## UNIVERSITY<sup>OF</sup> BIRMINGHAM University of Birmingham Research at Birmingham

### Decreased grey matter volumes in unaffected mothers of individuals with autism spectrum disorder reflect the broader autism endophenotype

An, Kyung-min; Ikeda, Takashi; Hirosawa, Tetsu; Yaoi, Ken; Yoshimura, Yuko; Hasegawa, Chiaki; Tanaka, Sanae; Saito, Daisuke; Kikuchi, Mitsuru

DOI: 10.1038/s41598-021-89393-z

License: Creative Commons: Attribution (CC BY)

Document Version Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

An, K, Ikeda, T, Hirosawa, T, Yaoi, K, Yoshimura, Y, Hasegawa, C, Tanaka, S, Saito, D & Kikuchi, M 2021, 'Decreased grey matter volumes in unaffected mothers of individuals with autism spectrum disorder reflect the broader autism endophenotype', *Scientific Reports*, vol. 11, no. 1, 10001. https://doi.org/10.1038/s41598-021-89393-z

Link to publication on Research at Birmingham portal

### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

#### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

# scientific reports



# **OPEN** Decreased grey matter volumes in unaffected mothers of individuals with autism spectrum disorder reflect the broader autism endophenotype

Kyung-min An<sup>1,2<sup>ICI</sup></sup>, Takashi Ikeda<sup>1,2</sup>, Tetsu Hirosawa<sup>1,2</sup>, Ken Yaoi<sup>1,2</sup>, Yuko Yoshimura<sup>1,2,3</sup>, Chiaki Hasegawa<sup>1</sup>, Sanae Tanaka<sup>1,2</sup>, Daisuke N. Saito<sup>1,2</sup> & Mitsuru Kikuchi<sup>1,2,4</sup>

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an early onset and a strong genetic origin. Unaffected relatives may present similar but subthreshold characteristics of ASD. This broader autism phenotype is especially prevalent in the parents of individuals with ASD, suggesting that it has heritable factors. Although previous studies have demonstrated brain morphometry differences in ASD, they are poorly understood in parents of individuals with ASD. Here, we estimated grey matter volume in 45 mothers of children with ASD (mASD) and 46 age-, sex-, and handednessmatched controls using whole-brain voxel-based morphometry analysis. The mASD group had smaller grey matter volume in the right middle temporal gyrus, temporoparietal junction, cerebellum, and parahippocampal gyrus compared with the control group. Furthermore, we analysed the correlations of these brain volumes with ASD behavioural characteristics using autism spectrum quotient (AQ) and systemizing quotient (SQ) scores, which measure general autistic traits and the drive to systemize. Smaller volumes in the middle temporal gyrus and temporoparietal junction correlated with higher SQ scores, and smaller volumes in the cerebellum and parahippocampal gyrus correlated with higher AQ scores. Our findings suggest that atypical grey matter volumes in mASD may represent one of the neurostructural endophenotypes of ASD.

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder that is characterized by social and communication deficits, restricted interests, and repetitive behaviours<sup>1</sup>. ASD may develop as a result of complex interactions between genetic vulnerability and environmental factors during critical neurodevelopmental periods<sup>2</sup>. Although the exact cause of ASD remains unclear, ASD is one of the most heritable major neurodevelopmental disorders<sup>3,4</sup>. A recent meta-analysis reported its heritability as between 61 and 91%, suggesting that ASD has a substantial genetic component<sup>5</sup>.

According to genetic epidemiological data, relatives of individuals with ASD express subclinical autism-like personality traits<sup>6,7</sup>. When Kanner and Asperger described autism, they reported that parents of individuals with ASD have autistic traits, such as mild obsessiveness, late speech onset, and problems relating to the outside world<sup>8,9</sup>. Most previous studies have reported that relatives of individuals with ASD experience more impaired communication, rigid behaviour, mentalizing deficits<sup>10-16</sup>, and general autistic traits<sup>17,18</sup> than the general population. In relatives of individuals with ASD, autistic traits have been observed not only in behavioural and cognitive aspects, but also in dysregulated neurochemical features, such as whole blood serotonin levels<sup>19</sup>, reelin levels<sup>20</sup>, and amino acid metabolism<sup>21</sup>.

It has been suggested that these types of subthreshold autistic traits are part of the broader autism phenotype (BAP)<sup>22</sup>. BAP traits are more prevalent in first-degree relatives of ASD probands compared with other groups,

<sup>1</sup>Research Center for Child Mental Development, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8640, Japan. <sup>2</sup>Division of Socio-Cognitive-Neuroscience, Department of Child Development, United Graduate School of Child Development, Osaka University, Kanazawa University, Hamamatsu University School of Medicine, Chiba University, and University of Fukui, Kanazawa, Japan. <sup>3</sup>Institute of Human and Social Sciences, Kanazawa University, Kanazawa, Japan. <sup>4</sup>Department of Psychiatry and Behavioral Science, Kanazawa University, Kanazawa, Japan. Memail: eirene.akmin@gmail.com; sdaisuke@med.kanazawa-u.ac.jp

which supports the assumption of the genetic heritability of ASD<sup>23,24</sup>. By studying the parents of individuals with ASD, it may be possible to further understand the different endophenotypes (also called intermediate pheno-types) of ASD<sup>25,26</sup>. An endophenotype is a heritable and quantitative trait that is intermediary between disease symptoms and the genes associated with the disease<sup>27</sup>.

Regarding brain structure and function in ASD, previous neuroimaging studies have reported that individuals with ASD show abnormalities in many brain regions, including the superior temporal sulcus, middle temporal gyrus (MTG), temporoparietal junction (TPJ), fusiform gyrus, amygdala, anterior cingulate cortex, medial prefrontal cortex, inferior frontal gyrus, hippocampus, parahippocampal gyrus, corpus callosum, and cerebellum<sup>28–34</sup>. Although atypical brain structures in ASD have frequently been reported, the brain structures of parents of individuals with ASD are poorly understood and findings remain controversial<sup>25,26,35,36</sup>. Rojas et al. reported that the parents of individuals with ASD showed greater left hippocampal volume than a control group<sup>36</sup>. Peterson et al. found that the parents of individuals with ASD had increased volumes in some brain areas, including the superior temporal gyri, inferior and middle frontal gyri, superior parietal lobule, and anterior cingulate, as well as decreased volume in the left anterior cerebellar hemisphere<sup>35</sup>. In contrast, Palmen et al. reported no significant differences in brain structure of parents of individuals with ASD compared with a control group<sup>26</sup>. The discrepant findings between previous studies on the parents of individuals with ASD may be the result of different analytical methods (e.g. manual tracing, automatic tracing, or whole-brain voxel-based morphometry [VBM]), subject numbers (which is related to statistical power), or sex distribution of subjects.

In the present study, we applied whole-brain VBM analysis to 45 mothers of children with ASD (mASD) and 46 age-, sex-, and handedness-matched controls. We compared grey matter (GM) volume between the mASD and control groups to investigate the heritable aspects of brain structure and the neuroendophenotypes of ASD. We hypothesized that the mASD group would show some of the atypical brain structure patterns that have been previously reported in individuals with ASD. Furthermore, we aimed to determine whether brain volume abnormalities in mASD are correlated with scores on the autism spectrum quotient (AQ) and the systemizing quotient (SQ), which measure general autistic traits and the drive to systemize<sup>37,38</sup>.

### Methods

**Participants.** We recruited 46 healthy mothers of children with ASD (mASD group) and 48 age-matched healthy mothers of typically developing children (control group). Owing to low data quality, we excluded the data of one participant from the mASD group and the data of two participants from the control group. We analysed the data of 45 healthy mothers of children with ASD for the mASD group (mean age = 38.33 years, standard deviation [SD] = 4.33). We confirmed the diagnoses of the children with ASD using the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) criteria<sup>1</sup>, the Diagnostic Interview for Social and Communication Disorders<sup>39</sup>, and/or the Autism Diagnostic Observational Schedule–Generic<sup>40</sup>. All diagnoses were confirmed by local psychiatrists and clinical speech therapists. We used data from 46 age-matched healthy mothers of typically developing children for the control group (mean age = 38.78 years, SD = 3.98). All participants were recruited from public nursery schools in Kanazawa city, Kanazawa University Hospital, and prefectural hospitals in Toyama. Parents who reported difficulties in daily life because of their own intelligence level, or who were being treated for any mental illness, were excluded from this study. None of the participants had received an official diagnosis of autism. All participants provided full written informed consent to participate in the study, and the procedures were approved by the ethics committee of Kanazawa University Hospital. All methods were performed in accordance with the Kanazawa University Hospital Ethics Committee guidelines and regulations.

The Edinburgh Handedness Inventory<sup>41</sup> revealed that most participants were right-handed, except for one left-handed and one ambidextrous participant per group. We matched the groups on age, sex, and handedness to reduce potential confounding factors.

To evaluate the autistic-like behavioural features of the two groups, we used the AQ, which measures autistic traits<sup>38</sup>, and the SQ, which measures the drive to systemize<sup>37</sup>. Both assessments are self-report questionnaires. Total AQ scores can range from 0 to 50; a higher AQ score indicates that the individual has more 'autistic-like' behaviours. Total SQ scores can range from 0 to 80; a higher SQ score corresponds to a greater drive to systemize and is a behavioural characteristic of ASD. Additional participant details are shown in Table 1.

**Magnetic resonance imaging (MRI) acquisition.** Structural MRI scans were acquired using a 1.5 T MRI scanner (SIGNA Explorer, GE Healthcare, Chicago, IL, USA) with a T1-weighted Fast SPGR sequence using the following parameters: repetition time = 8.364 ms, echo time = 3.424 ms, flip angle =  $12^\circ$ , field of view = 260 mm, matrix size =  $512 \times 512$  pixels, slice thickness = 1 mm, and 176 transaxial images.

**VBM analysis.** VBM was performed using the Computational Anatomical Toolbox 12 (CAT12; Structural Brain Mapping Group, Jena University Hospital, Jena, Germany) implemented in Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK).

T1-weighted anatomical images were corrected for bias-field inhomogeneities, and were then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF)<sup>42</sup>. The total GM, WM, and CSF volume was calculated as the total intracranial volume (TIV). Each tissue class was spatially normalized into the DARTEL template in Montreal Neurological Institute space, which is derived from 555 healthy subjects aged between 20 and 80 years from the IXI-database<sup>43</sup>. The segmentation process was further extended by accounting for partial volume estimations<sup>44</sup>. We tested data quality and sample homogeneity using Mahalanobis distance algorithms implemented in CAT12. Mahalanobis distance combines weighted overall image quality, which is a measure of noise and other image artefacts (e.g. motion) before preprocessing, and mean correlation, which is a measure of the data homogeneity after preprocessing. We excluded the data of one participant from the mASD group and

Characteristics	Controls $(n = 46)$	mASD $(n=45)$	t	Р
Age in years	$38.78 \pm 3.98$	$38.33 \pm 4.33$	0.516	0.607
Handedness (right/left/ambidextrous)	44/1/1	43/1/1		
AQ	$14.74 \pm 6.74$	$17.31 \pm 7.40$	- 1.734	0.086
SQ	$10.98\pm5.75$	$14.60 \pm 10.02$	- 2.109	0.039
TIV	$1396.44 \pm 88.17$	$1355.37 \pm 92.19$	2.172	0.033*
TGM	$619.62 \pm 37.97$	$606.73 \pm 37.79$	1.623	0.108
TWM	$486.82 \pm 42.48$	$464.50 \pm 39.75$	2.587	0.011*
CSF	$289.47 \pm 40.04$	$283.62\pm49.27$	0.623	0.535

**Table 1.** Participant characteristics. Means  $\pm$  standard deviations and accompanying statistics (two-sided *t*-tests) for participant characteristics. There were no significant differences in age, AQ score, or SQ score between the control and mASD groups (two-sample *t*-tests with FDR multiple corrections). TIVs were significantly different between the control and mASD groups. \**P*<0.05. *AQ* autism spectrum quotient, *mASD* mothers of individuals with autism spectrum disorder, *SQ* systemizing quotient, *TIV* total intracranial volume, *TGM* total grey matter volume, *TWM* total white matter volume, *CSF* cerebrospinal fluid, *FDR* false discovery rate.

the data of two participants from the control group, because the Mahalanobis distance was larger than 2 SDs for these data. For further analysis, we used data from 45 mASD group participants and 46 control group participants. The preprocessed scans were smoothed using a Gaussian kernel of 6 mm (full width at half maximum).

**Statistical analysis.** We compared absolute volumes of GM structures using modulated images. To analyse the GM differences between the mASD and control groups, we performed voxel-wise two-sample *t*-tests using the general linear model implemented in SPM12, which uses Gaussian random field theory. We used the covariates of total GM and age as potential confounders in the general linear model.

The clusters were considered significant at P < 0.05 after correcting for false discovery rate (FDR) comparisons (with initial peak-level thresholding at P < 0.001 and clusters > 200 voxels). Automated anatomical labelling was used to label the significant clusters<sup>45</sup>.

The volumes of the significant clusters were extracted, and Spearman's rho test was conducted with AQ and SQ scores using the Statistical Package for Social Sciences (SPSS, Version 25). For all statistical analyses, we used an alpha level of 0.05 with FDR multiple corrections.

**Ethics approval and consent to participate.** This study was approved by the ethics committee of Kanazawa University Hospital. After receiving a complete explanation of the study, all participants provided full written informed consent.

### Results

For autistic-like behavioural features, there was no significant difference in AQ and SQ scores between the two groups with FDR correction (AQ scores: t(89) = -1.734, P = 0.086; SQ scores: t(89) = -2.109, P = 0.039).

The VBM analysis demonstrated that GM volumes in several brain regions were smaller in the mASD group relative to the control group. Two clusters showed statistically significant differences between the mASD and control groups (Fig. 1).

We observed the first significant cluster in the right MTG (88.42%) and OUTSIDE (9.60%) regions (Table 2). The anatomical label "OUTSIDE" indicates that this part of the region is outside the brain parcellation. This cluster comprised the posterior part of the MTG and stretched into the parietal side. According to a previous study on brain anatomy of the TPJ<sup>46</sup>, the parietal part of this cluster can be defined as the brain region at or outside the posterior and inferior edge of the TPJ. The mASD group had smaller GM volume in this cluster compared with the control group (t(89) = 4.330, P = 0.000) (Fig. 2a,b). Furthermore, the mASD group also had smaller GM volume in the second cluster (t(89) = 3.528, P = 0.001) (Fig. 3a,b). The second cluster was labelled as the right cerebellum (85.71%) and the parahippocampal gyrus (9.07%) (Table 2). There were no significant increases in GM volume in the mASD group relative to the control group.

We also identified correlations between the significant GM volume clusters and behavioural traits, using Spearman's rho test. AQ scores were negatively correlated with the second cluster ( $\rho = -0.252$ , P = 0.016) (Fig. 3c). However, they were not correlated with the first cluster (P > 0.05). In contrast, SQ scores were negatively correlated with the first cluster ( $\rho = -0.249$ , P = 0.017) (Fig. 2c), but were not correlated with the second cluster (P > 0.05).

### Discussion

ASD is one of the most heritable major neurodevelopmental disorders. Unaffected relatives of individuals with ASD, and especially the parents of individuals with ASD, have been widely reported to have subclinical forms of behavioural and neurobiological patterns that are characteristic of ASD. This feature of the parents of individuals





### z -27 -22 -17 -12 -7 -2 3 8 13

**Figure 1.** Grey matter volume differences between the mASD and control groups. (a) Areas of decreased grey matter volume in the mASD group, compared with the control group, from the voxel-wise two-sample *t*-test. All clusters shown in the results survived thresholding at P < 0.05 after FDR correction. (b) Two clusters were significantly smaller in the mASD group. Numbers denote MNI coordinates. The colour intensity represents *t*-statistic values at the voxel level. The results are visualized on standard normalized T1-weighted images in selected slices and displayed in accordance with neurological convention (i.e. right hemisphere on the right). *mASD* mothers of individuals with autism spectrum disorder, *FDR* false discovery rate, *MNI* Montreal Neurological Institute.

č

with ASD has been termed the BAP. However, the brain structural features of parents of individuals with ASD are poorly understood and findings remain controversial.

In the present study, we observed the phenomenon of BAP through the subthreshold autistic-like behavioural features of mASD. We found qualitative differences in AQ and SQ scores between the mASD and control groups, although these were not significant when corrected for multiple comparisons. These findings suggest that parents of children with ASD have subclinical elevations in ASD traits.

To investigate the brain structural features of parents of individuals with ASD, we used VBM to examine brain GM volume in 45 unaffected mASD and 46 age-, sex-, and handedness-matched controls. We identified smaller GM volume in the MTG, TPJ, cerebellum, and parahippocampal gyrus in the mASD group. Moreover, we found that the volume of the significant MTG and TPJ cluster was negatively correlated with SQ scores, which assess the autistic drive to analyse or construct systems. Additionally, the volume of the significant cerebellum and parahippocampal gyrus cluster was negatively correlated with AQ scores, which measure autistic traits.

		Peak MNI coordinates in mm								
Cluster size	qFDR	x		у	z	Brain regions (AAL)				
mASD < control										
354	0.014	42		- 69	8	Temporal_Mid_R (88.42%)				
						OUTSIDE (9.60%)				
364	0.014	18		-41	-24	Cerebellum_4_5_R (54.67%)				
						Cerebellum_3_R (31.04%)				
						ParaHippocampal_R (9.07%)				
mASD>control										
None										

**Table 2.** Brain regions with significant volume differences between the mASD and control groups. Onlyclusters with qFDR < 0.05 and their maximum peak voxels are presented; only AAL-defined regions</td>comprising  $\geq$  5% of a cluster are listed. The "OUTSIDE" anatomical label indicates a part of the region outsidethe parcellation. AAL automated anatomical labelling, MNI Montreal Neurological Institute, mASD mothers ofindividuals with autism spectrum disorder, qFDR false discovery rate q-value.



### GM volumes in cluster

**Figure 2.** Grey matter volume differences between the mASD and control groups in the first cluster. (a) The first significant cluster was observed in the right middle temporal gyrus. (b) Grey matter volume of the cluster was significantly different between the mASD and control groups (t(89) = 4.330, P = 0.000). (c) Scatter plot showing negative correlation between the grey matter extraction of the cluster and SQ scores for all subjects. The grey matter volume of the cluster was negatively correlated with SQ scores ( $\rho = -0.249$ , P = 0.017). \*\*\*P < 0.001. *GM* grey matter, *mASD* mothers of individuals with autism spectrum disorder, *SQ* systemizing quotient.

The MTG is associated with language, emotion, and social cognition (i.e. theory of mind or mentalization)<sup>47-50</sup> and may be related to dysfunctions in mentalization and social processing in ASD<sup>51-56</sup>. Structural and functional imaging studies have shown that the MTG is atypical in individuals with ASD, but findings remain controversial. A previous study reported that an ASD group showed decreased GM volume in the MTG, similar to our findings that the mASD group had smaller MTG volume<sup>57</sup>. In contrast, several previous meta-analytic studies



**Figure 3.** Grey matter volume differences between the mASD and control groups in the second cluster. (a) The second significant cluster was observed in the right cerebellum and parahippocampal gyrus. (b) Grey matter volume of the cluster was significantly different between the mASD and control groups (t(89)=3.528, P=0.001). (c) Scatter plot showing negative correlation between the grey matter extraction of the cluster and AQ scores for all subjects. The grey matter volume of the cluster was negatively correlated with AQ scores ( $\rho$ =-0.252, P=0.016). \*\*P<0.01. *GM* grey matter, *mASD* mothers of individuals with autism spectrum disorder, *AQ* autism spectrum quotient.

found that an ASD group had increased GM volume in the MTG<sup>58,59</sup>. Other meta-analytic studies have reported both increased and decreased GM volume in the MTG in ASD participants<sup>60,61</sup>. Regarding brain connectivity, individuals with ASD have hypoconnectivity of the posterior part of the MTG, indicating an association between the MTG and social cognition<sup>62,63</sup>.

The TPJ is a multimodal association area that receives and integrates input from the thalamus and multiple sensory modalities. Abnormalities in the higher-order integration area have been associated with lack of a mentalizing ability (i.e. theory of mind)<sup>64,65</sup>. The TPJ may play an important role in mentalizing, and mentalizing deficits are considered a key characteristic of ASD<sup>66-70</sup>. Moreover, TPJ abnormalities are one of the most consistent findings of brain structure<sup>71,72</sup> and function<sup>67,73</sup> in ASD.

The MTG and TPJ have often been implicated as aspects of the social brain, along with the superior temporal sulcus, fusiform gyrus, amygdala, anterior cingulate cortex, medial prefrontal cortex, and inferior frontal gyrus<sup>28,29,74,75</sup>. Abnormalities in the social brain regions have been widely suggested to result in poor social interactions in individuals with ASD<sup>30,31,73,76–78</sup>.

In the present study, smaller GM volumes within the MTG and TPJ correlated with higher SQ scores. The SQ assesses the drive to systemize, analyse, control, and construct rule-based systems, and all these features are involved in ASD<sup>37</sup>. Systemizing characteristics may mean that an individual is more interested in objects and/ or rule-based systems than in social communication<sup>37,79</sup>. We thus speculate that a stronger drive to systemize is correlated with a smaller volume in social brain areas such as the MTG and TPJ. We suggest that the atypical GM volume of these social parts of the brain (i.e. the MTG and TPJ) may represent a potential neuroendophenotype of ASD.

We also identified a smaller volume in the cerebellum and parahippocampal gyrus of the mASD group. Although the cerebellum accounts for only 10% of the brain's volume, it contains over half of all brain neurons<sup>80</sup>. The cerebellum plays an integrative role in the brain and connects many brain regions<sup>32,81-84</sup>. The cerebellum receives sensory information and conveys outputs to influence motor function through the cerebello-thalamocortical loops<sup>84–86</sup>. The cerebello-thalamocortical loops also have interconnections with the cerebral cortices and contribute to cognitive processing, including visuospatial perception, auditory processing, executive functions,

and language skills<sup>81,83,84,86,87</sup>. The cerebellum is also linked to the frontal cortex<sup>88</sup> and is involved in high-order cognitive functions<sup>82,83</sup>. Together, these findings indicate that the cerebellum is associated not only with motor coordination, but also with various forms of cognitive processing<sup>81,89,90</sup>.

Cerebellar abnormalities have been reported in individuals with ASD from early life through to adulthood<sup>33,34,91-94</sup>. Several previous studies on brain structure in ASD have reported decreased GM volume in the cerebellum in ASD groups, similar to our findings for the mASD group<sup>58,59</sup>. However, some meta-analytic studies have found that ASD groups showed decreased as well as increased GM volume in the cerebellum<sup>60,95</sup>. Recently, cerebellar neuropathology has gained attention as a means of explaining the characteristics of ASD<sup>32,87,96</sup>. Cerebellar abnormalities may be related to some ASD characteristics, such as a high rate of motor dysfunction, atypical sensory responsiveness, and impaired communication<sup>97–99</sup>.

The parahippocampal gyrus is an important pathway to the hippocampus and mediates convergent neocortical information for memory representations<sup>100</sup>. Functional MRI studies have shown that the right anterior parahippocampal gyrus is involved in the interactions between memory and emotion<sup>101</sup>, and may contribute to involuntary reactions associated with contextual fear memory that result in avoidance behaviour<sup>102</sup>. Previous brain structure studies have reported that individuals with ASD have abnormal patterns in the parahippocampal gyrus<sup>34,103,104</sup>. Furthermore, a reduction in parahippocampal GM volume may be related to the tendency to ignore dangers in individuals with ASD<sup>104</sup>.

In the present study, smaller GM volumes within the cerebellum and parahippocampal gyrus were related to higher levels of autistic traits. The cerebellum and parahippocampal gyrus play a role in receiving information from the cerebral cortex, and contribute to influencing emotional processing and various types of cognitive processing. We speculate that abnormalities in these brain areas may result in an atypical mediating pattern for emotional and cognitive processing in ASD. The small GM volumes in these brain regions might be related to subclinical ASD behavioural features, and may reflect a heritable neurobiological feature of ASD.

Our findings did not replicate the results of previous structural MRI studies of parents of individuals with ASD. There have been three such studies and they have reported inconsistent findings<sup>26,35,36</sup>. Rojas et al. measured volume in the hippocampus and amygdala in ASD individuals, the parents of individuals with ASD, and control subjects using manual-tracing techniques<sup>36</sup>. Both ASD individuals and parents of individuals with ASD had increased left hippocampal volume compared with the control group. In contrast, Palmen et al. used a semiautomatic procedure to compare the volume of the total brain, cortical lobes, cerebral GM and WM, cerebellum, and ventricles in the parents of individuals with ASD and a control group<sup>26</sup>. They found no significant differences in brain volume between the two groups. Peterson et al. used a VBM-based approach to compare regional GM volumes between a relatively small number of subjects (23 parents of individuals with ASD and 23 control subjects; 15 mothers and 8 fathers per group)<sup>35</sup>. They reported that the parents of individuals with ASD had increased volumes of the superior temporal gyri, inferior and middle frontal gyri, superior parietal lobule, and anterior cingulate, as well as decreased left anterior cerebellar hemisphere volume. The discrepancies between these three studies may result from both different analytical methods (manual-tracing technique, semi-automatic technique, or VBM methods) and participant characteristics (the number or sex of subjects).

**Limitations.** In the present study, we examined the GM volume in mothers of children with ASD, to exclude any potential confounding factors related to sex. To increase the generalizability of our findings, additional studies should include data from the fathers of children with ASD. In addition, further studies are required to investigate the relationship between brain imaging and gene expression, to provide more solid evidence for BAP neuroendophenotypes. We used AQ and SQ scores to assess autistic-like behavioural features of the participants. A study limitation is that these are self-report measures. We found that a considerable part of the first cluster was outside the anatomy parcellations (i.e. outside the brain) and the second cluster spans biologically distinct structures. These results may have been affected by motion, although we checked for noise and discarded noisy data using the Mahalanobis distance algorithm. It is necessary to confirm the present results using motion detection techniques in the future study.

### Conclusions

Previous findings on brain structure in individuals with ASD and their parents are controversial. In the present study, we calculated GM volume in mASD and control groups using the whole-brain VBM method. We found that compared with the control group, the mASD group had smaller GM volumes in the MTG, TPJ, cerebellum, and parahippocampal gyrus. Our findings provide evidence to clarify controversial findings regarding intermediate neurobiological patterns observed in relatives of individuals with ASD, which we hope will ultimately help elucidate the underlying neurobiology of ASD. We suggest that these brain regions represent heritable brain structural features of ASD.

### Data availability

The datasets generated and/or analysed during the current study are not publicly available as they contain information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Received: 27 October 2020; Accepted: 26 April 2021 Published online: 11 May 2021

### References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. (2013).

- Rossignol, D. A., Genuis, S. J. & Frye, R. E. Environmental toxicants and autism spectrum disorders: A systematic review. *Transl. Psychiatry* 4, e360. https://doi.org/10.1038/tp.2014.4 (2014).
- Abrahams, B. S. & Geschwind, D. H. Advances in autism genetics: On the threshold of a new neurobiology. Nat. Rev. Genet. 9, 341–355. https://doi.org/10.1038/nrg2346 (2008).
- Levy, S. E., Mandell, D. S. & Schultz, R. T. Autism. Lancet 374, 1627–1638. https://doi.org/10.1016/S0140-6736(09)61376-3 (2009).
- Tick, B., Bolton, P., Happe, F., Rutter, M. & Rijsdijk, F. Heritability of autism spectrum disorders: A meta-analysis of twin studies. J. Child Psychol. Psychiatry 57, 585–595. https://doi.org/10.1111/jcpp.12499 (2016).
- Dell'Osso, L., Dalle Luche, R. & Maj, M. Adult autism spectrum as a transnosographic dimension. CNS Spectr. 21, 131–133. https://doi.org/10.1017/S1092852915000450 (2016).
- Freitag, C. M. The genetics of autistic disorders and its clinical relevance: A review of the literature. *Mol. Psychiatry* 12, 2–22. https://doi.org/10.1038/sj.mp.4001896 (2007).
- 8. Asperger, H. Die autistischen Psychopathen im Kindersalter. Arch. Psychiatr. Nervenkr. 117, 76-136 (1944).
- 9. Kanner, L. Autistic disturbances of affective contact. Nervous Child 2, 217-250 (1943).
- Baron-Cohen, S. & Hammer, J. Parents of children with Asperger syndrome: What is the cognitive phenotype?. J. Cogn. Neurosci. 9, 548–554 (1997).
- 11. Gerdts, J. & Bernier, R. The broader autism phenotype and its implications on the etiology and treatment of autism spectrum disorders. *Autism Res. Treat.* 2011, 545901. https://doi.org/10.1155/2011/545901 (2011).
- Gillberg, C., Gillberg, I. C. & Steffenburg, S. Siblings and parents of children with autism: A controlled population-based study. Dev. Med. Child Neurol. 34, 389–398. https://doi.org/10.1111/j.1469-8749.1992.tb11450.x (1992).
- Lainhart, J. E. et al. Autism, regression, and the broader autism phenotype. Am. J. Med. Genet. 113, 231–237. https://doi.org/10. 1002/ajmg.10615 (2002).
- 14. Landa, R. *et al.* Social language use in parents of autistic individuals. *Psychol. Med.* 22, 245–254. https://doi.org/10.1017/s0033 291700032918 (1992).
- 15. Piven, J. *et al.* Personality and language characteristics in parents from multiple-incidence autism families. *Am. J. Med. Genet.* **74**, 398–411 (1997).
- Sucksmith, E., Roth, I. & Hoekstra, R. A. Autistic traits below the clinical threshold: Re-examining the broader autism phenotype in the 21st century. *Neuropsychol. Rev.* 21, 360–389. https://doi.org/10.1007/s11065-011-9183-9 (2011).
- Hasegawa, C. *et al.* Broader autism phenotype in mothers predicts social responsiveness in young children with autism spectrum disorders. *Psychiatry Clin. Neurosci.* 69, 136–144. https://doi.org/10.1111/pcn.12210 (2015).
- Wheelwright, S., Auyeung, B., Allison, C. & Baron-Cohen, S. Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). *Mol. Autism* 1, 10. https://doi.org/10.1186/2040-2392-1-10 (2010).
- Leboyer, M. et al. Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relatives. Biol. Psychiatry 45, 158–163. https://doi.org/10.1016/s0006-3223(97)00532-5 (1999).
- Fatemi, S. H., Stary, J. M. & Egan, E. A. Reduced blood levels of reelin as a vulnerability factor in pathophysiology of autistic disorder. *Cell Mol. Neurobiol.* 22, 139–152. https://doi.org/10.1023/a:1019857620251 (2002).
- Aldred, S., Moore, K. M., Fitzgerald, M. & Waring, R. H. Plasma amino acid levels in children with autism and their families. J. Autism Dev. Disord. 33, 93–97. https://doi.org/10.1023/a:1022238706604 (2003).
- Piven, J., Palmer, P., Jacobi, D., Childress, D. & Arndt, S. Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. *Am. J. Psychiatry* 154, 185–190. https://doi.org/10.1176/ajp.154.2.185 (1997).
- Bailey, A., Palferman, S., Heavey, L. & Le Couteur, A. Autism: The phenotype in relatives. J. Autism Dev. Disord. 28, 369–392. https://doi.org/10.1023/a:1026048320785 (1998).
- Losh, M., Childress, D., Lam, K. & Piven, J. Defining key features of the broad autism phenotype: a comparison across parents of multiple- and single-incidence autism families. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147B, 424–433, doi:https://doi. org/10.1002/ajmg.b.30612 (2008).
- Billeci, L. et al. The broad autism (Endo)Phenotype: Neurostructural and neurofunctional correlates in parents of individuals with autism spectrum disorders. Front. Neurosci. 10, 346. https://doi.org/10.3389/fnins.2016.00346 (2016).
- Palmen, S. J. et al. Brain anatomy in non-affected parents of autistic probands: A MRI study. Psychol. Med. 35, 1411–1420. https:// doi.org/10.1017/S0033291705005015 (2005).
- Gottesman, I. I. & Gould, T. D. The endophenotype concept in psychiatry: Etymology and strategic intentions. Am. J. Psychiatry 160, 636–645. https://doi.org/10.1176/appi.ajp.160.4.636 (2003).
- 28. Adolphs, R. The neurobiology of social cognition. *Curr. Opin. Neurobiol.* **11**, 231–239. https://doi.org/10.1016/s0959-4388(00) 00202-6 (2001).
- Kennedy, D. P. & Adolphs, R. The social brain in psychiatric and neurological disorders. Trends Cogn. Sci. 16, 559–572. https:// doi.org/10.1016/j.tics.2012.09.006 (2012).
- Sato, W. et al. Reduced gray matter volume in the social brain network in adults with autism spectrum disorder. Front. Hum. Neurosci. 11, 395. https://doi.org/10.3389/fnhum.2017.00395 (2017).
- Williams, J. H. et al. Neural mechanisms of imitation and "mirror neuron" functioning in autistic spectrum disorder. Neuropsychologia 44, 610–621. https://doi.org/10.1016/j.neuropsychologia.2005.06.010 (2006).
- Wang, S. S., Kloth, A. D. & Badura, A. The cerebellum, sensitive periods, and autism. Neuron 83, 518–532. https://doi.org/10. 1016/j.neuron.2014.07.016 (2014).
- Stanfield, A. C. et al. Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur. Psychiatry 23, 289–299. https://doi.org/10.1016/j.eurpsy.2007.05.006 (2008).
- 34. Abell, F. et al. The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *NeuroReport* **10**, 1647–1651. https://doi.org/10.1097/00001756-199906030-00005 (1999).
- Peterson, E. et al. A voxel-based morphometry study of gray matter in parents of children with autism. NeuroReport 17, 1289– 1292. https://doi.org/10.1097/01.wnr.0000233087.15710.87 (2006).
- Rojas, D. C. *et al.* Hippocampus and amygdala volumes in parents of children with autistic disorder. *Am. J. Psychiatry* 161, 2038–2044. https://doi.org/10.1176/appi.ajp.161.11.2038 (2004).
- Baron-Cohen, S., Richler, J., Bisarya, D., Gurunathan, N. & Wheelwright, S. The systemizing quotient: An investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 358, 361–374. https://doi.org/10.1098/rstb.2002.1206 (2003).
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J. & Clubley, E. The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J. Autism Dev. Disord. 31, 5–17. https://doi.org/10.1023/a:1005653411471 (2001).
- Wing, L., Leekam, S. R., Libby, S. J., Gould, J. & Larcombe, M. The diagnostic interview for social and communication disorders: background, inter-rater reliability and clinical use. J. Child. Psychol. Psychiatry 43, 307–325. https://doi.org/10.1111/1469-7610. 00023 (2002).
- 40. Lord, C. *et al.* The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J. Autism Dev. Disord.* **30**, 205–223 (2000).

- Oldfield, R. C. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9, 97–113. https://doi. org/10.1016/0028-3932(71)90067-4 (1971).
- Ashburner, J. & Friston, K. J. Unified segmentation. Neuroimage 26, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018 (2005).
- Ashburner, J. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113. https://doi.org/10.1016/j.neuroimage. 2007.07.007 (2007).
- Tohka, J., Zijdenbos, A. & Evans, A. Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage 23, 84–97. https://doi.org/10.1016/j.neuroimage.2004.05.007 (2004).
- Tzourio-Mazoyer, N. *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289. https://doi.org/10.1006/nimg.2001.0978 (2002).
- Schurz, M., Tholen, M. G., Perner, J., Mars, R. B. & Sallet, J. Specifying the brain anatomy underlying temporo-parietal junction activations for theory of mind: A review using probabilistic atlases from different imaging modalities. *Hum. Brain Map.* 38, 4788–4805. https://doi.org/10.1002/hbm.23675 (2017).
- Haxby, J. V., Hoffman, E. A. & Gobbini, M. I. The distributed human neural system for face perception. *Trends Cogn. Sci.* 4, 223–233. https://doi.org/10.1016/s1364-6613(00)01482-0 (2000).
- Mosconi, M. W., Mack, P. B., McCarthy, G. & Pelphrey, K. A. Taking an "intentional stance" on eye-gaze shifts: A functional neuroimaging study of social perception in children. *Neuroimage* 27, 247–252. https://doi.org/10.1016/j.neuroimage.2005.03. 027 (2005).
- Vollm, B. A. *et al.* Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage* 29, 90–98. https://doi.org/10.1016/j.neuroimage.2005.07.022 (2006).
- Whitney, C., Jefferies, E. & Kircher, T. Heterogeneity of the left temporal lobe in semantic representation and control: Priming multiple versus single meanings of ambiguous words. *Cereb. Cortex* 21, 831–844. https://doi.org/10.1093/cercor/bhq148 (2011).
- Assaf, M. *et al.* Mentalizing and motivation neural function during social interactions in autism spectrum disorders. *Neuroimage Clin.* 3, 321–331. https://doi.org/10.1016/j.nicl.2013.09.005 (2013).
- Critchley, H. D. et al. The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 123(Pt 11), 2203–2212. https://doi.org/10.1093/brain/123.11.2203 (2000).
- Georgescu, A. L. et al. Neural correlates of "social gaze" processing in high-functioning autism under systematic variation of gaze duration. *Neuroimage Clin.* 3, 340–351. https://doi.org/10.1016/j.nicl.2013.08.014 (2013).
- Koshino, H. et al. fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. Cereb. Cortex 18, 289–300. https://doi.org/10.1093/cercor/bhm054 (2008).
- Monk, C. S. et al. Neural circuitry of emotional face processing in autism spectrum disorders. J. Psychiatry Neurosci. 35, 105–114. https://doi.org/10.1503/jpn.090085 (2010).
- von dem Hagen, E. A., Stoyanova, R. S., Rowe, J. B., Baron-Cohen, S. & Calder, A. J. Direct gaze elicits atypical activation of the theory-of-mind network in autism spectrum conditions. *Cereb. Cortex* 24, 1485–1492. https://doi.org/10.1093/cercor/bht003 (2014).
- Greimel, E. et al. Changes in grey matter development in autism spectrum disorder. Brain Struct. Funct. 218, 929–942. https:// doi.org/10.1007/s00429-012-0439-9 (2013).
- Lukito, S. *et al.* Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attentiondeficit/hyperactivity disorder and autism spectrum disorder. *Psychol. Med.* 50, 894–919. https://doi.org/10.1017/S003329172 0000574 (2020).
- Yang, X. et al. Brain gray matter alterations and associated demographic profiles in adults with autism spectrum disorder: A meta-analysis of voxel-based morphometry studies. Aust. N Z J. Psychiatry 50, 741–753. https://doi.org/10.1177/0004867415 623858 (2016).
- Cauda, F. et al. Grey matter abnormality in autism spectrum disorder: An activation likelihood estimation meta-analysis study. J. Neurol. Neurosurg. Psychiatry 82, 1304–1313. https://doi.org/10.1136/jnnp.2010.239111 (2011).
- Duerden, E. G., Mak-Fan, K. M., Taylor, M. J. & Roberts, S. W. Regional differences in grey and white matter in children and adults with autism spectrum disorders: An activation likelihood estimate (ALE) meta-analysis. *Autism Res.* 5, 49–66. https:// doi.org/10.1002/aur.235 (2012).
- Itahashi, T. et al. Alterations of local spontaneous brain activity and connectivity in adults with high-functioning autism spectrum disorder. Mol. Autism 6, 30. https://doi.org/10.1186/s13229-015-0026-z (2015).
- 63. Xu, J. *et al.* Specific functional connectivity patterns of middle temporal gyrus subregions in children and adults with autism spectrum disorder. *Autism Res.* 13, 410–422. https://doi.org/10.1002/aur.2239 (2020).
- 64. Adolphs, R. The social brain: Neural basis of social knowledge. Annu. Rev. Psychol. 60, 693–716. https://doi.org/10.1146/annur ev.psych.60.110707.163514 (2009).
- Gallagher, H. L. & Frith, C. D. Functional imaging of "theory of mind". Trends Cogn. Sci. 7, 77-83. https://doi.org/10.1016/ s1364-6613(02)00025-6 (2003).
- Baron-Cohen, S., Leslie, A. M. & Frith, U. Does the autistic child have a "theory of mind"?. Cognition 21, 37–46. https://doi.org/ 10.1016/0010-0277(85)90022-8 (1985).
- 67. Castelli, F., Frith, C., Happe, F. & Frith, U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain* **125**, 1839–1849. https://doi.org/10.1093/brain/awf189 (2002).
- 68. Frith, U. Mind blindness and the brain in autism. Neuron **32**, 969–979. https://doi.org/10.1016/s0896-6273(01)00552-9 (2001).
- Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., Consortium, M. A. & Baron-Cohen, S. Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. *Neuroimage* 56, 1832–1838. https://doi.org/10.1016/j. neuroimage.2011.02.067 (2011).
- Zilbovicius, M. et al. Autism, the superior temporal sulcus and social perception. Trends Neurosci. 29, 359–366. https://doi.org/ 10.1016/j.tins.2006.06.004 (2006).
- Boddaert, N. *et al.* Superior temporal sulcus anatomical abnormalities in childhood autism: A voxel-based morphometry MRI study. *Neuroimage* 23, 364–369. https://doi.org/10.1016/j.neuroimage.2004.06.016 (2004).
- 72. Levitt, J. G. et al. Cortical sulcal maps in autism. Cereb. Cortex 13, 728-735. https://doi.org/10.1093/cercor/13.7.728 (2003).
- Pelphrey, K. A. & Carter, E. J. Brain mechanisms for social perception: Lessons from autism and typical development. *Ann. N Y Acad. Sci.* 1145, 283–299. https://doi.org/10.1196/annals.1416.007 (2008).
- Blakemore, S. J., den Ouden, H., Choudhury, S. & Frith, C. Adolescent development of the neural circuitry for thinking about intentions. Soc. Cogn. Affect. Neurosci. 2, 130–139. https://doi.org/10.1093/scan/nsm009 (2007).
- Frith, C. D. & Frith, U. Implicit and explicit processes in social cognition. Neuron 60, 503–510. https://doi.org/10.1016/j.neuron. 2008.10.032 (2008).
- Dapretto, M. et al. Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. Nat. Neurosci. 9, 28–30. https://doi.org/10.1038/nn1611 (2006).
- Hadjikhani, N., Joseph, R. M., Snyder, J. & Tager-Flusberg, H. Anatomical differences in the mirror neuron system and social cognition network in autism. *Cereb. Cortex* 16, 1276–1282. https://doi.org/10.1093/cercor/bhj069 (2006).
- Patriquin, M. A., DeRamus, T., Libero, L. E., Laird, A. & Kana, R. K. Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. *Hum. Brain Map.* 37, 3957–3978. https://doi.org/10.1002/hbm.23288 (2016).

- Wheelwright, S. et al. Predicting autism spectrum quotient (AQ) from the systemizing quotient-revised (SQ-R) and empathy quotient (EQ). Brain Res. 1079, 47–56. https://doi.org/10.1016/j.brainres.2006.01.012 (2006).
- Herculano-Houzel, S. Coordinated scaling of cortical and cerebellar numbers of neurons. Front. Neuroanat. 4, 12. https://doi. org/10.3389/fnana.2010.00012 (2010).
- 81. Broussard, D. M. The Cerebellum: Learning Movement, Language, and Social Skills. (John Wiley & Sons, Inc., 2014).
- Schmahmann, J. D. Disorders of the cerebellum: Ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J. Neuropsychiatry Clin. Neurosci. 16, 367–378. https://doi.org/10.1176/jnp.16.3.367 (2004).
- Schmahmann, J. D. The role of the cerebellum in cognition and emotion: Personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. *Neuropsychol. Rev.* 20, 236–260. https://doi.org/10.1007/ s11065-010-9142-x (2010).
- Strick, P. L., Dum, R. P. & Fiez, J. A. Cerebellum and nonmotor function. Annu. Rev. Neurosci. 32, 413–434. https://doi.org/10. 1146/annurev.neuro.31.060407.125606 (2009).
- Prevosto, V., Graf, W. & Ugolini, G. Cerebellar inputs to intraparietal cortex areas LIP and MIP: Functional frameworks for adaptive control of eye movements, reaching, and arm/eye/head movement coordination. *Cereb. Cortex* 20, 214–228. https:// doi.org/10.1093/cercor/bhp091 (2010).
- Voogd, J., Schraa-Tam, C. K., van der Geest, J. N. & De Zeeuw, C. I. Visuomotor cerebellum in human and nonhuman primates. Cerebellum 11, 392–410. https://doi.org/10.1007/s12311-010-0204-7 (2012).
- Fatemi, S. H. et al. Consensus paper: Pathological role of the cerebellum in autism. Cerebellum 11, 777–807. https://doi.org/10. 1007/s12311-012-0355-9 (2012).
- Krienen, F. M. & Buckner, R. L. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cereb. Cortex* 19, 2485–2497. https://doi.org/10.1093/cercor/bhp135 (2009).
- Bolduc, M. E. et al. Regional cerebellar volumes predict functional outcome in children with cerebellar malformations. Cerebellum 11, 531–542. https://doi.org/10.1007/s12311-011-0312-z (2012).
- Bolduc, M. E. et al. Spectrum of neurodevelopmental disabilities in children with cerebellar malformations. Dev. Med. Child Neurol. 53, 409–416. https://doi.org/10.1111/j.1469-8749.2011.03929.x (2011).
- Becker, E. B. & Stoodley, C. J. Autism spectrum disorder and the cerebellum. *Int. Rev. Neurobiol.* 113, 1–34. https://doi.org/10. 1016/B978-0-12-418700-9.00001-0 (2013).
- Courchesne, E. et al. Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57, 245–254. https://doi.org/10.1212/wnl.57.2.245 (2001).
- Scott, J. A., Schumann, C. M., Goodlin-Jones, B. L. & Amaral, D. G. A comprehensive volumetric analysis of the cerebellum in children and adolescents with autism spectrum disorder. *Autism Res.* 2, 246–257. https://doi.org/10.1002/aur.97 (2009).
- 94. Wegiel, J. *et al.* The neuropathology of autism: Defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol.* **119**, 755–770. https://doi.org/10.1007/s00401-010-0655-4 (2010).
- 95. DeRamus, T. P. & Kana, R. K. Anatomical likelihood estimation meta-analysis of grey and white matter anomalies in autism spectrum disorders. *Neuroimage Clin.* **7**, 525–536. https://doi.org/10.1016/j.nicl.2014.11.004 (2015).
- Hampson, D. R. & Blatt, G. J. Autism spectrum disorders and neuropathology of the cerebellum. Front. Neurosci. 9, 420. https:// doi.org/10.3389/fnins.2015.00420 (2015).
- Leekam, S. R., Nieto, C., Libby, S. J., Wing, L. & Gould, J. Describing the sensory abnormalities of children and adults with autism. J. Autism Dev. Disord. 37, 894-910. https://doi.org/10.1007/s10803-006-0218-7 (2007).
- Markram, K. & Markram, H. The intense world theory: A unifying theory of the neurobiology of autism. *Front. Hum. Neurosci.* 4, 224. https://doi.org/10.3389/fnhum.2010.00224 (2010).
- Fournier, K. A., Hass, C. J., Naik, S. K., Lodha, N. & Cauraugh, J. H. Motor coordination in autism spectrum disorders: A synthesis and meta-analysis. J. Autism Dev. Disord. 40, 1227–1240. https://doi.org/10.1007/s10803-010-0981-3 (2010).
- Eichenbaum, H. A cortical-hippocampal system for declarative memory. Nat. Rev. Neurosci. 1, 41–50. https://doi.org/10.1038/ 35036213 (2000).
- Erk, S. et al. Emotional context modulates subsequent memory effect. Neuroimage 18, 439–447. https://doi.org/10.1016/s1053-8119(02)00015-0 (2003).
- Paquette, V. et al. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage 18, 401–409. https://doi.org/10.1016/s1053-8119(02)00030-7 (2003).
- Jiao, Y. *et al.* Predictive models of autism spectrum disorder based on brain regional cortical thickness. *Neuroimage* 50, 589–599. https://doi.org/10.1016/j.neuroimage.2009.12.047 (2010).
- Ke, X. et al. Voxel-based morphometry study on brain structure in children with high-functioning autism. NeuroReport 19, 921–925. https://doi.org/10.1097/WNR.0b013e328300edf3 (2008).

### Acknowledgements

The authors thank Sachiko Kitagawa, Yukiko Saotome, and Sumie Iwasaki for conducting the behavioural and MRI experiments. They also thank Mutsumi Ozawa and Yoko Morita for preparing the experiments. We particularly appreciate the help of the children and their parents who participated in this study.

### Author contributions

K.A. designed and conceptualized the study, analysed the data, drafted the manuscript, and revised the manuscript. T.I., K.Y., Y.Y., and D.N.S. recorded neuroimaging data and revised the manuscript. C.H. and S.T. contributed to ASD ascertainment and recorded neuroimaging and behavioural data. T.H. contributed to ASD ascertainment and revised the manuscript. M.K. secured funding, designed and conceptualized the study, contributed to ASD ascertainment, drafted the manuscript, and revised the manuscript.

### Funding

This work was supported by a grants from the Center of Innovation Program from the Japan Science and Technology Agency (https://www.coistream.osaka-u.ac.jp/en) and the Collaborative Resarch Program of the Collaborative Research Network for Asian Children with Developmental Disorders. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Competing interests

The authors declare no competing interests.

### Additional information

Correspondence and requests for materials should be addressed to K.A. or D.N.S.

Reprints and permissions information is available at www.nature.com/reprints.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021