical continuity between the insistence on sameness and anxiety constructs, potentially suggestive of an evolving manifestation of a latent vulnerability or trait. For example, it may be that what are perceived as anxiety symptoms in preschool gradually evolve to reflect a previously latent preference for sameness. Or, increasing insistence on sameness may serve as a means to control or avoid uncertainty,<sup>41</sup> ultimately limiting anxiety-provoking experiences. Consistent with prior analyses,<sup>5</sup> insistence on sameness and anxiety overlapped somewhat as constructs during the preschool period. It may be that high insistence on sameness represents an ASD-specific manifestation of anxiety for some (especially younger) children.



### Limitations

Results should be interpreted in light of several considerations. First, the statistical approach used assumes that there is no variation between individuals within a trajectory group.<sup>42</sup> Other less restrictive approaches may have yielded different results with potentially fewer trajectories identified.<sup>42</sup> Trajectory group assignments are probabilistic and therefore do not absolutely reflect the symptom

patterns of every individual assigned to that group. The CBCL is a parent-report measure, which captures childhood anxiety as observed by a parent and does not take into account other informants (e.g. children themselves or teachers). The ADI-R is also based on parent interview, which may have contributed to some degree of informant bias. The CBCL does not quantify specific subtypes of anxiety and may miss less traditional anxiety symptoms that can occur in ASD<sup>6</sup> (e.g. social fearfulness, unusual phobias, sensory-related anxiety or marked anxiety about transitions). Accordingly, we are unable to comment on the trajectories of specific anxiety subtypes. Longitudinal studies using multimethod, multi-informant and ASD-specific anxiety measures are needed. The validity of the CBCL anxiety subscale in populations with ASD and intellectual disability merits further study. The anxiety T-scores are also normed relative to a typically developing sample, and therefore reflect relative anxiety severity compared with peers, not true change. The ADI-R was assessed at only three time points, which may have missed more subtle/complex changes in insistence on sameness behaviour over childhood or contributed to reduced certainty in insistence on sameness group assignment. Elevated restricted/repetitive behaviour is required to meet criteria for an ASD diagnosis and study inclusion; this may have affected the distribution of insistence on sameness scores. Some group sizes, especially insistence on sameness group 3, included a significant minority of participants and outcome data points. Secular changes in the age at which ASD is identified should be considered when generalising results from this preschool cohort to the broader ASD community today. As well, baseline cognitive assessments at  $T_1$  may have underestimated later measured cognitive abilities in this sample. Longitudinal models did not account for time-varying covariates and only univariate predictors were examined. Therefore, models were unable to ascertain the relative contributions over time of other aspects of ASD phenotypes to anxiety trajectories. Data and statistical models are descriptive/observational in nature and we do not intend to imply causal associations between insistence on sameness and anxiety. ‘Sensory sensitivities’ were included under insistence on sameness items, as per previous use of this subscale; the role of sensory sensitivities, or other possible mediators of the anxiety–insistence on sameness association (e.g. intolerance of uncertainty) were not explored. Last, despite sensitivity analyses, there was a high proportion of participants with missing data.

## Implications

Of the children who had clinically elevated anxiety symptoms in middle childhood (i.e. between ages 8 and 11 years), the majority followed a trajectory in which moderate preschool anxiety gradually increased over time. This presents an important opportunity for prevention of or early intervention for anxiety in ASD. Children with high insistence on sameness as preschoolers were very likely to have high insistence on sameness in middle childhood as well as elevated current and/or future anxiety symptoms. Given the high and impairing rate of anxiety disorders in this population, prevention studies recruiting preschool-aged or early school-aged children are needed.

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## Supplementary material

Supplementary material is available online at <http://doi.org/10.1192/bjp.2020.127>.

## Data availability

The data that support the findings of this study are available on request from the corresponding author (D.B.). The data are not publicly available as they contain information that could compromise the privacy of research participants.

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## Author contributions

P.M., I.M.S., T.V., J.V., C.W., L.Z., T.B., E.D., M.E., S.G., W.J.U., A.Z.Z. and P.S. were responsible for study conceptualisation and design. D.A.B., S.V., E.P. and S.Z. formulated the specific research question. D.A.B. and E.P. conducted the statistical analyses. All authors contributed to writing and/or editing of the manuscript; all authors approved the final version.

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## Declaration of interest

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