Anatomical imbalance between cortical networks in autism

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Influential psychological models of autism spectrum disorder (ASD) have proposed that this prevalent developmental disorder results from impairment of global (integrative) information processing and overload of local (sensory) information. However, little neuroanatomical evidence consistent with this account has been reported. Here, we examined relative grey matter volumes (rGMVs) between three cortical networks, how they changed with age, and their relationship with core symptomatology.

Using public neuroimaging data of high-functioning ASD males and age-/sex-/IQ-matched controls, we first identified age-associated atypical increases in rGMVs of the regions of two sensory systems (auditory and visual networks), and an age-related aberrant decrease in rGMV of a task-control system (fronto-parietal network, FPN) in ASD children. While the enlarged rGMV of the auditory network in ASD adults was associated with the severity of autistic socio-communicational core symptom, that of the visual network was instead correlated with the severity of restricted and repetitive behaviours in ASD. Notably, the atypically decreased rGMV of FPN predicted both of the two core symptoms. These findings suggest that disproportionate undergrowth of a task-control system (FPN) may be a common anatomical basis for the two ASD core symptoms, and relative overgrowth of the two different sensory systems selectively compounds the distinct symptoms.

Autism spectrum disorder (ASD) is characterised by socio-communicational deficits and restricted and repetitive behaviours (RRB). In prominent psychological models, these symptoms have been accounted for as the behavioural expression of a functional imbalance between global and local information processing. For example, one model proposes that hyperactivity of primary sensory areas overloads higher-order cognitive processes in the autistic brains, resulting in impairment of integrative cognition and overemphasis on low-level perceptual information. Weak central coherence theory and enhanced perceptual functioning theory also suggest that detail-focused and overly-enhanced lower-level perception constitutes a vital part of ASD, supported by a recent behavioural study on auditory perception. In addition, underconnectivity theory and others propose that both the two core symptoms of ASD are associated with impairment of integration of global information. A recent review from a Bayesian perspective has also suggested that both of autistic social deficits and RRB may be due to an imbalance between sensory precision and top-down modulation of prior belief. Taken together, these psychological models suggest that the two core symptoms of ASD might be interpreted as impairment of global (integrative) information processing and overload of local (sensory) information.

However, despite many human neuroimaging studies investigating brain architectures of individuals with ASD, little neuroanatomical evidence for such an account has been found. Some structural characteristics, including aberrant volumes of amygdala and superior temporal gyrus, are associated with socio-communicational deficits of ASD. Other anatomical features, such as a smaller corpus callosum, are related to other non-social behaviours in ASD. Although these previous findings partially support the account of ASD implied by the psychological models, direct anatomical evidence for the hypothesis has not been reported.

We searched for such neuroanatomical evidence by hypothesising that such a functional imbalance between global (integrative) and local (sensory) information processing might be reflected in an anatomical imbalance between different large-scale brain networks with distinct cognitive and perceptual functions. Specifically, we set a working hypothesis that autistic core symptoms may be associated with relative anatomical immaturity of brain networks for integration of global information and reciprocal relative overgrowth of networks for lower-level perception.

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**Results**

**Age-related changes during childhood.** As a control, we first examined the baseline of the network-based rGMVs by comparing the nine network rGMVs between ASD and age-/IQ-matched TD individuals in a relatively early part of childhood (7 ≤ age ≤ 11), and found no significant difference between the two groups (\(P > 0.05\) in main effects and interactions in a repeated measures two-way ANOVA; Supplementary Fig. 2).

Next, using the entire childhood data (7 ≤ age ≤ 18), we found significant associations between age and rGMV of the regions constituting three networks (\(P_{\text{uncorrected}} < 0.05/9, P_{\text{Bonferroni-corrected}} < 0.05\); Fig. 2). In auditory and visual networks, the rGMVs showed positive correlations with age in ASD individuals (auditory, \(r = 0.32, P = 0.002\); visual, \(r = 0.43, P = 0.0002\); Fig. 2a), whereas such correlations were not seen in TD group (auditory, \(r = -0.097, P = 0.34\); visual, \(r = -0.079, P = 0.44\); Fig. 2b). In the fronto-parietal network (FPN), rGMV was negatively correlated with age in ASD individuals (\(r = -0.34, P = 0.0012\)), whilst that was positively associated in TD children (\(r = 0.44, P < 10^{-5}\)) (Fig. 2c). Moreover, the differences in correlations seen in the three networks were significant between ASD and TD groups (\(z > 2.8, P < 0.05\)). These significant age-rGMV associations were consistently observed in IQ-controlled partial correlations (Supplementary Table 2), and were robust against unspecific effects due to differences between the data collection sites (Table 2). We did not find such significant correlations in the other six networks.

These findings suggest that, in our high-functioning ASD population, rGMVs of auditory and visual networks atypically increase during childhood, and that of FPN abnormally decreases. In fact, we confirmed that such atypical anatomical development during childhood resulted in significant differences in network rGMVs between ASD and TD adults (18 < age ≤ 40) (\(F_{(8,746)} = 325.5, P < 0.0001\) as interactions in a repeated measure two-way ANOVA, \(P_{\text{Bonferroni-corrected}} < 0.05\) in post-hoc two-sample \(t\)-tests; Fig. 3). The rGMVs of auditory and visual networks were significantly larger in adult ASD group than in adult TD group (auditory, \(t_{(82)} = 3.8, P = 0.0003\); visual, \(t_{(82)} = 3.6, d = 0.75, P = 0.0004\) in two-sample \(t\)-tests), whereas that of FPN was significantly smaller in ASD (\(t_{(82)} = 5.6, d = 0.89, P < 0.0001\)).

**Associations with ASD symptoms.** Using the adult ASD data, we then examined whether these atypical anatomical developments were associated with severity of the core symptoms of ASD (Fig. 4).
The disproportionate overgrowth of rGMV of auditory network was correlated with severity of autistic socio-communicational deficits ($r = 0.51, P = 0.002$; Fig. 4a), whereas that of visual network was related with the extent of autistic RRB ($r = 0.56, P = 0.0004$; Fig. 4b). These correlations were specific to each core symptom ($z > 2.0, P < 0.05$).

These symptom-rGMV associations were consistently observed after effects of IQ and age were controlled (Supplementary Table 3) or even when they were calculated using different parts of the datasets (Table 3). In addition, the associations between severity of social symptoms and rGMV were qualitatively reproduced when the correlations were separately calculated for ADIR-social and ADIR-communication scores (Supplementary Fig. 3, Supplementary Table 4). We did not find such significant symptom-rGMV correlations in the other networks.

Furthermore, this anatomical imbalance between different networks and its relationship with autistic symptoms were consistently observed when such anatomical balance was quantified based on cortical thickness rather than GMV (Supplementary Fig. 4; Supplementary Methods).

In contrast, we could not find such significant rGMV-symptom correlations in data obtained from autistic children ($P > 0.15$). It is possibly because, as shown above (Fig. 2), ongoing developmental brain changes during childhood may act as a confounding factor and make it difficult to detect such neuroanatomy-symptom associations in the childhood dataset.

Regions responsible for symptom-rGMV associations. Finally, we searched for brain regions responsible for the significant correlations between rGMVs and ASD symptoms seen in the three brain networks (Fig. 5a). Regarding the associations with severity of socio-communicational deficits, rGMVs of medial prefrontal cortex (mPFC) in FPN and bilateral posterior insulae in auditory network were significantly related to such impairment (mPFC, $r = -0.61, P = 0.0009$; right posterior insula, $r = 0.57, P = 0.0003$; left posterior insula, $r = 0.47, P = 0.004$; $P_{FDR} < 0.05$; Fig. 5b). Regarding RRB, rGMVs of ventro-/dorso- lateral prefrontal cortex (VLPFC/DLFC) in FPN and three lateral occipital regions in visual network were associated with ADIR-RRB ($r > 0.40, P \leq 0.01$; $P_{FDR} < 0.05$; Fig. 5c). Such significant rGMV-symptom correlations were not found in the other regions. As discussed below, these significant associations found in specific brain regions were consistent with previous literature on autism and relevant cognitive functions.

Discussion

The current study has compared the anatomical balance among the nine cortical networks for high-functioning ASD and age-/sex-/IQ-matched TD groups, and found atypical age-related increases in rGMVs of auditory/visual networks and a decrease in rGMV of FPN in ASD children. In ASD adults, the increased rGMV of auditory network was specifically correlated with autistic socio-communicational deficit, whereas that of visual network was selectively associated with RRB. The disproportionate low rGMV of FPN was predictive of both of the two ASD core symptoms. These findings suggest that the relative undergrowth of FPN is an anatomical basis for the two autistic core symptoms, whereas disproportionate overgrowth of the two different sensory networks allows the diversity of these symptoms.
Network-based interpretation. According to network-based perspectives on functional and anatomical brain architectures, the auditory and visual networks are mainly involved with lower-level perception, whereas FPN supposedly controls attention, integrates the information processed in the other networks, and plays a central role in various cognitive functions. From such a viewpoint, if we assume a positive correlation between regional GMV and cognitive functions relevant to the regions, the current results are consistent with prominent theories of autism, and appear to support their collective hypothesis that ASD symptoms are interpreted as a behavioural expression of impairment of information integration and enhancement of low-level perceptual information processing.
Region-based interpretation. Specific brain regions were largely responsible for these significant associations between network rGMVs and symptom severity (Fig. 5).

For socio-communication deficits, the correlation with rGMV of FPN appeared to largely depend on atypical anatomical undergrowth of mPFC (Fig. 5b). Such a region is critically involved in various social cognition paradigms in neurotypical individuals and decreased mPFC activity is observed in ASD populations. In the auditory network, grey matter in bilateral posterior insulae was correlated with socio-communication deficits (Fig. 5b). Such increases in GMV in posterior insulae are associated with increased sensitivity to pain and tactile stimulation in neurotypical individuals; and such changes can be correlated with social deficits in autism. Therefore, it is reasonable to suggest that the relative overgrowth of posterior insulae might induce hypersensitivity in autism and compound socio-communicational deficits of ASD.

As for RRB, the relative undergrowth of DLPFC and VLPFC was responsible brain regions in FPN (Fig. 5c), which is consistent with previously reported associations between lateral prefrontal activity and performance of cognitive control in TD individuals and ASD group.

In the visual network, disproportionately overgrown bilateral extra-striate occipital regions are observed in autistic individuals (Fig. 5c), which is consistent with previously reported associations between lateral prefrontal activity and performance of cognitive control in TD individuals and ASD group.

Consistency with anatomical studies. It is difficult to directly compare the current findings with previous findings on GMV of autistic brains, because most of this literature directly examined GMV without calculating ratios of GMV between different regions or different networks. However, the current observations are consistent with some previous reports and meta-analytic results. For example, the atypically increased rGMV of the visual network that we observed in the ASD group is in accordance with a meta-analysis showing aberrant GMV increases of lateral occipital regions. The age-related overgrowth of the visual network is also consistent with another meta-analysis. In addition, this meta-analysis has also reported age-associated GMV decreases of parietal regions, which is congruent with the age-related rGMV decrease in FPN in the current study. Moreover, a recent longitudinal study has reported that frontal and parietal areas showed sharper age-related decreases in GMV than occipital regions, which is congruent with the dissociation of age-associated rGMV changes between FPN and visual network in this study.

Limitations. One of the main limitations of the current study is the cross-sectional study design using data collected from multiple sites. In theory, compared with estimation of GMV, calculation of rGMV is more robust...
against noise induced by the individual variability and difference across imaging sites. In addition, the main observations were qualitatively reproduced even when we calculated them using different parts of the datasets (Tables 2 and 3). However, ideally, developmental changes in brain anatomy should be investigated in a longitudinal design using the quality-controlled same MRI scanner\textsuperscript{10,13}.

Another limitation is the lack of consideration of any specific effects of puberty. Puberty has significant impacts on brain anatomy\textsuperscript{15,17,49,50}, but the current observations did not consider these effects because the ABIDE database did not include such information. For the same technical reason, we could not investigate changes in network-based anatomical balance during toddlerhood and early childhood before the age of seven.

We need to be careful when interpreting and potentially generalising the current observations. First, the current findings do not directly indicate an imbalance of absolute values of network GMV in autistic brains. The rGMV used in the current analysis is an abstract index used to estimate neuroanatomical balance between networks, and therefore it can be different from the absolute values of GMV. Second, the current findings could be affected by the way in which we defined the regions of interest (ROIs). Specifically, the ROI coordinates and network classifications were based on previous functional neuroimaging studies of TD individuals\textsuperscript{29,30}, and so may not reflect the ASD population. Finally, we cannot conclude that the structural imbalance between the three networks we observed is an underlying cause of ASD. As it is possible to reliably diagnose autism in two-year-old children, a more extensive study covering the whole childhood is needed to better understand the developmental changes in brain anatomy.

Figure 5. (a) Using data of ASD adults, we searched ROIs in auditory, visual, and fronto-parietal networks for focal regions whose rGMVs were significantly correlated with ASD severity. The sizes of the circles represent the magnitudes of the symptom-rGMV correlations. (b) In auditory network, rGMVs of bilateral dorsal posterior insulae had significant positive correlations with socio-communicational deficits, whereas rGMV of medial prefrontal cortex (mPFC) in FPN showed a negative correlation. (c) In visual network, rGMVs of three lateral occipital regions in visual network were positively correlated with RRB, and those of two dorso-/ventro-lateral prefrontal cortical regions (DLPFC/VLPFC) in FPN showed negative correlations.
children, our findings concerning older ASD individuals (i.e., ≥7 years old) might not represent a primary pathological mechanism of this developmental disorder but instead reflect compensatory neuroanatomical processes emerging during childhood and adolescence in individuals with ASD.

Conclusion
Using publicly shared neuroimaging datasets, the current study has examined anatomical balance between large-scale brain networks in autism and matched controls. Consequently, we have found atypical relative overgrowth of brain regions in FPN and disproportionate undergrowth of auditory and visual networks. Moreover, this relative undergrowth of the two different sensory systems is selectively correlated with two different core symptoms of autism, and this relative overgrowth of FPN is related to both of the autistic behaviours. These findings provide empirical evidence for several prominent autism theories, and support for a network-based framework of unified understanding of seemingly diverse ASD symptoms.

Materials and Methods
Data. Anatomical data were selected from T1-weighted MRI images of 468 autistic individuals who were diagnosed as ASD based on DSM-IV-TR and 560 TD controls that were recorded in 3.0T MRI scanners in multiple institutes, and now are shared in ABIDE29. According to the data repository, the data collection was approved by the corresponding local Institutional Review Boards, and was performed in accordance with the corresponding institutional regulations (i.e., Review Boards and their regulations in New York University, Pittsburgh University, San Diego State University, University California Los Angeles, California Institute of Technology, and Trinity Centre for Health Sciences). Written informed consents were obtained from all the participants. The data were fully anonymised before being publicly shared. The imaging protocols are considered to be equivalent across different institutes (T1-weighted protocol; TR ≃ 2.5 s, TE ≃ 3 ms, thickness ≃ 1.1 mm).

First, we systematically selected MRI images that were recorded from right-handed high-functioning ASD males who had average or above-average intelligence (full IQ ≥ 80) evaluated by WISC, WASI, or WAIS, and were given Autism Diagnostic Interview-Revised (ADI-R) scores. Individuals who had medication history of anti-psychotic drugs or took any medication on the scanning day were also excluded (Supplementary Fig. 1). The right handedness was determined based on the demographic data sheet accompanied by the MRI dataset (i.e., ‘R’ in Handedness Category or positive number in Handedness Scores). Second, we classified the participants into childhood group (age ≤ 18) and adult group (18 < age), and obtained data of 89 ASD children (7 ≤ age ≤ 18) and those of 34 ASD adults (18 < age ≤ 40). Finally, we selected data of TD individuals by matching their sex, IQ, age, handedness, and institutes collecting data, and gathered data of 96 TD children and those of 50 TD adults.

There was no significant difference in any of age, IQ, and distribution of recording sites between ASD and TD groups (Table 1). Moreover, no significant difference in age and IQ was seen between the data collection sites (P ≥ 0.1 in one-way analysis of variance; Supplementary Table 1).

We used ADIR scores rather than Autism Diagnostic Observations Schedule (ADOS) scores, because the number of ASD adults scored by ADIR (N = 123) was larger than that of ADOS (N = 82). For the same reason, the current study employed only male data (ASD, N = 123) rather than female data (ASD, N = 15).

Data processing. These anatomical MRI images were preprocessed for the following GMV analysis in SPM1253. They were segmented into grey matter, white matter, and cerebrospinal fluid in the native space using the New Segment Toolbox54. The segmented grey matter images underwent alignment, warp to a template space, resampling down to 1.5 mm isotropic voxels, and registration to a participant-specific template with the DARTEL Toolbox55. Using deformation parameters estimated by the DARTEL toolbox, the grey matter images were normalised to MNI spaces and smoothed with a Gaussian kernel (FWHM ≃ 8 mm). Because this preprocessing procedures in DARTEL Toolbox included a so-called modulation process to preserve the volume of a particular tissue within a voxel (see Section 25.5.3 in SPM12 manual in www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf), signal values in the resultant preprocessed images were supposed to represent GMV in the voxels. The images were then normalised by being divided by the whole-brain GMV. This normalisation was expected to control for not only individual differences in whole brain volumes but also unspecific differences between the data collection sites.

For each image, we extracted GMVs of 213 cortical ROIs, which were defined as 4 mm-radius spheres whose centre coordinates were determined in previous functional neuroimaging studies. To focus on cortical networks, we excluded 51 ROIs with 'subcortical' or 'uncertain' labels from the original 264 ROIs. The GMV of each ROI was determined as the average GMV of the corresponding 4 mm-radius sphere. Because the minimum distance between the 213 ROIs was 10.0 mm, we set the radius of the ROI sphere at 4 mm and avoided overlap between different ROI areas. We then classified the ROIs into the nine cortical networks29,30 (Fig. 1a,b), calculated a mean GMV for each network by averaging GMVs across the ROIs constituting each network, and estimated a relative GMV (rGMV) for each network by normalising the mean GMVs among the networks. The rGMVs are thus considered to represent anatomical balance between the nine cortical networks for each participant. Note that no ROI was shared between different networks.

This ROI classification was indirectly through calculating inter-volumetric correlations between GMVs of the ROIs as follows: for example, in TD adult group, for each network (e.g., FPN), we first averaged the across-participant GMV correlations between the ROIs belonging to the specific network (here, FPN). In the meantime, we also estimated the average of the GMV correlations between the ROIs in the network (i.e., ROIs in FPN) and ROIs belonging to the other eight networks (ROIs in the networks rather than FPN). We repeated this procedure for every network in every participant group. As a result, we confirmed that, for all the networks in all the participant groups, the within-network inter-volumetric correlations were larger than the between-network
correlations. This contrast was also supported by statistical tests (ASD children: $t_8 = 3.4$, $P_{\text{uncorrected}} = 0.008$; ASD adults: $t_8 = 4.0$, $P_{\text{uncorrected}} = 0.003$; TD children: $t_8 = 4.3$, $P_{\text{uncorrected}} = 0.002$; TD adults: $t_8 = 3.6$, $P_{\text{uncorrected}} = 0.007$ in paired t-tests; all $P_{\text{FDR}} < 0.05$). The current study focused on the brain regions in the network (i.e., nodes) but not on the connections between them (i.e., edges), because the dataset did not contain neuroimaging data to evaluate anatomical connections in individual brains.

**Associations with age during childhood.** As a baseline, we first compared rGMVs of a relatively early part of the childhood data ($7 \leq \text{age} \leq 11$) between ASD and TD groups with a repeated measures two-way ANOVA of rGMV (two types of group [ASD/TD] \times nine types of network). This age threshold (i.e., age of 11) was chosen to reduce effects of puberty with keeping the sample size. Demographic properties were controlled between the 34 ASD and 12 TD children (age, IQ: $t_8 = 3.6$, $P_{\text{FDR}} < 0.05$ in paired t-tests).

Next, using the entire childhood data ($7 \leq \text{age} \leq 18$), we calculated Pearson's correlation coefficients between age and network rGMVs, and compared them between ASD and TD children. To minimise effects of IQ we also estimated partial correlations controlled by Full, Verbal, and Performance IQ. The statistical significance was adjusted by Bonferroni correction for multiple comparisons across the nine networks ($\alpha = 0.05/9$).

To evaluate unspecific effects of differences in data collection sites on the observed associations, we repeatedly calculated the age-rGMV correlations using different subsets of the data excluding datasets collected in different institutes.

**Associations with symptoms in adults.** Using the adult data, we first compared rGMVs between ASD and TD groups with a repeated measures two-way ANOVA (two types of group [ASD/TD] \times nine types of network) and post-hoc two-sample t-tests adjusted by Bonferroni correction. We then calculated correlation coefficients between the network rGMVs and individual severity of ASD. The rGMV for an ROI belonging to a certain network was calculated as the ratio of the GMV of the ROI to the summation of average GMVs of all the other networks:

$$r_{\text{GMV}} = \frac{\text{GMV of ROI}}{\sum_{k \neq j} \text{average GMV of Network}_k}$$

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To evaluate unspecific effects of differences in data collection sites on the observed associations, we repeatedly calculated the age-rGMV correlations using different subsets of the data excluding datasets collected in different institutes.

**ROI-based associations with symptoms.** Finally, we searched for ROIs responsible for the significant associations between network rGMVs and ASD severity. The rGMV for an ROI belonging to a certain network was calculated as the ratio of the GMV of the ROI to the summation of average GMVs of all the other networks as follows: (rGMV of ROI, in Network,) = (GMV of ROI)/\sum_{k \neq j} (average GMV of Network_k). We then estimated correlation coefficients between the ROI rGMVs and ASD severity, and searched for ROIs whose correlations were statistically significant. The significance was corrected for multiple comparisons across the ROIs included in the corresponding network by setting false discovery rate (FDR) at 0.05. We used FDR-based correction because the application of Bonferroni correction to this case, which consisted of $\geq 12$ comparisons, was too conservative and likely to increase false negative.

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Author Contributions
T.W. and G.R. designed the study. T.W. analysed the data. T.W. and G.R. wrote the manuscript.

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