



White and gray matter correlates of theory of mind in autism: a voxel-based morphometry study

Firat Soyly¹ · Kaitlyn May¹ · Rajesh Kana²

Received: 7 June 2022 / Accepted: 2 July 2023

© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract

Autism spectrum disorder (ASD) is characterized by difficulties in theory of mind (ToM) and social communication. Studying structural and functional correlates of ToM in the brain and how autistic and nonautistic groups differ in terms of these correlates can help with diagnosis and understanding the biological mechanisms of ASD. In this study, we investigated white matter volume (WMV) and gray matter volume (GMV) differences between matching autistic and nonautistic samples, and how these structural features relate to age and ToM skills, indexed by the Reading the Mind in the Eyes (RMIE) measure. The results showed widespread GMV and WMV differences between the two groups in regions crucial for social processes. The autistic group did not express the typically observed negative GMV and positive WMV correlations with age at the same level as the nonautistic group, pointing to abnormalities in developmental structural changes. In addition, we found differences between the two groups in how GMV relates to ToM, particularly in the left frontal regions, and how WMV relates to ToM, mostly in the cingulate and corpus callosum. Finally, GMV in the left insula, a region that is part of the salience network, was found to be crucial in distinguishing ToM performance between the two groups.

Keywords Autism · Gray matter · White matter · Social cognition · Theory of mind · Voxel-based morphometry

Introduction

Functional and structural neuroimaging studies during the past two decades have provided valuable insights into the complex neurobiology of autism spectrum disorder (ASD). ASD is primarily characterized by restrictive or repetitive patterns of interests and behaviors, and difficulties in social communication and interpersonal understanding (Happé and Frith 2006; Isaksson et al. 2019; Velikonja et al. 2019). Many autistic individuals experience diminished functional and social skills (Sasson et al. 2017), often resulting in social isolation (Howlin et al. 2013; Orsmond et al. 2013) and an overall lower quality of life (Billstedt et al. 2011; Heijst and Geurts 2015; Mazurek 2014). Autism Spectrum Disorder (ASD) typically manifests in early childhood and can lead

to difficulties in social, academic, and occupational settings as individuals exhibit symptoms of the disorder (American Psychiatric Association 2013). While neuroimaging has provided important insights into understanding ASD, firm and reliable biomarkers for the disorder have been rather elusive. Among the structural imaging findings, a few have been consistent and replicated, such as larger brain volume during the early years of development (Courchesne et al. 2001; Sacco et al. 2015), smaller corpus callosum (Just et al. 2007; Lefebvre et al. 2015; Loomba et al. 2021), and altered organization of the prefrontal cortex (Morgan et al. 2012; Stoner et al. 2014).

Extensive work demonstrates abnormal cortical growth, cortical thickness, and overall overgrowth of the prefrontal cortex during childhood in ASD (Carper and Courchesne 2005; DeRamus and Kana 2015; Schumann et al. 2010). The prefrontal cortex (PFC) is essential for navigating the complexity of social interactions and plays a key role in evaluating social appropriateness and moral judgments (Forbes and Grafman 2010), monitoring reward and punishment, and predicting outcomes (Amodio and Frith 2006). A longitudinal study on toddlers with ASD revealed an overgrowth of the cerebrum, particularly frontal, temporal, and cingulate

✉ Firat Soyly
fsoyly@ua.edu

¹ Educational Psychology Program, The University of Alabama, Tuscaloosa, USA

² Department of Psychology, & the Center for Innovative Research in Autism, University of Alabama, Tuscaloosa, USA

cortices, in early childhood (Schumann et al. 2010). This early frontal cortex overgrowth is followed by a reduction in total brain volume during later childhood and adolescence (Courchesne et al. 2011a, b) and normalization of cortical thickness in mid- to late-childhood (Zielinski et al. 2014). Moreover, a postmortem study of children aged 2 to 15 years showed a massive increase in the number of neurons in the dorsolateral and medial prefrontal cortices in ASD compared to TD children and adolescents (Courchesne et al. 2011a, b). These growth patterns have been suggested to underlie many impairments in social interaction and emotion processing that are characteristic of ASD.

One issue with structural studies on ASD is the lack of consistency in findings on region-specific gray matter volume (GMV) and white matter volume (WMV). For example, both higher and lower GMV compared to controls have been reported in the temporal lobe, limbic system, and cerebellum of older autistic adults (Abell et al. 1999; Craig et al. 2007). Therefore, there is a need for more studies with larger samples and meta-analysis studies aggregating findings across many studies. A meta-analysis of voxel-based morphometry (VBM) studies comparing autistic and nonautistic adults revealed higher GMV in the cerebellum, middle temporal gyrus, right anterior cingulate cortex, caudate, insula, the fusiform gyrus, precuneus, and posterior cingulate cortex, and lower gray matter (GM) in the cerebellar tonsil, inferior parietal lobule, middle temporal gyrus, right amygdala, insula, and middle temporal gyrus (Cauda et al. 2011). Another meta-analysis study suggests age-related decreases in GMV and WMV within parietal and inferior temporal regions, and GMV increases in frontal and anterior-temporal regions (DeRamus and Kana 2015). In a separate meta-analysis, Nickl-Jockschat et al. (2012a, b) reported structural anomalies in the lateral occipital lobe, pericentral region, medial temporal lobe, basal ganglia, and right parietal operculum for autistic adults.

Since ASD involves deficits in social cognition, the relation between structural brain features and social abilities, in particular *theory of mind* (ToM) has been subject to study. Social cognition (SC) involves a collection of skills, including ToM and recognition and processing of facial expression, vocal tone, and other social cues (Frith 2008). The social brain, a set of brain regions found to be central to SC, is comprised of the prefrontal cortex (PFC), amygdala, thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), superior temporal sulcus (STS), temporo-parietal junction (TPJ), occipitotemporal regions, and fusiform gyrus, somatosensory cortex, and motor cortex (Eack et al. 2017; Han et al. 2021). Emerging work highlights structural abnormalities in the social brain as paramount to social impairments in ASD (Johnson et al. 2005; Sato et al. 2017; Williams et al. 2001). Identification of functionally relevant neuroanatomical abnormalities in ASD will expand

our understanding of how subtle deviations in neurological development impact autistic behaviors and overall development. Moreover, because of the substantial heterogeneity of ASD, finding firm and reliable structural biomarkers to identify ASD subtypes may facilitate earlier diagnosis. However, existing research differs substantially in the location and direction (i.e., increased or decreased) of identified abnormalities in GMV and WMV.

Gray matter volume

A number of studies have reported decreased GMV in social brain regions in ASD, including the inferior occipital gyrus (IOG) (Ecker et al. 2013; Hadjikhani et al. 2006), middle and inferior frontal gyrus (IFG) (Craig et al. 2007; Ecker et al. 2013; Hadjikhani et al. 2006; Toal et al. 2010), middle temporal gyrus (MTG) (Craig et al. 2007; Ecker et al. 2013; Hadjikhani et al. 2006; Mueller et al. 2013), amygdala (Craig et al. 2007; Lai et al. 2015), inferior frontal gyrus (IFG) (Hadjikhani et al. 2006; Mueller et al. 2013), OFC (Craig et al. 2007; Hadjikhani et al. 2006), and dorsomedial prefrontal cortex (DMPFC) (Abell et al. 1999; Hadjikhani et al. 2006). These GMV abnormalities have also been found to be associated with behavioral differences and the severity in ASD, and such differences in GMV were able to distinguish autistic from nonautistic individuals (Sato et al. 2017).

Anatomical differences in amygdala have been shown from human neuroimaging and animal studies, specifically early enlargement in childhood correlating with social cognition deficit severity (Ecker 2017), followed by a reduction in size in adolescence and into adulthood, at which point autistic adults show smaller GMV in the amygdala compared to nonautistics (Radeloff et al. 2014). GM abnormalities in temporal regions have also been reported, including reduced GMV in the STS and MTG in infancy (Xiao et al. 2014), early childhood (Retico et al. 2016), adolescence (Lim et al. 2015), and adulthood in ASD (McAlonan et al. 2005). However, some research does indicate higher GMV in the MTG and STG in autistic adults (Waiter et al. 2004). When compared to autistic adults, autistic children show significantly reduced GM concentration in the STG, a key region in social communication (Boddaert et al. 2004). Organization of the fusiform gyrus and its connections with amygdala in the autistic brain have likewise been shown to differ from controls in neuroimaging studies. Specifically, multiple studies report higher volume in the left hemisphere of the posterior fusiform gyrus in controls (Libero et al. 2014; Troncel et al. 2013). Anterior cingulate cortex differences have been reported, especially in the organization of neurons and volumetric increases (Cauda et al. 2011; Kana et al. 2007, 2009). Finally, ample research suggests that reduced GMV within the PFC may potentially subserve some of the SC difficulties autistic individuals experience (Luna et al. 2002;

Schulte-Rüther et al. 2011). Despite widespread structural alterations reported in autistic social brain, some inconsistency across findings, and less evidence of network-level alterations, is noteworthy (Duerden et al. 2012; Yang et al. 2016).

White matter volume

Substantial research demonstrates alterations of white matter in social brain regions in ASD may be related to some of the impairments in social behavior. For instance, reduced tract integrity of the superior longitudinal fasciculus (SLF), which has projections to the STS and IFG—two key regions of the social brain—has been shown to be associated with impairments in social interaction (Libero et al. 2016; Lo et al. 2017). Widespread WMV reductions in the frontal, parietal, and temporal regions in ASD have been linked to deficits in social awareness and empathy (d’Albis et al. 2018). WMV reduction in the amygdala has also been cited as a contributor to difficulties in ToM in ASD (Gibbard et al. 2018). In addition, reduced fractional anisotropy (FA) of white matter (WM) connections in the insula and temporal lobe have been reported in ASD and linked to impairments in social awareness and cognitive empathy in adult autistic males (d’Albis et al. 2018). Short-tract connectivity abnormalities in the temporal lobe and insula are associated with various SC skills, such as social awareness, language structure, pragmatics, and empathy (d’Albis et al. 2018). Specifically, this body of work has shown increased frontotemporal and orbitofrontal connections (Eack et al. 2017) and decreased cortical thickness in these regions (Park et al. 2018). Diffusion tensor imaging (DTI) studies report a consistent reduction in FA and an increase in mean diffusivity in WM. Decreased FA is most frequently reported in the corpus callosum (Travers et al. 2012), superior longitudinal fasciculus (Im et al. 2018), and occipitofrontal fasciculus (Noriuchi et al. 2010) but has also been reported in WM of the ventromedial prefrontal cortices, ACC, and TPJ (Barnea-Goraly et al. 2004).

Historically, neuroimaging research has placed considerable focus on GM abnormalities, with lesser consideration of WM abnormalities. Reading WM atypicality in a larger context of the disorder is particularly important when considering social impairments, as damage to WM tracts between social regions has been shown to be a key feature of some social disorders (Wang and Olson 2018). Moreover, because WM enables the operation and coordination of long-range networks, WM may be especially crucial to social cognition given that the social network is quite widespread. Therefore, broadening the understanding of the structural features of the ASD social brain, like WM integrity, is a necessary step to understanding the neurobiology of social dysfunction in ASD. Moreover, because maturation or deterioration of WM

throughout the lifespan has been shown to largely contribute to the development or diminishing of social skills (Johansen-Berg 2010; Thomas et al. 2008), expanding research on WM differences in ASD could provide insight into socio-cognitive changes across development (Scherf et al. 2015) or in response to intervention (Rosenblau et al. 2020).

Current study

To better understand structural correlates of autism, the current study uses voxel-based morphometry (VBM) to compare an autistic sample with a matching control sample in terms of whole-brain GMV and WMV, and how these measures relate to ToM. VBM detects anatomical differences between groups of participants by conducting statistical tests across all voxels of images to identify volume differences between groups. It is particularly sensitive to differences in GM and WM while (discounting) large-scale volumetric differences by aligning each image to a template and prior probability match, thereby reducing error in normalization and segmentation (Ashburner and Friston 2001). VBM can identify microstructural differences in brain anatomy between groups without the need for pre-determined regions of interest (Scarpazza and Simone 2016). In this study, we not only focus on the structural differences between the autistic and nonautistic participants but also investigate how these structural features relate to age and theory-of-mind (ToM) skills.

Methods

Participants

Data from 111 participants were used across two diagnostic groups; autistic ($N=54$, 48 males), and nonautistic ($N=57$, 53 males). All participants were native English speakers. The data used in this study come from a wider dataset that includes fMRI and various behavioral data, which were reported in previous studies (e.g., Libero et al. 2014; Murdaugh et al. 2012). The autistic participants were previously clinically diagnosed with ASD and participants in both groups did not report having any other neuropsychological conditions. Both groups had relatively young samples (including both children and adults); the autistic group had an average age of 18.26 years (range 8–33, SD: 5.97) and the nonautistic group 17.92 years (range 8–34, SD: 6.73). The two groups did not differ in terms of age ($t[113]=0.28$, $p=0.78$) and full-scale IQ (FSIQ) of the Wechsler Abbreviated Scale of Intelligence – WASI (autistic: $M=109.92$, $SD=15.24$, nonautistic: $M=112.69$, $SD=12.08$, $t[93.36]=-1.02$, $p=0.31$).

Reading the mind in the eyes (RMIE) task

The RMIE test is commonly used to measure ToM. The children's version of the RMIE task was used for all participants (Baron-Cohen et al. 2001). The participants were shown 28 black and white photographs of the eye region of faces on a computer using PowerPoint slides and were asked to choose and point to which word out of 4 choices best described what the person shown in the photo is thinking or feeling. The score reported reflects the number of pictures that were correctly identified. The two groups significantly differed in their RMIE scores, the autistic group ($M=18.83$, $SD=3.29$) having lower scores than the nonautistic group ($M=20.51$, $SD=2.41$), $t(96.98)=-3.05$, $p=0.003$.

MRI data acquisition

Structural MRI data were collected using a Siemens 3 Tesla Allegra scanner (Siemens Healthcare, Erlangen, Germany) at the University of Alabama, Birmingham neuroimaging facility. High-resolution T1-weighted 3D structural images were acquired for each participant, with the following parameters: TR=2300 ms, TE=3.36 ms, matrix size=256×256, field of view=240 mm, slice thickness=1 mm, number of slices=160.

MRI preprocessing

Data were analyzed on an Ubuntu Linux 21.04 (<http://ubuntu.com>) computer, with SPM12 (Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm>), in addition to a combination of Matlab toolboxes and custom scripts. T1-weighted images were segmented into GMV and WMV with the Computational Anatomy Toolbox (CAT12; <http://dbm.neuro.uni-jena.de/cat12/>) segmentation tool. For child subjects (age < 18, $M=12.6$, $SD=2.5$, $N=54$), a customized age- and sex-matched tissue probability map (TPM) was created using the Template-O-Matic toolbox (Wilke et al. 2008), and this TPM map was used during the segmentation step. For adult subjects (age > 18, $M=23.28$, $SD=4.09$, $N=57$), the default TPM that comes with the Computational Anatomy Toolbox (CAT12) was used for the segmentation step. The segmented images were then warped to the DARTEL template and normalized to the Montreal Neurological Institute (MNI) template with 1.5 mm isotropic voxels and an 8 mm³ Gaussian kernel for smoothing. Each participant's total intracranial volume (TIV) was extracted using the "Estimate TIV" function. "Display one slice for all images" function and the image quality ratings (IQR) generated by CAT12, which consider both noise (e.g., head motion) and spatial resolution, were used to examine data

quality. No issues were spotted during the visual inspection and the IQRs for all images were above the "satisfactory" threshold (i.e., C; 0.75).

Whole-brain analysis

The whole-brain analysis was conducted separately for GMV and WMV, using the same procedures. For both analyses, multiple regression models were used, where the diagnostic group was a factor with two levels (autistic vs. nonautistic), and TIV, sex, age, and RMIE scores were covariates. An additional regressor was added separately for age and RMIE for the interaction of these covariates with the group factor. Voxels outside of the brain were excluded using an absolute threshold mask of 0.1. Noise smoothness values for the design specification were estimated using the AFNI 3dFWHMx (<https://afni.nimh.nih.gov>) function, with the "-acf" (spatial autocorrelation function) option and using the ResMS (estimated residual variance image) file as the input. 3dClustSim was used to calculate (using Monte Carlo simulations) the whole brain cluster thresholds, using the ACF values as inputs. This process provided appropriate control for type I errors for an uncorrected, voxelwise $p < 0.001$, which corresponds to a clusterwise $p < 0.05$, corrected for the multiple comparisons in the whole brain analysis. F-contracts were created to test the interaction across group, age, and RMIE, between group and age, and group and RMIE. A simple slope analysis of the Johnson–Neyman method was used to probe the three-way interaction, T-contracts were created to test how age and RMIE separately correlate with GMV and WMV. The same t-contracts were used for the entire sample, and separately for the autistic and nonautistic groups. Finally, a t-contrast was used to examine the GMV and WMV differences between the two groups.

Regions of interest (ROIs)

The first set of ROIs included regions showing interactions between the diagnostic group (autistic vs. nonautistic) factor and RMIE, separately for the whole-brain GMV and WMV analyses. Then, correlations with RMIE for each cluster were calculated, separately for GMV and WMV, to assess the interactions observed in the whole-brain analysis. A second set of ROIs were extracted, including the clusters showing a correlation with RMIE, both for GMV and WMV, for the whole sample.

GMV and WMV values for both sets of clusters—showing an interaction between group and RMIE in the group analysis and showing a correlation with RMIE for the whole sample analysis—were used in a step-wise linear multiple regression analysis with RMIE as the dependent factor. The purpose of the step-wise regression procedure was to build a model that involves both GMV and WMV as predictors of

RMIE and assess which factors best contribute to the prediction of RMIE.

Across all ROI analyses, MarsBar (<http://marsbar.sourceforge.net/>) was used to create mask images using SPM12 clusters. A custom Matlab script was used to extract GMV and WMV values from each ROI for each participant (https://github.com/firatsoylu/extractGMV/blob/05fa0fba0fa55aeda9b8f0228ba2a1d1c27542fb/Extract_GMV.m). 3D visualizations on the glass brain were produced using MRIcroGL (<https://www.nitrc.org/projects/mricrogl/>) and GIMP (<https://www.gimp.org>).

Results

GMV results

GMV: whole-brain results

The whole-brain GMV results showed significant clusters for the three-way Group x Age x RMIE, and the two-way Group x Age and Group x RMIE interactions (Table 1, Fig. 1). There were widespread clusters, covering most of the cortex, showing a negative correlation between age and

Table 1 Results of the whole-brain GMV analysis

Region label	Extent	<i>t</i>	MNI			Region label	Extent	<i>t</i>	MNI		
			x	y	z				x	y	z
<i>Group X Age X RMIE interaction</i>						<i>Nonautistic – autistic</i>					
R rectal G	642	11.47	5	39	−23	L sup. med. fron	111	3.79	−14	36	29
L rectal G	112	18.49	−15	21	−15	L supp. motor	364	4.16	−9	9	74
L insula	116	13.99	−45	3	5	<i>Autistic: negative corr. with RMIE</i>					
L mid. cingulate	329	18.76	−17	−20	42	R cerebellum 8	643	4.07	21	−48	−56
L mid. frontal G	122	16.83	−28	15	42	<i>Autistic: positive corr. with RMIE</i>					
<i>Group X RMIE interaction</i>						Left mid. occ	148	4.11	−21	−92	15
R rectal G	228	19.16	5	41	−23	L postcentral	122	3.86	−47	−23	53
L sup. orbital G	123	16.83	−15	21	−15	<i>Nonautistic: positive corr. with RMIE</i>					
L mid. cingulate	111	14.58	−17	−20	42	R rectal G	984	4.29	6	42	−20
L mid. frontal G	121	17.89	−29	15	44	L mid. cingulate	260	3.97	−17	−20	42
L insula	168	15.60	−39	5	5	L mid. frontal G	113	3.92	−32	17	48
<i>Positive corr. with RMIE</i>						<i>Autistic: negative corr. with Age</i>					
R hippocampus	404	4.40	33	−15	−21	R insula	62,460	6.84	47	−6	5
L orbital G	332	3.94	−9	41	−26	L postcentral G	10,097	5.67	−44	−26	53
R precentral G	150	3.80	54	−8	23	R pallidum	185	4.92	−18	0	4.5
<i>Group X Age interaction</i>						L sup. medial G	494	4.27	−47	6	42
R inf. temp. G	381	17.72	35	0	−39	R cerebellum 8	312	28.5	29	−45	−42
L rectal G	136	19.45	−3	50	−21	R cerebellum 8	175	4.22	50	−60	−48
<i>Negative corr. with age</i>						R rectal G	124	3.52	8	45	−23
R mid. cingulate	214,627	10.89	3	−29	45	L OFC	276	3.93	−29	35	−20
L cerebellum 8	316	6.06	−30	−47	−42	<i>Autistic: positive corr. with age</i>					
L pallidum	511	5.54	−18	−3	2	Left fusiform	476	5.10	−26	−9	−36
L cerebellum 8	161	4.26	−12	−60	−41	Right thalamus	118	4.62	21	−18	6
L fusiform	133	3.74	−42	−28	−26	<i>Nonautistic: negative corr. with age</i>					
L inf. occ	376	4.09	−47	−69	−8	R mid. cingulate	156,743	9.25	5	−30	45
<i>Positive corr. with age</i>						L inf. occ	228	3.70	−51	−71	−6
R thalamus	249	6.60	23	−18	8	L pallidum	357	4.54	−18	−3	1.5
L hippocampus	126	4.99	−21	−23	−8	R mid. temp	360	3.85	44	−71	−2
L parahipp. G	480	4.89	−20	−11	−39	<i>Nonautistic: positive corr. with age</i>					
<i>Autistic – nonautistic</i>						R thalamus	119	4.60	23	−18	8
R anterior cing	488	4.97	6	2	−3						
R caudate	157	3.65	15	2	26						
L inf. parietal	227	4.88	−62	−41	47						
R postcentral G	232	3.93	21	−39	63						

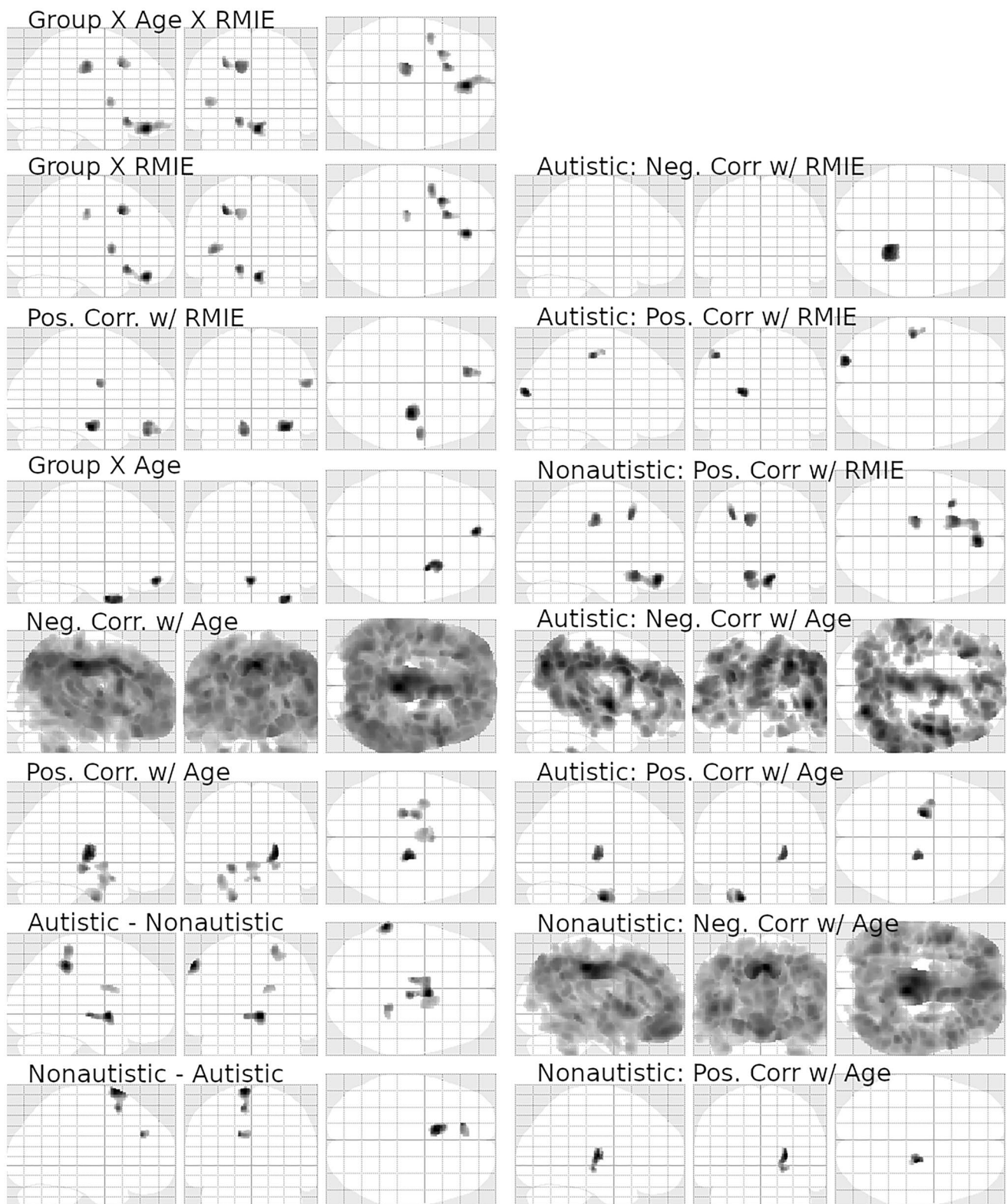


Fig. 1 Whole-brain GMV analysis results, showing significant clusters for all interactions and main effects (Table 1)

GMV. In addition, there were three smaller subcortical clusters showing a positive correlation between age and GMV. While there were no significant clusters showing a negative correlation between RMIE and GMV, there were three clusters showing a positive correlation.

GMV: group by age by RMIE interaction

The significant three-way Group X Age X RMIE interaction was further probed with the simple slope analysis of the Johnson–Neyman method, using the *Interactions* package (Long 2019) in R (R Core Team 2022). GMV values were extracted from each of the five clusters that emerged from the three-way interaction. Then separate linear regression models were built, separately for each group (autistic and nonautistic), where cluster GMV was the dependent variable and age and RMIE were independent variables. The regression models were used in the Johnson–Neyman simple slope analysis, where RMIE was the predictor and age was the moderator variable. The results showed age intervals where RMIE is a significant predictor of GMV in the five clusters, separately for each group (Fig. 2). The age range for the autistic group was 8–33 y/o and 8–34.4 y/o for the nonautistic group.

GMV: group by RMIE and group by age interactions

Separate correlation analyses were conducted, for each group (autistic and nonautistic), to explore the relation between age and GMV, and RMIE and GMV, in each of the respective ROIs that showed a two-way interaction in the whole-brain analysis (Fig. 3).

The clusters from the Group X RMIE interaction consistently showed positive correlations between RMIE and GMV for the nonautistic group, whereas the same correlations showed a negative trend for the autistic group. A different pattern emerged for the clusters from the Group X AGE interaction, where the nonautistic group showed a negative correlation between age and GMV across all four clusters, and the autistic group showed either a positive or weak negative correlation (Figs. 3, 4).

GMV: correlations with RMIE

There were three clusters where GMV showed positive correlations with RMIE for the entire sample—right hippocampus, left orbital gyrus, and right precentral gyrus and no clusters showed any negative correlations (Fig. 4). GMV values were extracted from these ROIs for later regression analysis.

WMV results

WMV: whole-brain results

The whole-brain WMV results showed significant clusters for the three-way Group x Age x RMIE and the two-way Group x RMIE interactions, where no significant clusters were found for the Group X Age interaction (Table 2, Fig. 5). There were widespread clusters, covering most of the cortex, showing a positive correlation between age and WMV. There was a single cluster in the left cerebellum showing a negative correlation between age and WMV. While there were no significant clusters showing a positive correlation between RMIE and WMV, there was a single cluster, in the left cuneus, showing a negative correlation.

WMV: group by age by RMIE interaction

Similar to the GMV analysis, the significant three-way Group X Age X RMIE interaction in the left hippocampus was further probed with the simple slope analysis of the Johnson–Neyman method. Neither of the groups showed significant age intervals for the left hippocampus cluster (Fig. 6).

WMV: group by RMIE interaction

WMV values for the five clusters from the Group X RMIE interaction were extracted and correlation analyses were conducted, separately for each group (Fig. 7). None of the correlations were significant. Across the five clusters—corpus callosum, left superior ACC, left hippocampus, left middle cingulate gyrus, and superior ACC, the autistic group showed positive trending correlations ($r=0.189, 0.087, 0.135, 0.251, \text{ and } 0.037$, respectively), and the nonautistic group showed weaker positive or negative correlations ($r=-0.1, 0.001, 0.037, \text{ and } -0.174$, respectively).

RMIE regression

A stepwise multiple linear regression analysis was conducted, with RMIE as the dependent variable, and age, group, and cluster GMV and WMV values as independent variables. All clusters that showed either a Group X RMIE interaction or a main effect of RMIE (correlation with GMV or WMV) in the GMV and WMV whole-brain analysis were included (total of 13 clusters; 8 GMV and 5 WMV; Table 3). The goal of this regression was to bring together the clusters from both the GMV and WMV analyses to find the best combined model that predicts RMIE. The *Stepwiselm* function from the Matlab Statistics and Machine Learning Toolbox was used. *Stepwiselm* starts with a constant linear regression model and uses forward and backward regression

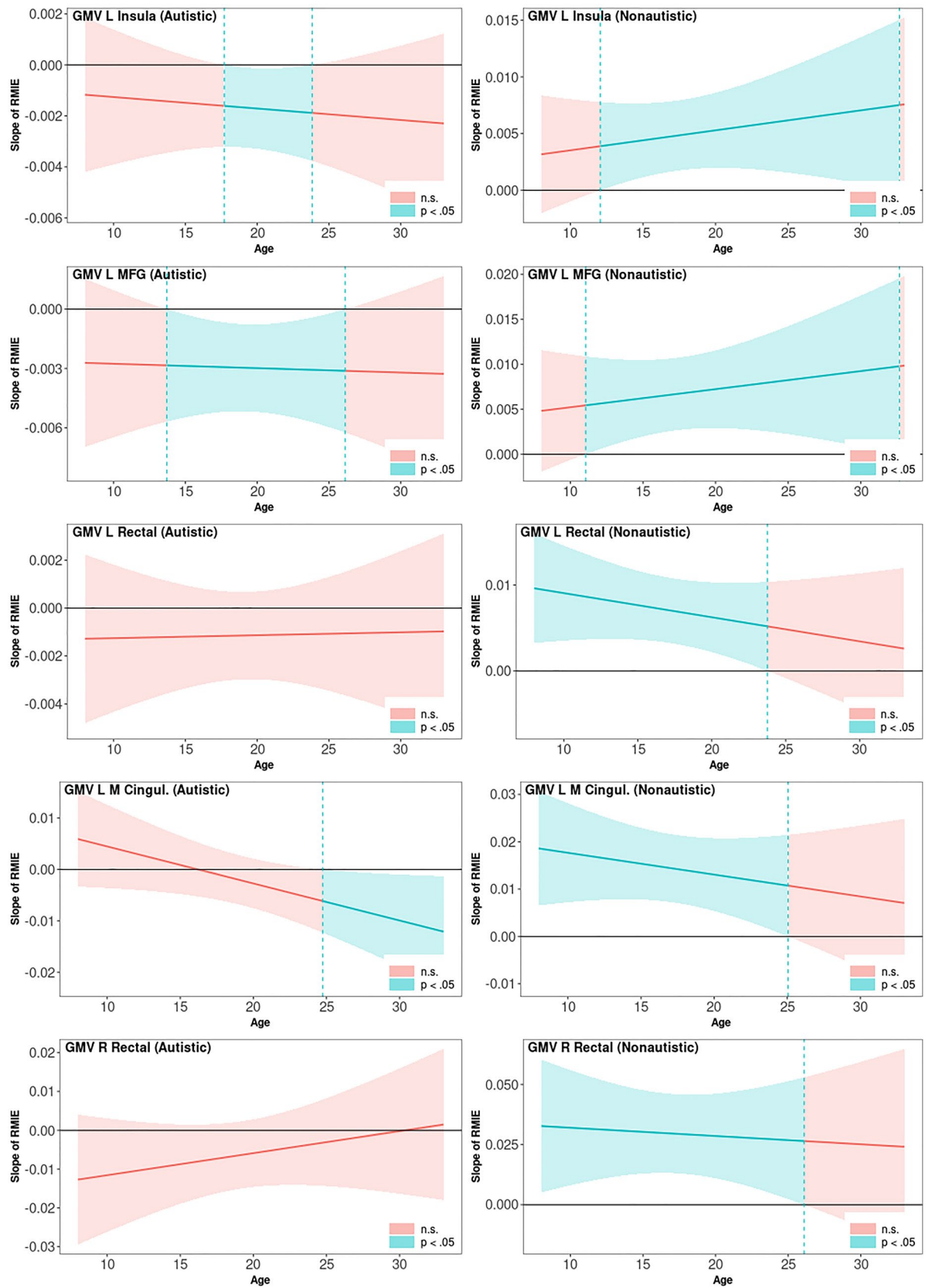


Fig. 2 Results of the simple slope analysis with the Johnson–Neyman method for the five significant GMV clusters that emerged from the Group X Age X RMIE interaction, separately for each group (left: autistic, right: nonautistic). The turquoise areas indicate age intervals where RMIE significantly predicts GMV

to add or remove variables and interactions. Variables and interactions that show a $p < 0.05$ are kept in the model, until all variables and interactions are considered. The resulting model has the highest predictive power (highest value of R^2) with a minimum number of variables.

The resulting model included six terms (excluding the intercept); the group term, three GMV clusters—left insula, right hippocampus, and right precentral gyrus—and an interaction term with one of these clusters, left insula, and one WMV cluster in the left cuneus (Table 4.). The adjusted R^2 was 0.38, indicating that the model explained 38% of the variance in RMIE, with a p value of less than 0.0001 (Table 4).

Discussion

The findings in the study address brain structural differences between the autistic and nonautistic groups, the relation between age, and GMV and WMV, and how ToM ability relates to GMV and WMV. Overall, the results show group differences in brain structure, and how GMV and WMV relate to age and ToM.

GMV and WMV group differences

The autistic, relative to the nonautistic, group showed higher GMV in four clusters in the right ACC, caudate, postcentral gyrus, and the left inferior parietal area; and showed lower GMV in the left medial superior frontal gyrus and the left supplementary motor area. These results are consistent with previous research on GMV abnormalities in autism (Duerden et al. 2012; Yang et al. 2016). In addition, studies also have reported reduced activation in these regions in autistic individuals when performing social tasks (Sato et al. 2012). There have been some inconsistencies in findings relating to the social brain in autism, with most studies documenting alterations in GMV in specific social brain regions rather than evidence of widespread differences. Our data indicate that widespread GMV abnormalities may be a key feature of autism, extending the proposal of a structurally and functionally different social brain in autism (Emery and Perrett 2000; Frith and Frith 2007; Sato et al. 2017).

The WMV differences were all subcortical, with the autistic group showing larger WMV in two clusters—the cerebellum area 9 and the midbrain—and smaller WMV in an anterior segment of the corpus callosum. Lower WMV

in the anterior portions of the corpus callosum in autistic individuals is consistent with previous studies of cortical morphometry (Aoki et al. 2013; Just et al. 2007) and frequently correlates with communication or social impairments (Alexander et al. 2007; Dimond et al. 2019; Gibbard et al. 2013). Collectively, our results document widespread structural differences in regions critical to social processes. Because social processes are complex by nature, requiring coordination of multiple regions, the widespread nature of GMV and WMV abnormalities may make integrated and holistic processing, which is central to social cognition, difficult. In sum, it is possible that these subtle deviations in GMV and WMV across several regions of the social brain are critical to social difficulties in autism.

The relationship between age, and GMV and WMV

For the entire sample, there were extensive clusters covering most of the GMV that negatively correlated with age. Conversely, there were only a few clusters exhibiting a positive correlation with age: the right thalamus, the left hippocampus, and the left parahippocampal gyrus. It is interesting to note that these regions were found to be developing structurally and functionally in association with age, experience, and development (e.g., social skills, memory) (Gauthier et al. 2000; Maguire et al. 2003). Overall, the nonautistic group had more extensive clusters, covering most gray matter tissue, showing a negative correlation with age, while the autistic group had relatively less coverage of a positive correlation of GMV and age. Paralleling previous studies (Bakhtiari et al. 2012; Thompson et al. 2020), most subcortical WM tissue showed a positive correlation with age, including the cerebellum, and the brainstem.

GMV and WMV changes with age are driven by different, and sometimes opposing, forces. Overall, while pruning leads to an overall decrease in GMV, the WMV increases due to increased connectivity across the brain regions (Brain Development Cooperative Group 2012; Hagmann et al. 2010). However, in specific regions, active specialization leads to skill and experience-related increases in GMV (Kodama et al. 2018; Tang et al. 2020). Previous research shows region- and hemispheric-specific alterations in the developmental patterns of social brain regions (Greimel et al. 2013). These changes have been shown to closely parallel shifts in social functions attributed to these regions (Gogtay et al. 2004).

The relationship between RMIE, and GMV and WMV

The RMIE task provides a measure of ToM skills. The relationship between the RMIE scores and the structural brain features can help understand the anatomical relevance of different regions and their potential role in mental state

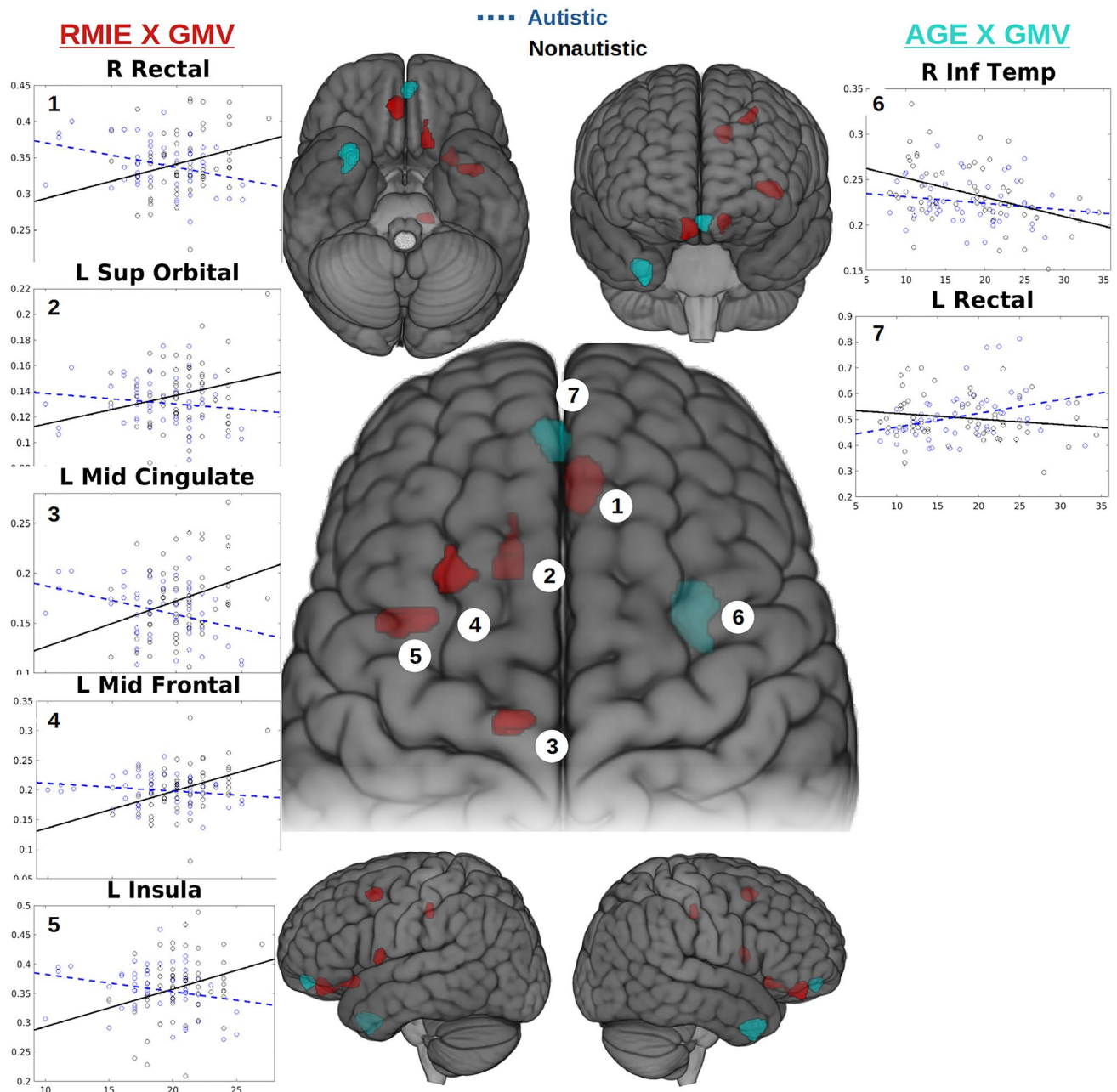


Fig. 3 Significant GMV clusters from the Group X RMIE (on the left) and Group X Age (on the right) interactions

attribution. For the entire sample, there were three clusters, in the right hippocampus, right precentral gyrus, and the left orbital gyrus, that showed a positive GMV correlation with RMIE, while there were no clusters showing a negative correlation.

The group by RMIE interaction showed five clusters, where RMIE positively correlated with GMV for the nonautistic group, while there were negative or no correlations for the autistic group. These anterior clusters included distinct regions of the social network, such as the orbital,

prefrontal, and cingulate cortices. These results suggest that social experiences (Kolb et al. 2012) and the development of memory and social skills (Naito 2003; Spreng 2013) lead to higher GMV in the nonautistic group in these distinct regions, while the same theory of mind skill-related GMV increase is not observed for the autistic group. Alternatively, because increases in GMV in middle frontal regions are attributed to deficits in executive functioning (EF) (Yaxu et al. 2020), which are frequently impaired in autism (see May and Kana 2020 for a meta-analysis) and

Fig. 4 Correlations of RMIE and Age with GMV across the two groups in regions showing a Group X RMIE and Group X Age interaction. The numbers indicate the Pearson coefficients and * indicates significant correlations

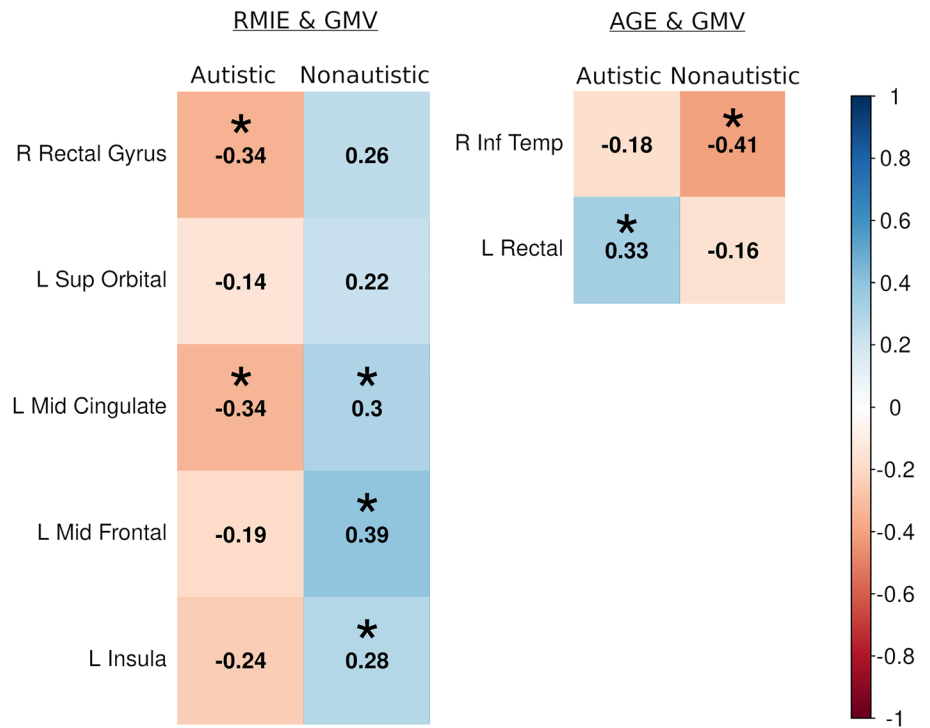


Table 2 Results of the whole-brain WMV analysis

Region label	Extent	t	MNI			Region label	Extent	t	MNI		
			x	y	z				x	y	z
<i>Group X Age X RMIE interaction</i>						<i>Autistic group: negative corr. with RMIE</i>					
L hippocampus	257	15.66	−32	−36	0	L Post. OFC	318	4.38	−41	32	−15
<i>Group X RMIE interaction</i>						<i>Nonautistic Group: Negative corr. with RMIE</i>					
R mid cingulate	310	16.08	23	−3	47	Corpus callosum	905	4.89	0	23	20
Sup. ACC	176	19.56	0	23	20	L cuneus	376	4.73	−12	−83	29
L Sup. ACC	167	14.59	−23	36	17	L hippocampus	495	4.01	−29	−41	3
L hippocampus	165	15.26	−32	−36	0	L ACC	469	3.83	−23	36	15
Corpus callosum	148	15.67	0	−9	18	L precentral	153	3.63	−30	0	42
<i>Negative Corr. with RMIE</i>						Corpus callosum	226	3.57	−3	−9	21
L cuneus	283	4.75	−14	−84	30	<i>Autistic group: negative corr. with age</i>					
<i>Negative corr. with age</i>						L cerebellum 8	146	4.48	−39	−50	−50
L cerebellum 7b	207	5.26	−42	−50	−44	<i>Autistic group: positive corr. with age</i>					
<i>Positive corr. with age</i>						R ant. cerebellum	7329	5.12	−6	−41	−53
White matter	122,704	9.30	20	−15	33	R inf. Temporal	590	4.91	48	−44	−9
<i>Autistic – nonautistic</i>						R fusiform	1518	4.14	45	−23	−18
R cerebellum 9	131	4.06	6	−50	−65	R rectal	186	3.97	11	14	−14
Midbrain	171	3.75	−2	−35	−3	L fusiform	145	3.91	−29	−5	−35
<i>Nonautistic – autistic</i>						R Inf. occipital	195	4.52	36	−66	−9
Corpus Callosum	531	4.17	0	27	−6	R Mid. cingulate	40,089	6.12	21	−6	31.5
						R precuneus	170	3.82	24	−56	24
						<i>Nonautistic group: positive corr. with age</i>					
						R caudate nucleus	82,603	7.65	20	−20	29
						L mid. occ	360	3.91	−32	−80	5

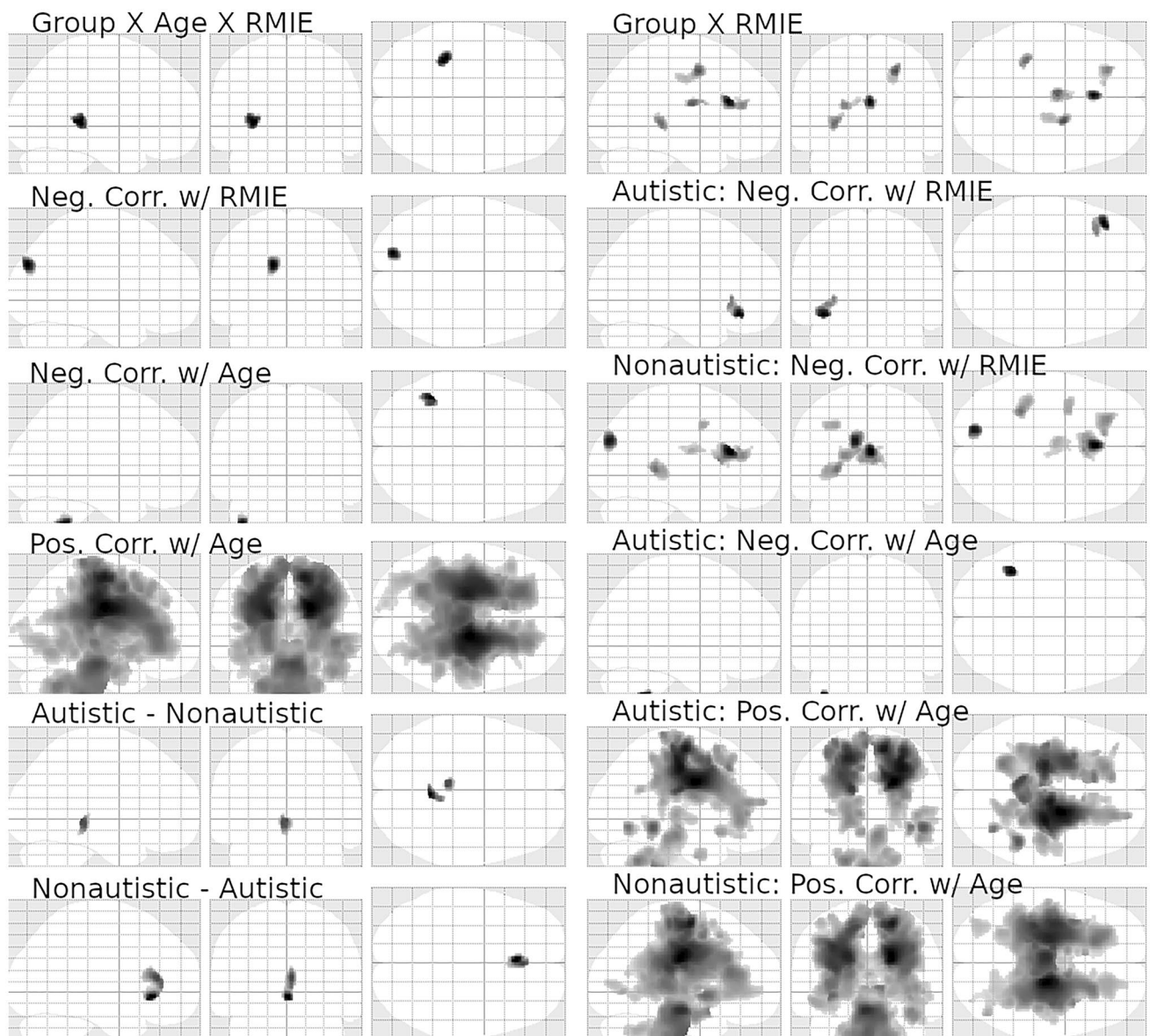


Fig. 5 Results of the whole-brain WMV analysis

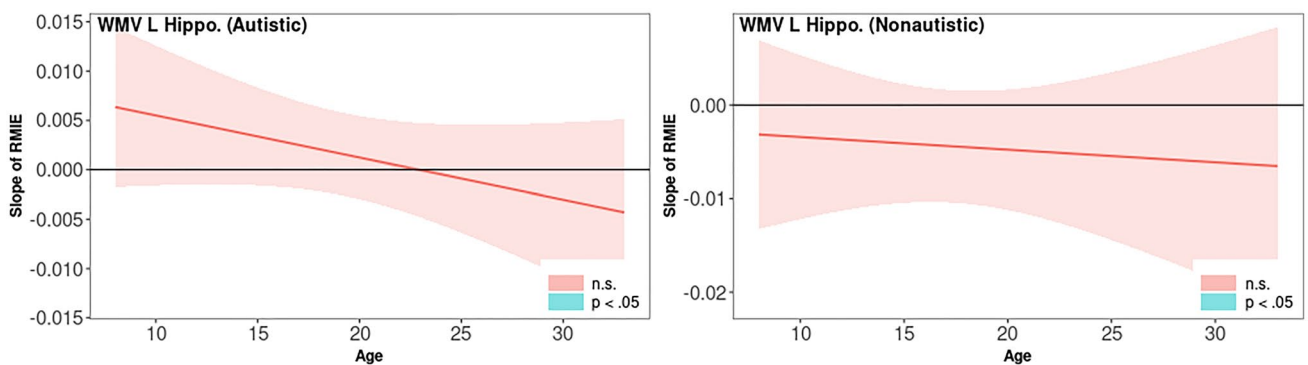


Fig. 6 Results of the simple slope analysis with the Johnson–Neyman method for the left hippocampus cluster that emerged from the Group X Age X RMIE interaction, separately for each group (left: autistic, right: nonautistic)

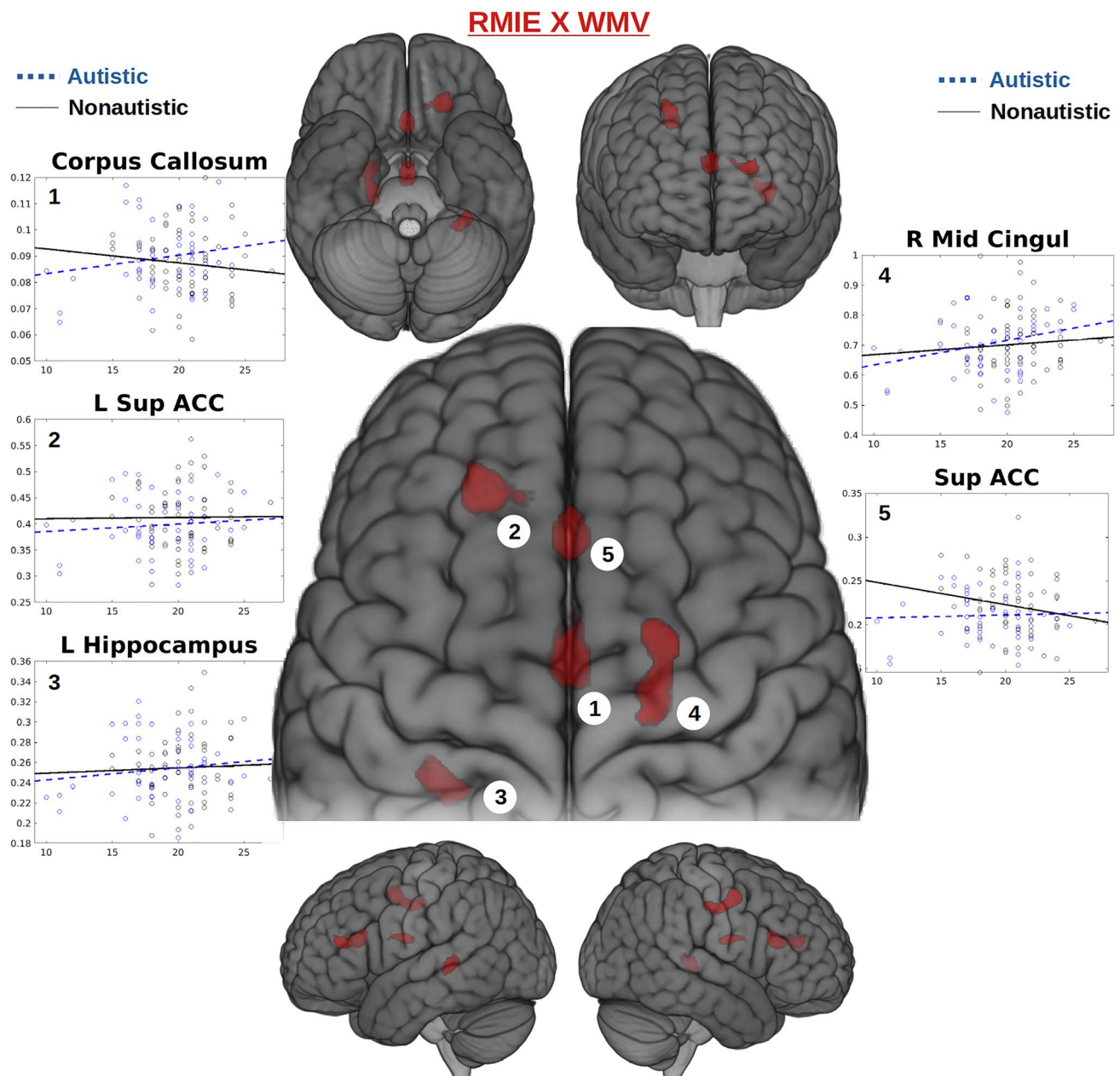


Fig. 7 The four clusters showing an interaction between Group and RMIE in the whole-brain WMV analysis. The X-axis shows the RMIE scores and the Y-axis the WMV, for the nonautistic and autistic groups

strongly correlate with ToM (Jones et al. 2018), the lack of a positive correlation with RMIE scores for the autistic group might be associated with a broader difficulty with cognitive control or executive function that likewise affects RMIE task performance. The group by RMIE interaction results parallel previous studies showing that GMV differences in frontal regions reliably discriminate between autistic and nonautistic groups, with GMV reductions associated with increased social communication and interaction impairments (Hyde et al. 2010; Patriquin et al. 2016). Sato et al. (2017) likewise

documented positive correlations between RMIE scores and GMV in the left temporoparietal junction with nonautistic participants, but not with autistic ones.

The simple slope analysis of the five clusters that emerged from the three-way, group by age by RMIE, interaction provided further insights into how the relation between RMIE and GMV is modulated by age, across the two groups. In two clusters, left insula and left MFG, the nonautistic group showed large age intervals where GMV positively correlated with RMIE, while there were more limited age intervals,

Table 3 Clusters included in the stepwise regression model

Region label	Extent	MNI		
		x	y	z
<i>Group X RMIE interaction (GMV)</i>				
R rectal G	228	5	41	−23
L sup. orbital G	123	−15	21	−15
L mid. cingulate	111	−17	−20	42
L mid. frontal G	121	−29	15	44
L insula	168	−39	5	5
<i>Positive corr. with RMIE (GMV)</i>				
R hippocampus	404	33	−15	−21
L orbital G	332	−9	41	−26
R precentral G	150	54	−8	23
<i>Group X RMIE interaction (WMV)</i>				
R Mid cingulate	310	23	−3	47
Sup. ACC	176	0	23	20
L sup. ACC	167	−23	36	17
L hippocampus	165	−32	−36	0
Corpus callosum	148	0	−9	18
<i>Negative corr. with RMIE (WMV)</i>				
L cuneus	238	−14	−84	30

Table 4 Multiple regression model produced by the stepwise regression procedure

	Estimate	SE	t	p
(Intercept)	21.69	4.082	5.313	<0.0001
Group	−9.38	4.438	−2.113	0.037
L Insula (GMV)	−40.569	8.377	−3.91	0.0002
R Hippocampus (GMV)	15.102	3.312	4.56	<0.0001
R Precentral G. (GMV)	19.077	7.524	2.536	0.0127
L Cuneus (WMV)	−7.717	3.086	−2.501	0.0114
Group * L Insula (GMV)	33.831	12.874	2.628	0.01

Number of observations: 111, Error degrees of freedom: 104

Root mean squared error: 2.42

R-squared: 0.378, Adjusted R-Squared: 0.342

F-statistic vs. constant model: 10.5, *p* value <0.0001

where GMV showed negative and weaker correlations with RMIE for the autistic group. In three clusters, left mid. cingulate, and left and right rectal gyri, the nonautistic group showed large age intervals where GMV negatively correlated with RMIE, whereas for the same clusters, only the left mid. cingulate cluster showed a late (<~25 yrs) significant age interval, where GMV negatively correlated with GMV. The left insula and the left MFG stand out among these five clusters in that the strength of the correlation between GMV and RMIE increases with age for the nonautistic group, while the slope of RMIE decreases with age for the rest of the clusters (left and right rectal and left mid.

cingulate). Abnormalities in insular function and structure in autism have been shown across multiple studies (see Nomi et al. 2019 for a review). Additionally, in a large-scale meta-analysis, comprising 15,892 individuals, reduced insular and cingulate GMV was found to be a common structural substrate across six mental conditions (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety) (Goodkind et al. 2015). While the insula has many different functions associated with sensory and bodily processes—with high-level connectivity, with ACC, STS, amygdala among other regions—it has been proposed that structural and functional abnormalities with the insula are central to autism, based on the role of the insula in social and affective processes (Uddin and Menon 2009).

Even though STS, one of the regions in the social brain network (Eack et al. 2017) has been consistently found to be associated with gaze perception in functional studies (e.g., Kana et al. 2016), we did not find any relation between GMV and RMIE in the STS. This is not surprising, given that a functional association between a task and a region does not warrant an association between GMV and task performance in the same region. Collectively, these results indicate that GMV abnormalities in the regions discussed may be associated with socio-cognitive difficulties in ASD.

In the WMV results for the entire sample, there was a single cluster, in the left cuneus, which showed a negative correlation with RMIE, while there were no positive correlations. The three-way group by age by RMIE interaction produced one cluster in the left hippocampus. The simple slope analysis for the left hippocampus did not show any significant age intervals for either group.

There were interactions between the group factor and RMIE in five clusters: right mid. cingulate, sup. ACC, left sup. ACC, left hippocampus and the surrounding white matter tissue, and corpus callosum, also overlapping with the hippocampal commissure. The ROI analysis showed that across the five clusters, the autistic group showed a positive correlation between WMV and RMIE, whereas the nonautistic group showed weaker positive correlations in the right mid. cingulate, left sup. ACC and left hippocampus, and negative correlations in the corpus callosum and superior ACC. These findings are in line with existing literature demonstrating increased ACC connectivity in early life in autism (Uddin et al. 2013a, b), which can be interpreted as less prominent hemispheric specialization and higher reliance on inter-hemispheric communication for ToM processing for the autistic group.

To understand how GMV and WMV together relate to RMIE and assess the potential of these measures to predict RMIE, a multiple regression model was constructed, including all clusters that showed a main effect or an interaction involving RMIE at the entire sample level (total of 14 clusters; 8 GMV and 6 WMV), in addition to age and group

variables. The stepwise procedure produced a model that included the left insula, right hippocampus, right precentral GMV, the group and left insula GMV interaction, the left cuneus WMV, and the group factor as significant terms. The model explained 38% of the variance in RMIE scores. The interaction between L insula GMV and group may indicate the impact of GMV alterations in determining connectivity within the salience network, which supports responses to meaningful stimuli (Seeley et al. 2007). The left insula merges pertinent information and regulates activity between the salience network and other cognitive networks (Menon and Uddin 2010; Uddin 2015). Increased connectivity of the salience network has been reported in children with autism and linked to the severity of autistic traits in autistic adults (Martino et al. 2009; Uddin et al. 2013b). Separately, increased connectivity in this region is related to sensory over-responsivity (Green et al. 2016). As social cognition is supported by interactions between two networks—the default mode network, associated with socio-cognitive/mentalizing network, and the salience network supporting socio-affective cognition—it may be that the salience network is important to recruiting relevant ToM regions during social cognition tasks (Kanske et al. 2015; Schurz et al. 2020). This interpretation is supported by research demonstrating that integration between these networks increases during ToM tasks and results in more effortful, controlled processing (Shine and Poldrack 2018).

Conclusions

The results of this study contribute to the existing literature on structural correlates of autism and ToM. Even though structural correlates of ASD have been extensively studied in previous work, inconsistencies limit the reliability of findings. In this study, our goal was not only to compare the whole brain white and gray matter volume in the autistic and nonautistic groups, but also to investigate how the structural features relate to age and theory of mind skills. The results showed widespread GMV and WMV differences in regions crucial for social processes. For the entire sample, extensive clusters covering the cortex showed a negative correlation between age and GMV, while extensive subcortical regions showed a positive correlation between age and WMV. The comparison of the two groups showed that the autistic group did not express the typically observed negative GMV and positive WMV correlations with age at the same level as the nonautistic group, pointing to extensive abnormalities in age-related structural changes.

The ROI analysis based on the clusters that emerged from the group by RMIE interaction showed multiple distributed, mostly left, frontal clusters, associated with social processing and executive functions, that showed a positive

correlation between RMIE and GMV for the nonautistic group, where the same clusters either did not show a correlation or showed a negative correlation for the autistic group.

The group by RMIE WMV interaction results showed five clusters, including the corpus callosum, and anterior and middle cingulate cortices. The ROI analysis showed that in the corpus callosum and superior ACC, the nonautistic group showed a negative correlation between WMV and RMIE, whereas the autistic group showed weaker, positive trending correlations. This might possibly point to higher lateralization and less reliance on inter-hemispheric communication for the nonautistic group.

The stepwise multiple linear regression analysis, which combined WMV and GMV clusters as predictors of RMIE scores, indicated that GMV in distributed regions can help predict ToM performance. In addition, GMV in insula, a region that is part of the salience network and participates in a diverse set of functions, emerges as a prominent region in distinguishing ToM performance between the two groups. Overall, these findings can be helpful for future multimodal modeling efforts for predicting mental state attribution.

Author contributions FS: Conceptualization, methodology, analysis, software, writing, and editing. KM: Writing and editing. RK: Data collection, conceptualization, methodology, writing, and editing.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability Thresholded statistical maps for all contrasts presented in the results are available at <https://identifiers.org/neurovault.collection:13948>. The raw data and analysis scripts that support the findings of this study are available from the corresponding author, FS, upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Alabama.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

- Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happé F, Frith C, Frith U (1999) The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *NeuroReport* 10(8):1647–1651
- Alexander AL, Lee JE, Lazar M, Boudos R, DuBray MB, Oakes TR, Miller JN, Lu J, Jeong E-K, McMahon WM, Bigler ED, Lainhart JE (2007) Diffusion tensor imaging of the corpus callosum in

- autism. *Neuroimage* 34(1):61–73. <https://doi.org/10.1016/j.neuroimage.2006.08.032>
- American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5, vol 5. American Psychiatric Association.
- Amodio DM, Frith CD (2006) Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci* 7(4):268–277. <https://doi.org/10.1038/nrn1884>
- Aoki Y, Abe O, Nippashi Y, Yamasue H (2013) Comparison of white matter integrity between autism spectrum disorder subjects and typically developing individuals: a meta-analysis of diffusion tensor imaging tractography studies. *Mol Autism* 4(1):25. <https://doi.org/10.1186/2040-2392-4-25>
- Ashburner J, Friston KJ (2001) Why voxel-based morphometry should be used. *Neuroimage* 14(6):1238–1243. <https://doi.org/10.1006/nimg.2001.0961>
- Bakhtiari R, Zürcher NR, Rogier O, Russo B, Hippolyte L, Granziera C, Araabi BN, Ahmadabadi MN, Hadjikhani N (2012) Differences in white matter reflect atypical developmental trajectory in autism: a tract-based spatial statistics study. *NeuroImage Clin* 1(1):48–56. <https://doi.org/10.1016/j.nicl.2012.09.001>
- Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL (2004) White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biol Psychiatry* 55(3):323–326. <https://doi.org/10.1016/j.biopsych.2003.10.022>
- Baron-Cohen S, Wheelwright S, Spong A, Scahill V, Lawson J (2001) Are intuitive physics and intuitive psychology independent? A test with children with Asperger Syndrome. *J Dev Learn Disord* 4(1):47–78
- Billstedt E, Gillberg IC, Gillberg C (2011) Aspects of quality of life in adults diagnosed with autism in childhood: a population-based study. *Autism Int J Res Pract* 15(1):7–20. <https://doi.org/10.1177/1362361309346066>
- Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet M-H, Barthélémy C, Mouren M-C, Artiges E, Samson Y, Brunelle F, Frackowiak RSJ, Zilbovicius M (2004) Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage* 23(1):364–369. <https://doi.org/10.1016/j.neuroimage.2004.06.016>
- Brain Development Cooperative Group (2012) Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI study of normal brain development. *Cereb Cortex* 22(1):1–12. <https://doi.org/10.1093/cercor/bhr018>
- Carper RA, Courchesne E (2005) Localized enlargement of the frontal cortex in early autism. *Biol Psychiatry* 57(2):126–133. <https://doi.org/10.1016/j.biopsych.2004.11.005>
- Cauda F, Geda E, Sacco K, D'Agata F, Duca S, Geminiani G, Keller R (2011) Grey matter abnormality in autism spectrum disorder: an activation likelihood estimation meta-analysis study. *J Neurol Neurosurg Psychiatry* 82(12):1304–1313. <https://doi.org/10.1136/jnnp.2010.239111>
- Courchesne E, Campbell K, Solso S (2011a) Brain growth across the life span in autism: age-specific changes in anatomical pathology. *Brain Res* 1380:138–145. <https://doi.org/10.1016/j.brainres.2010.09.101>
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY (2001) Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology* 57(2):245–254. <https://doi.org/10.1212/wnl.57.2.245>
- Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C, Hallett MJ, Barnes CC, Pierce K (2011b) Neuron number and size in prefrontal cortex of children with autism. *JAMA* 306(18):2001–2010. <https://doi.org/10.1001/jama.2011.1638>
- Craig M, Zaman SH, Daly EM, Cutter WJ, Robertson DMW, Hallahan B, Toal F, Reed S, Ambikapathy A, Brammer M, Murphy CM, Murphy DGM (2007) Women with autistic-spectrum disorder: magnetic resonance imaging study of brain anatomy. *Br J Psychiatry* 191(3):224–228. <https://doi.org/10.1192/bjp.bp.106.034603>
- d'Albis M-A, Guevara P, Guevara M, Laidi C, Boisgontier J, Sarrazin S, Duclap D, Delorme R, Bolognani F, Czech C, Bouquet C, Moal ML-L, Holiga S, Amestoy A, Scheid I, Gaman A, Leboyer M, Poupon C, Mangin J-F, Houenou J (2018) Local structural connectivity is associated with social cognition in autism spectrum disorder. *Brain J Neurol* 141(12):3472–3481. <https://doi.org/10.1093/brain/awy275>
- DeRamus TP, Kana RK (2015) 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>
- Dimond D, Schuetze M, Smith RE, Dhollander T, Cho I, Vinette S, Eycke KT, Lebel C, McCrimmon A, Dewey D, Connelly A, Bray S (2019) Reduced white matter fiber density in autism spectrum disorder. *Cereb Cortex* 29(4):1778–1788. <https://doi.org/10.1093/cercor/bhy348>
- Duerden EG, Oatley HK, Mak-Fan KM, McGrath PA, Taylor MJ, Szatmari P, Roberts SW (2012) Risk factors associated with self-injurious behaviors in children and adolescents with autism spectrum disorders. *J Autism Dev Disord* 42(11):2460–2470. <https://doi.org/10.1007/s10803-012-1497-9>
- Eack SM, Wojtalik JA, Keshavan MS, Minshew NJ (2017) Socio-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. *Schizophr Res* 183:102–109. <https://doi.org/10.1016/j.schres.2017.03.009>
- Ecker C (2017) The neuroanatomy of autism spectrum disorder: an overview of structural neuroimaging findings and their translatability to the clinical setting. *Autism* 21(1):18–28. <https://doi.org/10.1177/1362361315627136>
- Ecker C, Ginestet C, Feng Y, Johnston P, Lombardo MV, Lai M-C, Suckling J, Palaniyappan L, Daly E, Murphy CM, Williams SC, Bullmore ET, Baron-Cohen S, Brammer M, Murphy DGM, MRC AIMS Consortium, for the (2013) Brain surface anatomy in adults with autism: the relationship between surface area, cortical thickness, and autistic symptoms. *JAMA Psychiat* 70(1):59–70. <https://doi.org/10.1001/jamapsychiatry.2013.265>
- Emery NJ, Perrett DI (2000) How can studies of the monkey brain help us to understand “theory of mind” and autism in humans? In: Baron-Cohen S, Tager-Flusberg H, Cohen DJ (eds) Understanding other minds: perspectives from developmental cognitive neuroscience. Oxford University Press, pp 274–305
- Forbes CE, Grafman J (2010) The role of the human prefrontal cortex in social cognition and moral judgment. *Annu Rev Neurosci* 33:299–324. <https://doi.org/10.1146/annurev-neuro-060909-153230>
- Frith CD (2008) Social cognition. *Philos Trans R Soc B Biol Sci* 363(1499):2033–2039. <https://doi.org/10.1098/rstb.2008.0005>
- Frith CD, Frith U (2007) Social cognition in humans. *Curr Biol* 17(16):724–732. <https://doi.org/10.1016/j.cub.2007.05.068>
- Gauthier I, Skudlarski P, Gore JC, Anderson AW (2000) Expertise for cars and birds recruits brain areas involved in face recognition. *Nat Neurosci* 3:191–197
- Gibbard CR, Ren J, Seunarine KK, Clayden JD, Skuse DH, Clark CA (2013) White matter microstructure correlates with autism trait severity in a combined clinical–control sample of high-functioning adults. *NeuroImage Clin* 3:106–114. <https://doi.org/10.1016/j.nicl.2013.07.007>
- Gibbard CR, Ren J, Skuse DH, Clayden JD, Clark CA (2018) Structural connectivity of the amygdala in young adults with autism

- spectrum disorder. *Hum Brain Mapp* 39(3):1270–1282. <https://doi.org/10.1002/hbm.23915>
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM (2004) Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 101(21):8174–8179. <https://doi.org/10.1073/pnas.0402680101>
- Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, Ortega BN, Zaiko YV, Roach EL, Korgaonkar MS, Grieve SM, Galatzer-Levy I, Fox PT, Etkin A (2015) Identification of a common neurobiological substrate for mental illness. *JAMA Psychiat* 72(4):305. <https://doi.org/10.1001/jamapsychiatry.2014.2206>
- Green SA, Hernandez L, Bookheimer SY, Dapretto M (2016) Salience network connectivity in autism is related to brain and behavioral markers of sensory overresponsivity. *J Am Acad Child Adolesc Psychiatry* 55(7):618–626. <https://doi.org/10.1016/j.jaac.2016.04.013>
- Greimel E, Nehrkorn B, Schulte-Rüther M, Fink G, Nickl-Jockschat T, Herpertz-Dahlmann B, Konrad K, Eickhoff S (2013) Changes in grey matter development in autism spectrum disorder. *Brain Struct Funct* 218(4):929–942. <https://doi.org/10.1007/s00429-012-0439-9>
- Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. *Cereb Cortex* 16(9):1276–1282
- Hagmann P, Sporns O, Madan N, Cammoun L, Pienaar R, Wedeen VJ, Meuli R, Thiran J-P, Grant PE (2010) White matter maturation reshapes structural connectivity in the late developing human brain. *Proc Natl Acad Sci USA* 107(44):19067–19072. <https://doi.org/10.1073/pnas.1009073107>
- Han M, Jiang G, Luo H, Shao Y (2021) Neurobiological bases of social networks. *Front Psychol*. <https://doi.org/10.3389/fpsyg.2021.626337>
- Happé F, Frith U (2006) The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J Autism Dev Disord* 36(1):5–25. <https://doi.org/10.1007/s10803-005-0039-0>
- Hotier S, Leroy F, Boisgontier J, Laidi C, Mangin J-F, Delorme R, Bolognani F, Czech C, Bouquet C, Toledano E, Bouvard M, Petit J, Mishchenko M, d'Albis M-A, Gras D, Gaman A, Scheid I, Leboyer M, Zalla T, Houenou J (2017) Social cognition in autism is associated with the neurodevelopment of the posterior superior temporal sulcus. *Acta Psychiatr Scand* 136(5):517–525. <https://doi.org/10.1111/acps.12814>
- Howlin P, Moss P, Savage S, Rutter M (2013) Social outcomes in mid- to later adulthood among individuals diagnosed with autism and average nonverbal IQ as children. *J Am Acad Child Adolesc Psychiatry* 52(6):572–658. <https://doi.org/10.1016/j.jaac.2013.02.017>
- Hyde KL, Samson F, Evans AC, Mottron L (2010) Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Hum Brain Mapp* 31(4):556–566. <https://doi.org/10.1002/hbm.20887>
- Im WY, Ha JH, Kim EJ, Cheon K-A, Cho J, Song D-H (2018) Impaired white matter integrity and social cognition in high-function autism: diffusion tensor imaging study. *Psychiatry Investig* 15(3):292–299. <https://doi.org/10.30773/pi.2017.08.15>
- Isaksson J, Westeinde AV, Cauvet É, Kuja-Halkola R, Lundin K, Neufeld J, Willfors C, Bölte S (2019) Social cognition in autism and other neurodevelopmental disorders: a co-twin control study. *J Autism Dev Disord* 49(7):2838–2848. <https://doi.org/10.1007/s10803-019-04001-4>
- Johansen-Berg H (2010) Behavioural relevance of variation in white matter microstructure. *Curr Opin Neurol* 23(4):351–358. <https://doi.org/10.1097/WCO.0b013e32833b7631>
- Johnson MH, Griffin R, Csibra G, Halit H, Farroni T, de Haan M, Tucker LA, Baron-Cohen S, Richards J (2005) The emergence of the social brain network: evidence from typical and atypical development. *Dev Psychopathol* 17(3):599–619. <https://doi.org/10.1017/S0954579405050297>
- Jones CRG, Simonoff E, Baird G, Pickles A, Marsden AJS, Tregay J, Happé F, Charman T (2018) The association between theory of mind, executive function, and the symptoms of autism spectrum disorder. *Autism Res* 11(1):95–109. <https://doi.org/10.1002/aur.1873>
- Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007) Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cereb Cortex* 17:951–961. <https://doi.org/10.1093/cercor/bh1006>
- Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA (2009) Atypical frontal-posterior synchronization of theory of mind regions in autism during mental state attribution. *Soc Neurosci* 4(2):135–152. <https://doi.org/10.1080/17470910802198510>
- Kana RK, Keller TA, Minshew NJ, Just MA (2007) Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. *Biol Psychiatry* 62(3):198–206. <https://doi.org/10.1016/j.biopsych.2006.08.004>
- Kana RK, Patriquin MA, Black BS, Channell MM, Wicker B (2016) Altered medial frontal and superior temporal response to implicit processing of emotions in autism: implicit processing of emotions in autism. *Autism Res* 9(1):55–66. <https://doi.org/10.1002/aur.1496>
- Kanske P, Böckler A, Trautwein F-M, Singer T (2015) Dissecting the social brain: introducing the EmpaToM to reveal distinct neural networks and brain-behavior relations for empathy and theory of mind. *Neuroimage* 122:6–19. <https://doi.org/10.1016/j.neuroimage.2015.07.082>
- Kodama M, Ono T, Yamashita F, Ebata H, Liu M, Kasuga S, Ushiba J (2018) Structural gray matter changes in the hippocampus and the primary motor cortex on an-hour-to-one-day scale can predict arm-reaching performance improvement. *Front Hum Neurosci*. <https://doi.org/10.3389/fnhum.2018.00209>
- Kolb B, Mychasiuk R, Muhammad A, Li Y, Frost DO, Gibb R (2012) Experience and the developing prefrontal cortex. *Proc Natl Acad Sci USA* 109:17186–17193. <https://doi.org/10.1073/pnas.1121251109>
- Lai M-C, Baron-Cohen S, Buxbaum JD (2015) Understanding autism in the light of sex/gender. *Mol Autism* 6:24. <https://doi.org/10.1186/s13229-015-0021-4>
- Lefebvre A, Beggiano A, Bourgeron T, Toro R (2015) Neuroanatomical diversity of corpus callosum and brain volume in autism: meta-analysis, analysis of the autism brain imaging data exchange project, and simulation. *Biol Psychiatry* 78(2):126–134. <https://doi.org/10.1016/j.biopsych.2015.02.010>
- Libero LE, DeRamus TP, Deshpande HD, Kana RK (2014) Surface-based morphometry of the cortical architecture of autism spectrum disorders: volume, thickness, area, and gyrification. *Neuropsychologia* 62(1):1–10. <https://doi.org/10.1016/j.neuropsychologia.2014.07.001>
- Libero LE, Nordahl CW, Li DD, Ferrer E, Rogers SJ, Amaral DG (2016) Persistence of megalencephaly in a subgroup of young boys with autism spectrum disorder. *Autism Res* 9(11):1169–1182. <https://doi.org/10.1002/aur.1643>
- Lim L, Chantiluke K, Cubillo AI, Smith AB, Simmons A, Mehta MA, Rubia K (2015) Disorder-specific grey matter deficits in attention deficit hyperactivity disorder relative to autism spectrum

- disorder. *Psychol Med* 45(5):965–976. <https://doi.org/10.1017/S0033291714001974>
- Lo Y-C, Chen Y-J, Hsu Y-C, Tseng W-YI, Gau SS-F (2017) Reduced tract integrity of the model for social communication is a neural substrate of social communication deficits in autism spectrum disorder. *J Child Psychol Psychiatry* 58(5):576–585. <https://doi.org/10.1111/jcpp.12641>
- Long JA (2019) Interactions: comprehensive, user-friendly toolkit for probing interactions. <https://cran.r-project.org/package=interactions>
- Loomba N, Beckerson ME, Ammons CJ, Maximo JO, Kana RK (2021) Corpus callosum size and homotopic connectivity in autism spectrum disorder. *Psychiatry Res Neuroimaging* 313:111301. <https://doi.org/10.1016/j.pscychresns.2021.111301>
- Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, Sweeney JA (2002) Neocortical system abnormalities in autism: an fMRI study of spatial working memory. *Neurology* 59(6):834–840. <https://doi.org/10.1212/wnl.59.6.834>
- Maguire EA, Spiers HJ, Good CD, Hartley T, Frackowiak RSJ, Burgess N (2003) Navigation expertise and the human hippocampus: a structural brain imaging analysis. *Hippocampus* 13(2):250–259. <https://doi.org/10.1002/hipo.10087>
- Martino AD, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP (2009) Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol Psychiatry* 65(1):63–74. <https://doi.org/10.1016/j.biopsych.2008.09.022>
- May KE, Kana RK (2020) Frontoparietal network in executive functioning in autism spectrum disorder. *Autism Res* 13(10):1762–1777. <https://doi.org/10.1002/aur.2403>
- Mazurek MO (2014) Loneliness, friendship, and well-being in adults with autism spectrum disorders. *Autism Int J Res Pract* 18(3):223–232. <https://doi.org/10.1177/1362361312474121>
- Mcalonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, Yip L, Murphy DGM, Chua SE (2005) Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. *Brain J Neurol* 128(2):268–276. <https://doi.org/10.1093/brain/awh332>
- Menon V, Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function NIH Public Access Author Manuscript Introduction and overview. *Brain Struct Funct* 214(5–6):655–667. <https://doi.org/10.1007/s00429-010-0262-0>
- Morgan JT, Chana G, Abramson I, Semendeferi K, Courchesne E, Everall IP (2012) Abnormal microglial-neuronal spatial organization in the dorsolateral prefrontal cortex in autism. *Brain Res* 1456:72–81. <https://doi.org/10.1016/j.brainres.2012.03.036>
- Mueller S, Wang D, Fox MD, Yeo BTT, Sepulcre J, Sabuncu MR, Shafee R, Lu J, Liu H (2013) Individual variability in functional connectivity architecture of the human brain. *Neuron* 77(3):586–595. <https://doi.org/10.1016/j.neuron.2012.12.028>
- Murdaugh DL, Shinkareva SV, Deshpande HR, Wang J, Pennick MR, Kana RK (2012) Differential deactivation during mentalizing and classification of autism based on default mode network connectivity. *PLoS ONE* 7(11):e50064. <https://doi.org/10.1371/journal.pone.0050064>
- Naito M (2003) The relationship between theory of mind and episodic memory: evidence for the development of autonoetic consciousness. *J Exp Child Psychol* 85(4):312–336. [https://doi.org/10.1016/s0022-0965\(03\)00075-4](https://doi.org/10.1016/s0022-0965(03)00075-4)
- Nickl-Jockschat T, Habel U, Maria Michel T, Manning J, Laird AR, Fox PT, Schneider F, Eickhoff SB (2012a) Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Hum Brain Mapp* 33(6):1470–1489. <https://doi.org/10.1002/hbm.21299>
- Nickl-Jockschat T, Habel U, Michel TM, Manning J, Laird AR, Fox PT, Schneider F, Eickhoff SB (2012b) Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Hum Brain Mapp* 33(6):1470–1489. <https://doi.org/10.1002/hbm.21299>
- Nomi JS, Molnar-Szakacs I, Uddin LQ (2019) Insular function in autism: update and future directions in neuroimaging and interventions. *Prog Neuropsychopharmacol Biol Psychiatry* 89:412–426. <https://doi.org/10.1016/j.pnpbp.2018.10.015>
- Noriuchi M, Kikuchi Y, Yoshiura T, Kira R, Shigeto H, Hara T, Tobimatsu S, Kamio Y (2010) Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder. *Brain Res* 1362:141–149. <https://doi.org/10.1016/j.brainres.2010.09.051>
- Orsmond GI, Shattuck PT, Cooper BP, Sterzing PR, Anderson KA (2013) Social participation among young adults with an autism spectrum disorder. *J Autism Dev Disord* 43(11):2710–2719. <https://doi.org/10.1007/s10803-013-1833-8>
- Park MTM, Raznahan A, Shaw P, Gogtay N, Lerch JP, Chakravarty MM (2018) Neuroanatomical phenotypes in mental illness: identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. *J Psychiatry Neurosci* 43(3):201–212. <https://doi.org/10.1503/jpn.170094>
- Patriquin MA, DeRamus T, Libero LE, Laird A, Kana RK (2016) Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. *Hum Brain Mapp* 37(11):3957–3978. <https://doi.org/10.1002/hbm.23288>
- R Core Team (2022) R: a language and environment for statistical computing. R Foundation for Statistical Computing. <https://www.R-project.org/>
- Radeloff D, Ciaramidaro A, Siniatchkin M, Hainz D, Schlitt S, Weber B, Poustka F, Bölte S, Walter H, Freitag CM (2014) Structural alterations of the social brain: a comparison between schizophrenia and autism. *PLoS ONE* 9(9):1–9. <https://doi.org/10.1371/journal.pone.0106539>
- Retico A, Giuliano A, Tancredi R, Cosenza A, Apicella F, Narzisi A, Biagi L, Tosetti M, Muratori F, Calderoni S (2016) The effect of gender on the neuroanatomy of children with autism spectrum disorders: a support vector machine case-control study. *Mol Autism* 7(5):1–20. <https://doi.org/10.1186/s13229-015-0067-3>
- Rosenblau G, O'Connell G, Heekeren HR, Dziobek I (2020) Neurobiological mechanisms of social cognition treatment in high-functioning adults with autism spectrum disorder. *Psychol Med* 50(14):2374–2384. <https://doi.org/10.1017/S0033291719002472>
- Sacco R, Gabriele S, Persico AM (2015) Head circumference and brain size in autism spectrum disorder: a systematic review and meta-analysis. *Psychiatry Res* 234(2):239–251. <https://doi.org/10.1016/j.pscychresns.2015.08.016>
- Sasson NJ, Faso DJ, Nugent J, Lovell S, Kennedy DP, Grossman RB (2017) Neurotypical peers are less willing to interact with those with autism based on thin slice judgments. *Sci Rep* 7(1):1–10. <https://doi.org/10.1038/srep40700>
- Sato W, Kochiyama T, Uono S, Yoshimura S, Kubota Y, Sawada R, Sakihama M, Toichi M (2017) Reduced gray matter volume in the social brain network in adults with autism spectrum disorder. *Front Hum Neurosci* 11(395):1–12. <https://doi.org/10.3389/fnhum.2017.00395>
- Sato W, Toichi M, Uono S, Kochiyama T (2012) Impaired social brain network for processing dynamic facial expressions in autism spectrum disorders. *BMC Neurosci*. <https://doi.org/10.1186/1471-2202-13-99>
- Scarpazza C, Simone MD (2016) Voxel-based morphometry: current perspectives. *Neurosci Neuroecon* 5:19–35. <https://doi.org/10.2147/NAN.S66439>
- Scherf KS, Elbich D, Minshew N, Behrmann M (2015) Individual differences in symptom severity and behavior predict neural

- activation during face processing in adolescents with autism. *NeuroImage Clin* 7:53–67. <https://doi.org/10.1016/j.nicl.2014.11.003>
- Schulte-Rüther M, Greimel E, Markowitsch HJ, Kamp-Becker I, Remschmidt H, Fink GR, Piefke M (2011) Dysfunctions in brain networks supporting empathy: an fMRI study in adults with autism spectrum disorders. *Soc Neurosci* 6(1):1–21. <https://doi.org/10.1080/17470911003708032>
- Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E (2010) Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci* 30(12):4419–4427. <https://doi.org/10.1523/JNEUROSCI.5714-09.2010>
- Schurz M, Maliske L, Kanske P (2020) Cross-network interactions in social cognition: a review of findings on task related brain activation and connectivity. *Cortex J Study Nervous Syst Behav* 130:142–157. <https://doi.org/10.1016/j.cortex.2020.05.006>
- Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27(9):2349–2356. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>
- Shine JM, Poldrack RA (2018) Principles of dynamic network reconfiguration across diverse brain states. *Neuroimage* 180:396–405. <https://doi.org/10.1016/j.neuroimage.2017.08.010>
- Spreng RN (2013) Examining the role of memory in social cognition. *Front Psychol*. <https://doi.org/10.3389/fpsyg.2013.00437>
- Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, Wynshaw-Boris A, Colamarino SA, Lein ES, Courchesne E (2014) Patches of disorganization in the neocortex of children with autism. *N Engl J Med* 370(13):1209–1219. <https://doi.org/10.1056/NEJMoa1307491>
- Tang R, Friston KJ, Tang Y-Y (2020) Brief mindfulness meditation induces gray matter changes in a brain hub. *Neural Plast*. <https://doi.org/10.1155/2020/8830005>
- Thomas C, Moya L, Avidan G, Humphreys K, Jung KJ, Peterson MA, Behrmann M (2008) Reduction in white matter connectivity, revealed by diffusion tensor imaging, May account for age-related changes in face perception. *J Cogn Neurosci* 20(2):268–284. <https://doi.org/10.1162/jocn.2008.20025>
- Thompson A, Shahidiani A, Fritz A, O'Muircheartaigh J, Walker L, D'Almeida V, Murphy C, Daly E, Murphy D, Williams S, Deoni S, Ecker C (2020) Age-related differences in white matter diffusion measures in autism spectrum condition. *Mol Autism* 11(1):1–36. <https://doi.org/10.1186/s13229-020-00325-6>
- Toal F, Daly EM, Page L, Deeley Q, Hallahan B, Bloemen O, Cutter WJ, Brammer MJ, Curran S, Robertson D, Murphy C, Murphy KC, Murphy DGM (2010) Clinical and anatomical heterogeneity in autistic spectrum disorder: a structural MRI study. *Psychol Med* 40(7):1171–1181. <https://doi.org/10.1017/S0033291709991541>
- Travers BG, Adluru N, Ennis C, Tromp DPM, Destiche D, Doran S, Bigler ED, Lange N, Lainhart JE, Alexander AL (2012) Diffusion tensor imaging in autism spectrum disorder: a review. *Autism Res* 5(5):289–313. <https://doi.org/10.1002/aur.1243>
- Trontel HG, Duffield TC, Bigler ED, Froehlich A, Prigge MBD, Nielsen JA, Cooperrider JR, Cariello AN, Travers BG, Anderson JS, Zielinski BA, Alexander A, Lange N, Lainhart JE (2013) Fusiform correlates of facial memory in autism. *Behav Sci*. <https://doi.org/10.3390/bs3030348>
- Uddin LQ (2015) Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci* 16(1):55–61. <https://doi.org/10.1038/nrn3857>
- Uddin LQ, Menon V (2009) The anterior insula in autism: under-connected and under-examined. *Neurosci Biobehav Rev* 33(8):1198–1203. <https://doi.org/10.1016/j.neubiorev.2009.06.002>
- Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, Ryali S, Menon V (2013a) Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiat* 70(8):869. <https://doi.org/10.1001/jamapsychiatry.2013.104>
- Uddin LQ, Supekar K, Menon V (2013b) Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front Hum Neurosci*. <https://doi.org/10.3389/fnhum.2013.00458>
- van Heijst B, Geurts HM (2015) Quality of life in autism across the lifespan: a meta-analysis. *Autism Int J Res Pract* 19(2):158–167. <https://doi.org/10.1177/1362361313517053>
- Velikonja T, Fett A-K, Velthorst E (2019) Patterns of nonsocial and social cognitive functioning in adults with autism spectrum disorder: a systematic review and meta-analysis. *JAMA Psychiat* 76(2):135–151. <https://doi.org/10.1001/jamapsychiatry.2018.3645>
- Waiter GD, Williams JHG, Murray AD, Gilchrist A, Perrett DI, Whiten A (2004) A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. *Neuroimage* 22(2):619–625. <https://doi.org/10.1016/j.neuroimage.2004.02.029>
- Wang Y, Olson IR (2018) The original social network: White matter and social cognition. *Trends Cogn Sci* 22(6):504–516. <https://doi.org/10.1016/j.tics.2018.03.005>
- Wilke M, Holland SK, Altaye M, Gaser C (2008) Template-O-Matic: a toolbox for creating customized pediatric templates. *Neuroimage* 41(3):903–913. <https://doi.org/10.1016/j.neuroimage.2008.02.056>
- Williams JHG, Whiten A, Suddendorf T, Perrett DI (2001) Imitation, mirror neurons and autism. *Neurosci Biobehav Rev* 25(4):287–295
- Xiao Z, Qiu T, Ke X, Xiao X, Xiao T, Liang F, Zou B, Huang H, Fang H, Chu K, Zhang J, Liu Y (2014) Autism spectrum disorder as early neurodevelopmental disorder: evidence from the brain imaging abnormalities in 2–3 years old toddlers. *J Autism Dev Disord* 44(7):1633–1640. <https://doi.org/10.1007/s10803-014-2033-x>
- Yang DY-J, Beam D, Pelphrey KA, Abdullahi S, Jou RJ (2016) Cortical morphological markers in children with autism: a structural magnetic resonance imaging study of thickness, area, volume, and gyrification. *Mol Autism* 7(11):1–14. <https://doi.org/10.1186/s13229-016-0076-x>
- Yaxu Y, Ren Z, Ward J, Jiang Q (2020) Atypical brain structures as a function of gray matter volume (GMV) and gray matter density (GMD) in young adults relating to autism spectrum traits. *Front Psychol*. <https://doi.org/10.3389/fpsyg.2020.00523>
- Zielinski BA, Prigge MBD, Nielsen JA, Froehlich AL, Abildskov TJ, Anderson JS, Fletcher PT, Zygmunt KM, Travers BG, Lange N, Alexander AL, Bigler ED, Lainhart JE (2014) Longitudinal changes in cortical thickness in autism and typical development. *Brain J Neurol* 137(6):1799–1812. <https://doi.org/10.1093/brain/awu083>

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

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.