



the other disorder (Grzadzinski et al., 2011; Grzadzinski et al., 2016; Reiersen et al., 2008). Co-occurrence happens not only in core but also in non-core symptoms, such as hyper- and hypo-sensitivity (Little et al., 2018; Ohta et al., 2019; Pan et al., 2009). Besides the overlap in these clinical symptoms, ASD and ADHD show familial co-aggregation (Ghirardi et al., 2018; Jokiranta-Olkonemi et al., 2016), suggesting their shared genetic etiology (Stergiakouli et al., 2017). Although results vary, neuroimaging studies demonstrated some similarities in atypical cortical structure, white matter, and function (Ameis et al., 2016; Brieber et al., 2007; Chantiluke et al., 2014; Christakou et al., 2013). On top of such shared atypicality, neural bases of ASD symptoms in individuals with ADHD are similar to those in individuals with ASD (Baribeau et al., 2019). These overlapping features contribute, at least in part, to the within-diagnosis heterogeneity and inconsistency in findings from studies contrasting diagnostic groups (Insel, 2014). Identifying highly biologically homogeneous subtypes, independent of the clinical diagnosis, is an urgent need in the research field of developmental disorders.

In this context, previous functional MRI studies focused on features that ensure phenotypic homogeneity in ASD, in ADHD, and in both (Kernbach et al., 2018; Lin et al., 2018; Tang et al., 2019). However, findings are mixed. While a study including individuals with ADHD highly homogeneous in terms of demographic characteristics showed high homogeneity in neural characteristics within the diagnostic boundary (Lin et al., 2018), another study with a larger sample size showed neural heterogeneity within ASD diagnosis (Tang et al., 2019). Of note, a study with both ASD and ADHD detected brain transdiagnostic features that map clinical characteristics independent of diagnoses (Kernbach et al., 2018). Two studies attempted to subtype clinical participants to address the unstable numbers of subtypes (Kernbach et al., 2018; Lin et al., 2018). One possible reason for instability is too many degrees of feature utilized to subtype. Indeed, two studies relying on structural MRI, which has a smaller number of degrees of feature than fMRI, used different clustering methods aimed to subtype individuals with ASD reported the optimal number of subtypes as three (Chen et al., 2019; Hong et al., 2018). Another possible reason is that previous clustering methods relied on the similarity of fMRI signal among subjects and can be vulnerable to confounding signal related to non-pathophysiological characteristics. Thus, they might have reflected normal inter-subject variability, rather than highlighting the heterogeneity.

To address these issues from previous studies, we recruited adult males with ASD and those with ADHD as well as adult male neurotypical controls (NTC) and applied Heterogeneity through Discriminative Analysis (HYDRA) to structural MRI data (Varol et al., 2017). HYDRA is a hybrid method where clustering and classification are conducted simultaneously. A standard classification approach (e.g., support vector machine) attempts to identify the pathophysiological features spanning the clinical group from the NTC group by drawing a decision boundary between the groups without considering the heterogeneity within the clinical group. In contrast, HYDRA attempts to find subtypes within the clinical group while maximizing margin boundaries between the clinical and NTC groups. This unique ability allows us to identify biologically homogeneous subtypes, each of which preserve different aspects of pathophysiological features of developmental disorders, i.e., differences to typically developing controls, rather than picking up features which have a non-pathophysiological origin, such as head motion, bed vibration, or instability of magnetic field strength. As they reflect

Participants

MRI data of 148 adult males with a developmental disorder(s) (99 primary ASD diagnosis and 49 primary ADHD diagnosis) as well as 105 NTC participants were selected from a larger sample. Thirteen individuals had both diagnoses. Because of the nature of the current study aimed to transdiagnostically subtype people, we gave priority to people with a single diagnosis to include. Thus, the number of people with dual diagnoses is smaller than the estimated. The diagnostic process of the current study is detailed elsewhere (Ohta et al., 2019). Briefly, a multidisciplinary team, including psychiatrists and psychologists, reviewed developmental history and made clinical diagnoses according to the DSM-IV-TR criteria. A diagnosis of ASD was further supported by the Autism Diagnostic Observation Schedule-1 or -2 (ADOS) ($n = 74$) (Gotham et al., 2009; Gotham et al., 2007). Five individuals did not satisfy the diagnostic criteria of ASD on the ADOS (four had a total score of 6; one had a total score of 7 but the communication score was 1). In these cases, at least two psychiatrists carefully reviewed the charts and confirmed the clinical diagnosis. ASD and ADHD traits were evaluated using the Autism Spectrum Quotient and Conners' Adult ADHD Rating Scales, respectively (Baron-Cohen et al., 2001; Conners et al., 1999). The intelligence quotient (IQ) of participants in clinical groups was estimated using either the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) or WAIS-Revised (WAIS-R) (Wechsler, 1997; Wechsler and De Lemos, 1981). Seventy-two participants were taking medication at the time of scan (36 ASD and 36 ADHD). NTC participants were recruited via an advertisement or through an acquaintance. A lack of any psychiatric diagnosis in the NTC group was confirmed using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Full-scale IQ in the NTC group was estimated using a Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). Exclusion criteria for all the participants included taking antipsychotics, any history of head trauma, any serious medical condition, substance abuse, or IQ below 80.

2.2. MRI data acquisition

All MRI data were acquired using a 3.0 T MRI scanner (MAGNETOM Verio, Siemens Medical Systems, Erlangen, Germany) with a 12-channel head coil. T1-weighted images were acquired with an MPRAGE sequence (TR: 2.3 s, TE: 2.98 ms, flip angle: 9°, FOV: 256 mm, matrix size: 256 × 256, slice thickness: 1 mm, 240 sagittal slices, voxel size: 1 × 1 × 1 mm).

2.3. Structural MRI data preprocessing

Structural MRI data was processed using FreeSurfer version 6.0.1 (Dale et al., 1999; Fischl et al., 1999). This algorithm performs a series of preprocessing steps, including spatial normalization, bias field correction, intensity normalization, skull-stripping, segmentation, and reconstruction of surface mesh. We computed the aforementioned two parameters: CT and SA. For each parameter, we, then, extracted the mean values using the Schäfer's 400 cortical atlas that parcellated cortex into functionally homogeneous parcels using intrinsic functional connectivity (Schaefer et al., 2018). To test the robustness of findings against atlas choice, we also computed the mean values using Destrieux's cortical atlas (Destrieux et al., 2010). At the same time, utilizing a different atlas challenges the stability of the findings against the degree of features as the Destrieux's cortical atlas consists of 148 regions of interest (ROIs) while the Schaefer's 400 cortical atlas consists of 400

controlling age and handedness as nuisance covariates, we defined neuroanatomical subtypes, regardless of clinical diagnoses. This method is based on the classification framework, in which it compares participants with developmental disorders and NTCs to identify k clusters within the group of participants with developmental disorders in a data-driven manner. We set the hyperparameters, such as the number of iterations, that of consensus clustering steps, and regularization parameter, based on a previous study (Varol et al., 2017). Consistent with previous studies with this method, we set multiple clustering solutions from two to 10 clusters, to obtain a range of possible solutions. The adjusted rand index (ARI) was computed using 10-fold cross-validation to assess the stability of each clustering solution. In this study, we considered a solution with the highest ARI value as the optimal number of clusters (Steinley, 2004). Once the optimal number of clusters was determined, a permutation test with 5000 iterations was then performed to examine its statistical significance. At each iteration, labels were shuffled. HYDRA was then applied, and the ARI for the shuffled data was computed to construct the null distribution. The actual ARI was then compared to the null distribution to examine its statistical significance. The threshold for statistical significance was set to $P < 0.05$. To further confirm the stability of clustering solutions, we computed two additional metrics, the Hamming distance and the Rand index, representing dissimilarity and similarity, respectively, between different clustering solutions. Thus, lower Hamming distance and higher Rand index indicate more stable clustering solutions.

2.5. Statistical analyses

2.5.1. Clinical characteristics of each subtype

2.5.1.1. Two-group comparison. Once subtypes were identified, two-tailed, two-sample tests were performed, to investigate differences in clinical characteristics, such as age, handedness, IQ, AQ, and CAARS, among subtypes as well as differences between subtype and the NTC group. The threshold of statistical significance was set at $P < 0.05$ after false discovery rate (FDR) correction. Chi-square tests examined whether the likelihood of the diagnosis of ASD or ADHD is statistically significantly different from the chance.

2.5.1.2. Three-group comparison. One-way analysis of variance (ANOVA) was performed to examine the effects of primary diagnoses on demographic characteristics. The threshold of statistical significance was set at $P < 0.05$ for demographic characteristics, while those for cortical parameters were set at $P < 0.05$ after FDR correction.

2.6. Cortical characteristics of subtypes

We conducted two-tailed, two-sample tests to examine differences in cortical parameters among subtypes as well as differences between subtype and the NTC group. The threshold of statistical significance was set at $P < 0.05$ after false discovery rate (FDR) correction. The analyses were conducted for CT and SA, separately.

2.7. A convergence of area with differences

Once statistically significant differences were observed between subtypes and the NTC group, conjunction analyses were performed to identify brain regions consistently exhibiting alterations across conditions. To increase the interpretability of results, we also calculate the

consistency across four HYDRA (2 at $k=2$ inclusion criteria), we calculate dice coefficients while considering the subtypes obtained using the functional atlas including individuals with dual diagnoses as a reference. These analyses were performed in CT and SA, separately.

2.9. Conventional comparison between diagnostic groups

2.9.1. Demographic characteristics

Age, handedness, IQ, AQ, and CAARS scores were compared across three diagnostic groups (ASD, ADHD, and NTC) using ANOVA. Statistical threshold was set at $P < 0.05$ with FDR correction. Turkey's post-hoc analyses were conducted when ANOVA showed statistical significance.

2.10. Cortical parameters

In HYDRA, we adopted a whole-brain approach instead of focusing on ROI. To examine regional differences in cortical parameters between diagnostic groups, we conducted a conventional ANOVA. We utilized the functional atlas and set statistical significance at $P < 0.05$ after FDR correction. All analyses were conducted in Matlab.

3. Results

3.1. Number of subtypes

With 10-fold cross-validation, HYDRA using CT identified that two subtypes (i.e., $k = 2$) showed the highest ARI ($\text{ARI} = 0.85 \pm 0.02$ [mean $\pm$ standard deviation]) and the highest statistical significance ($p < 0.001$), indicating that the individuals with developmental disorders were clustered into two subtypes (CT-subtype1 and CT-subtype2). The number of clusters remained two when we conducted HYDRA with SA ($\text{ARI} = 0.75 \pm 0.02$, $p < 0.001$) (SA-subtype1 and SA-subtype2). The optimal numbers of subtypes were unchanged even when excluding 13 people with a dual diagnosis and/or using the anatomical atlas (Supplementary Fig. 1). Furthermore, the optimal numbers of subtypes was corroborated by the supplementary exploration of two additional metrics, i.e., the Hamming distance (CT: 0.12 ± 0.03 , SA: 0.08 ± 0.03) or Rand index (CT: 0.89 ± 0.02 , SA: 0.92 ± 0.03 ; Supplementary Fig. 2) to assess cluster stability.

3.2. Clinical characteristics of each subtype

Forty-nine individuals with ASD and 25 people with ADHD were assigned to CT-subtype1, while CT-subtype2 included 50 individuals with ASD and 24 individuals with ADHD (Supplementary Table 1). Chi-square test showed that the likelihood of a diagnosis of ASD or ADHD did not statistically significantly different from the chance. There was no significant difference in clinical symptoms between these two subtypes. Similarly, the statistical differences in the diagnosis likelihood or clinical symptoms severity were not observed even when excluding individuals with dual diagnoses and/or using the anatomical atlas (Supplementary Table 1). The results with SA were substantially similar to CT (Supplementary Table 2).

3.3. Cortical characteristics of subtypes

3.3.1. CT

The independent t-tests showed that compared with NTC individuals who were assigned to CT-subtype1 had high CT values in

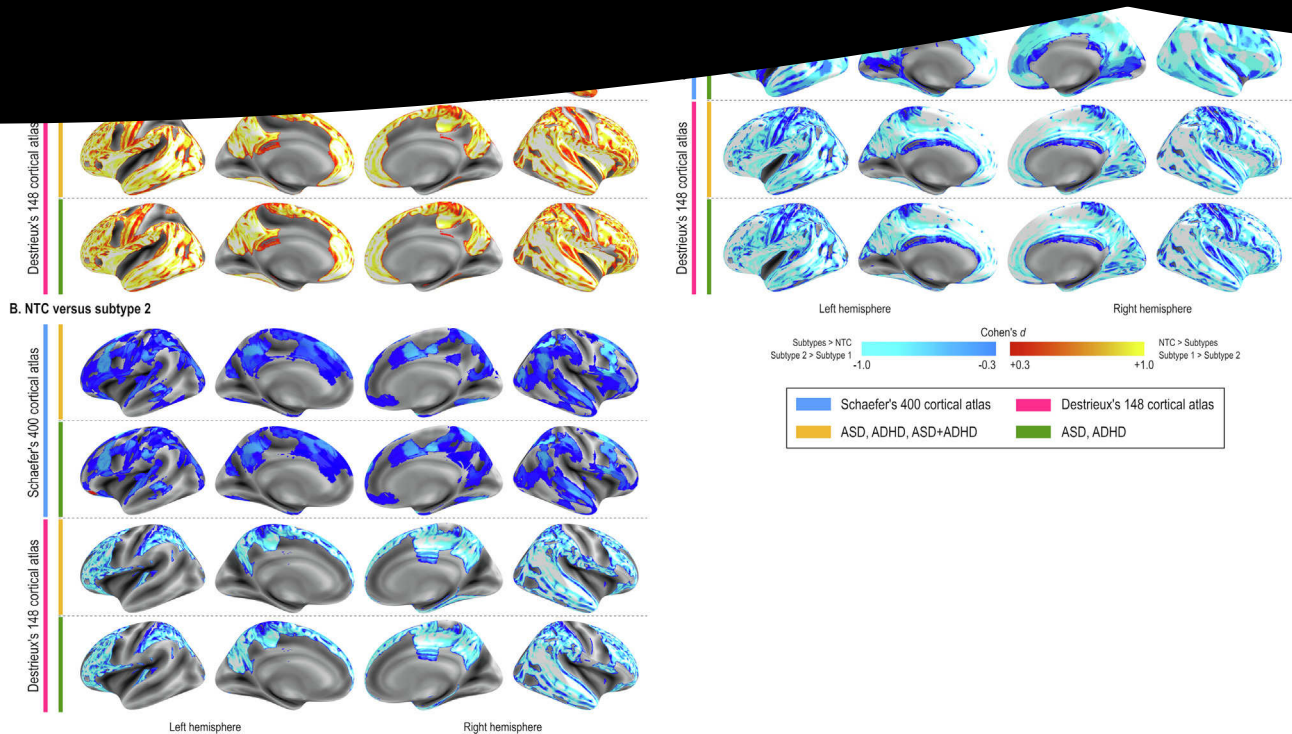


Fig. 1. Results of cortical thickness subtyping. The difference in cortical thickness (CT) between neurotypical controls (NTC) and CT-subtype1 is shown (A). The difference was diffusely distributed with little exception, such as the primary vision area, dorsal anterior cingulate cortex. Compared with the NTC, CT-subtype2 also showed diffusely low CT values with the largest difference in the dorsolateral prefrontal cortex. The area with the significant difference in CT values between CT-subtype1 and CT-subtype2 covers almost the entire brain. The threshold of statistical significance was set at $P < 0.05$ after FDR correction.

diffuse brain regions (Fig. 1A 1st row). This pattern did not change in the sensitivity analysis excluding people with dual diagnoses (Fig. 1A 2nd row), as well as utilizing the anatomical atlas to extract CT values (Fig. 1A 3rd and 4th rows).

3.3.2. SA

The analysis with SA showed relatively localized differences between subtypes and NTC. The SA-subtype1 showed a large area of SA difference in the medial region while less was observed in the lateral region with the largest difference in the primary motor and sensory areas (Fig. 2A 1st row). SA-subtype2 showed even less area of SA difference in the medial part. On the other hand, the posterior insula showed a large SA value difference between SA-subtype2 and NTC (Fig. 2B 1st row). This pattern did not change with other sub-analyses (Fig. 2A.B 2nd-4th rows). SA-subtype1 and SA-subtype2 showed diffuse areas with differences in SA values (Fig. 2C).

3.4. A convergence of area with differences

CT-subtypes exhibited diffuse albeit an inverse pattern of alterations when compared to the NTC group. Both subtypes exhibited alterations mainly in the dorsal attention, default mode, fronto-parietal, and ventral attention networks (Fig. 3A). On the other hand, SA-subtypes exhibited relatively localized alterations. SA-subtype1 exhibited right-dominant alterations mainly in the limbic network, while SA-subtype2 showed alterations in the somatomotor and limbic networks (Fig. 3B).

3.5. Membership consistency

3.5.1. CT

Compared with the primary CT results (HYDRA using the functional atlas including those with dual diagnoses), the HYDRA using the functional atlas excluding those with dual diagnoses showed the dice coefficient of 0.96. On the other hand, HYDRA using the anatomical atlas showed high consistency with the primary CT results with (0.94) and without (0.95) people with dual diagnoses.

3.5.2. SA

Compared with the primary SA results, the functional atlas analysis excluding people with dual diagnoses (0.99) and the anatomical atlas analyses with (0.90) and without (0.88) individuals with dual diagnoses revealed high consistency in membership.

3.6. Conventional comparison between diagnostic groups

3.6.1. Demographic characteristics

There were no statistically significant differences in age, handedness, or IQ across three diagnostic groups (ASD, ADHD, and NTC) (see Supplementary Table 3). With a few exceptions in subscales, AQ scores were higher in individuals with ASD compared with individuals with ADHD, whose AQ scores were higher than TD. Likewise, CAARS scores were generally higher in individuals with ADHD compared with people with ASD, and individuals with ASD had higher CAARS scores compared with NTC.

3.6.2. Cortical parameters

ANOVA showed that there were no statistically significant group

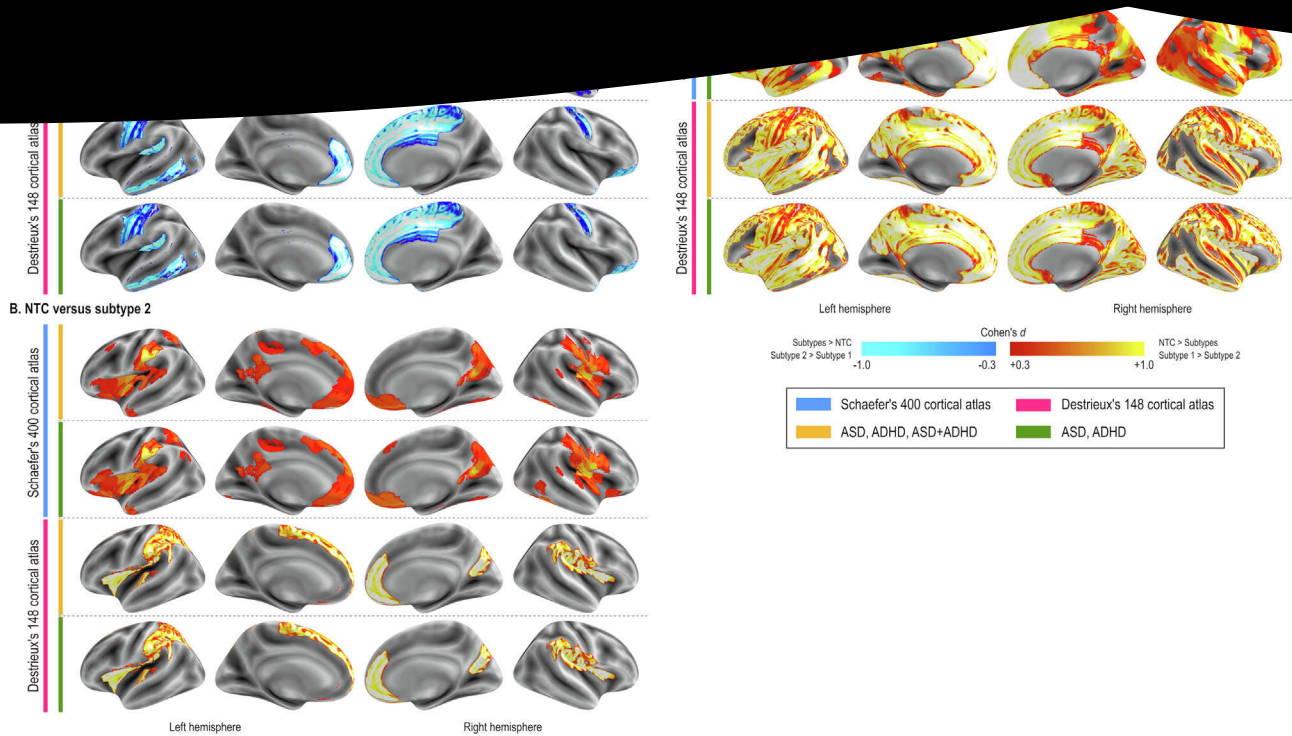


Fig. 2. Results of surface area subtyping. The difference in surface area (SA) between neurotypical controls (NTC) and SA-subtype1 is shown (A). The similar pattern was observed when we utilized the functional atlas with (the first row) or without individuals with dual diagnoses (the second row) and when we adopted the anatomical atlas (the third and fourth rows). Sub-panel B shows the results of comparison between NTC against SA-subtype2, while subpanel C shows the difference in SA values between SA-subtype1 and SA-subtype2. The threshold of statistical significance was set at $P < 0.05$ after FDR correction.

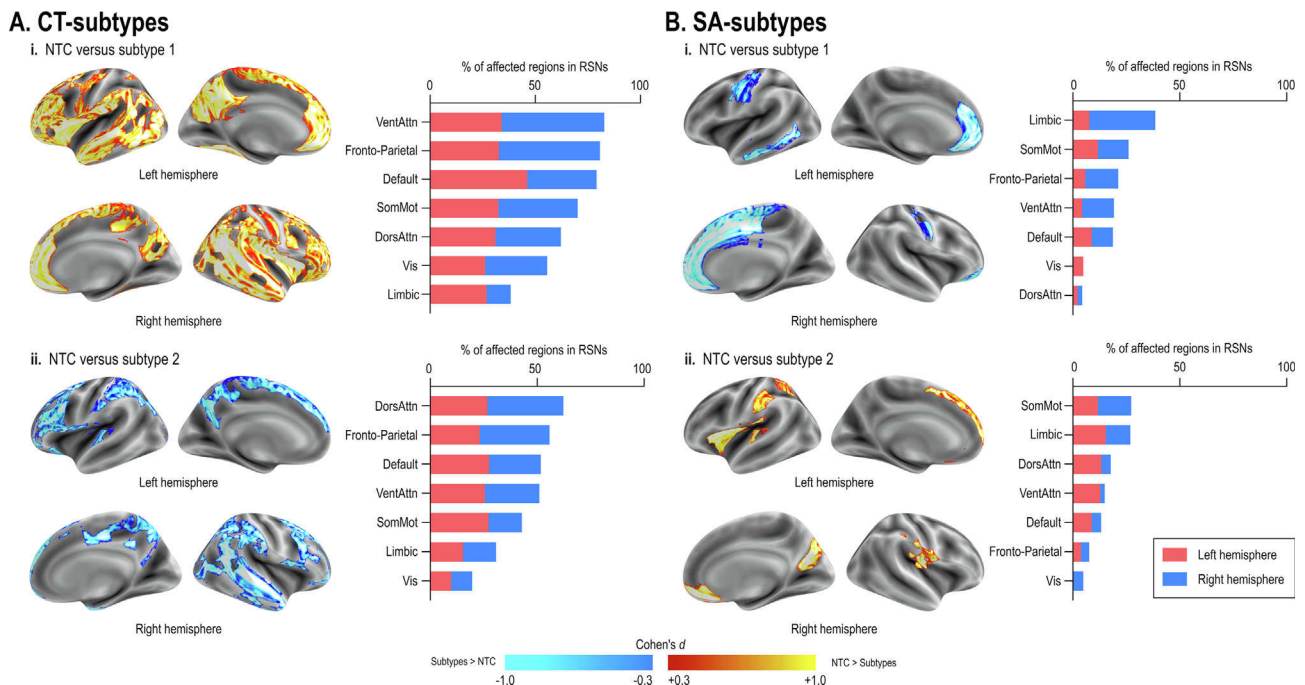


Fig. 3. Convergence of area across subtypes. Although we defined the results of HYDRA using the functional atlas with the whole participants, we conducted other three analyses utilizing the anatomical atlas (2 atlases) and with/without people with dual diagnoses (2 inclusion criteria for individuals). The subpanels (A) show the convergence of the results across the subtypes (left panel) and the percentage of area affected in each resting state network (right panel). We performed the same analyses adopted SA. The convergence of the area affected across subtypes (2 atlases $\times$ 2 participants inclusion criteria) was shown in the subpanel (B).

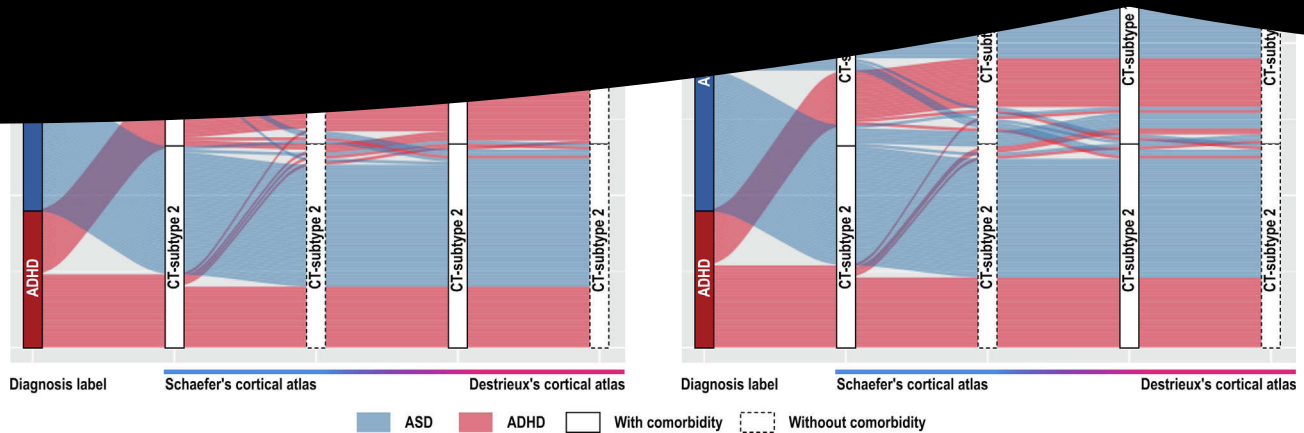


Fig. 4. Sanky diagram across the diagnoses and subtypes. Cortical thickness (CT) The current study enrolled 99 individuals with autism spectrum disorder (ASD) and 49 individuals with attention-deficit/hyperactivity disorder (ADHD). Fifty-two individuals with ASD and 23 individuals with ADHD were assigned to the CT-subtype1, while 47 individuals with ASD and 26 individuals with ADHD were assigned to CT-subtype2, when we run the analysis using CT values extracted from the functional atlas (the left column). Further, we conducted the analyses excluding people with dual diagnoses and utilizing an anatomical atlas instead of the functional atlas. Across these four analyses, 45 individuals with ASD and 18 individuals with ADHD were consistently assigned to the subtype1, while 40 people with ASD and 20 people with ADHD were consistently assigned to the subtype2. Surface area (SA) In the SA analysis using a functional atlas, 49 individuals with ASD and 20 individuals with ADHD were assigned to SA-subtype1, while 50 individuals with ASD and 29 individuals with ADHD were assigned to SA-subtype2. Across the four analyses, 40 individuals with ASD and 16 people with ADHD were consistently assigned to the subtype1. On the other hand, 39 individuals with ASD and 23 individuals with ADHD were consistently assigned to the subtype2.

differences in CT or SA across diagnostic groups (Fig. 4).

4. Discussion

Using a novel approach, we aimed to transdiagnostically subtype, based on structural MRI features, individuals with developmental disorders to reach high homogeneity in cortical characteristics. As we expected, the number of subtypes was stable in both CT and SA. Further, the membership assignment was robust against the atlas (functional vs. anatomical) and exclusion of individuals with dual diagnoses (ASD + ADHD). In addition, the biologically homogeneous subtypes did not match clinical diagnoses. However, in contrast to our expectation, biologically homogeneous subtypes did not show any phenotypic homogeneity.

The current study showed the same number of subtypes as the diagnoses (ASD and ADHD). Further, the analyses showed the stability of the membership against differences in atlas and participants. In general, the larger number of features resulted in overfitting and the greater number of subtypes, while a relatively smaller number of features exhibited stability in the clustering results. Given that structural MRI data has fewer features due to the lack of temporal resolution compared with fMRI, utilizing structural MRI may explain the stability of the results. Besides, the robustness against the number of features in structural data was shown by demonstrating the same number of subtypes using two different atlases (148 vs. 400 ROIs). At the same time, although a number of studies have reported atypical brain structure in individuals with ASD and those with ADHD (Anagnostou and Taylor, 2011; Vaidya, 2012), using structural data might have led to the negative findings that subtypes do not match clinical diagnoses. There are some potential reasons for the negative findings. First, a number of hypotheses on atypical functional connectivity were launched as potential pathophysiology in developmental disorder. For example, dysconnectivity within default mode network, atypical large-scale brain network, and imbalance between networks were considered in individuals with ADHD (Castellanos and Proal, 2012; Konrad and Eickhoff, 2010; Qian et al., 2019). In terms of ASD, atypical connectivity is reported even more

often than in ADHD. For instance, a long-distance hypo- and short-distance hyper-connectivity hypothesis is still one of the compelling pathophysiology (Kana et al., 2014). Further, a number of fMRI studies reported atypical network parameters in ASD (e.g. (Wilkes and Lewis, 2018)). Second, in addition to functional connectivity, atypical structural connectivity is often reported in both ASD and ADHD (Uddin et al., 2017). However, as the cortical parameters did not address structural nor functional connectivity, they may not be the best way to examine pathophysiology of developmental disorders. It should be noted that the current findings cannot be generalized to fMRI nor diffusion tensor imaging. Future research with the multimodal data is expected to address this concern.

Although subtypes showed a diffuse difference, convergence analyses showed that brain regions in the ventral attention, fronto-parietal, and default mode networks were most affected in the CT subtyping. Albeit different modalities, the current findings were, at least in part, consistent with the findings of prior studies that attempted to subtype people with developmental disorders with a data-driven approach. Concretely, they demonstrated that brain-derived subtypes were characterized by functional connectivity involving default mode network in both transdiagnostic (Kernbach et al., 2018) and within diagnostic approaches (Tang et al., 2019). Intriguingly, Subtype1 of both CT and SA showed atypical values in the medial prefrontal cortex where prior studies contrasting individuals with ASD and NTC consistently showed atypicality with different modalities (Aoki et al., 2012; Carlisi et al., 2017). Given that meta-analyses of studies contrasting people with ADHD against NTC also showed atypicality in the brain region (Aoki et al., 2013; Norman et al., 2016), these results might have represented either the categorical effect of the diagnosis or the subclinical traits of the other disorder. A future study that disentangles the effects of both traits and diagnoses is expected.

There are some more possible reasons for the current findings showing that biologically homogeneous subtypes do not show homogeneity in phenotype, which is not consistent with one prior study that showed significant performance to classify ASD from ADHD using structural MRI data (Lim et al., 2013). First, although we deem that our

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Appendix A. Supplementary data

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