Shared or distinct? Neuroanatomical underpinnings of ASD in carriers and non-carriers of the 22q11.2 microdeletion

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Abstract

Background: A crucial step to understanding the mechanistic underpinnings of autism spectrum disorder, is to examine if the biological underpinnings of ASD in genetic high-risk conditions, like 22q11.2 Deletion Syndrome (22q11.2DS), are similar to those in idiopathic illness. This study aimed to examine if ASD symptomatology in 22q11.2DS is underpinned by the same – or distinct – neural systems that mediate these symptoms in non-deletion carriers.

Methods: We examined vertex-wise estimates of regional cortical volume (rCV), surface area (SA), and cortical thickness across 131 individuals (6-25 years), including (1) $n=50$ individuals with 22q11.2DS, with and without ASD, and (2) $n=81$ individuals without the deletion, including idiopathic ASD. We employed a 2-by-2 factorial design to identify neuroanatomical variability associated with the main effects of 22q11.2DS and ASD, as well as their interaction. Further, using canonical correlation analysis (CCA), we compared neuroanatomical variability associated with the complex (i.e. multivariate) clinical phenotype of ASD between 22q11.2 deletion carriers and non-carriers.

Results: The set of brain regions associated with the main effect of 22q11.2DS was distinct from the neuroanatomical underpinnings of the main effect of ASD. Moreover, significant 22q11.2DS-by-ASD interactions were observed for rCV and SA in the dorsolateral prefrontal cortex, precentral gyrus, and posterior cingulate cortex, suggesting that neuroanatomy of ASD is significantly modulated by 22q11.2DS ($p<0.01$). We further established that the multivariate patterns of neuroanatomical variability associated with differences in symptom profiles significantly differed between 22q11.2 deletion carriers and non-carriers ($RV_{\text{coef}}=0.06$, $p<0.7$ vs. $RV_{\text{coef}}=0.196$, $p<0.0001$).

Limitations: We employed a multicenter design to overcome single-site recruitment limitations, however, FreeSurfer derived measures of surface anatomy have been shown to be highly reliable across scanner platforms and field-strengths'. Further, we controlled for gender to address the differing distribution between idiopathic ASD individuals and the other groups. Nonetheless, the gender distribution in our sample reflects that of the respective populations, adding to the generalizability of our results. Last, we included individuals with a relatively wide age range (i.e. 6-25 years).

Conclusions: Our findings indicate that brain mechanisms underlying ASD, associated with specific genetic etiology, diverge from those in idiopathic ASD.

Background

22q11.2 Deletion Syndrome (22q11.2DS) is a genetic condition resulting from a microdeletion at the q11.2 band of chromosome 22 (1). The estimated prevalence of 22q11.2DS is about 1 in 4000 (2), with an equal proportion of affected males and females (3). This makes 22q11.2DS the most common microdeletion syndrome in the general population (4, 5). While all individuals with 22q11.2DS display a deletion within the same locus of chromosome 22, the phenotypic consequences of the deletion are both complex and variable (6). These encompass congenital and somatic features, as well as neuropsychiatric

conditions. For example, there are high rates of comorbid neuropsychiatric conditions such as; autism spectrum disorder (ASD; ranging from 18 to 58% until early adulthood) (7-10), attention deficit hyperactivity disorder (ADHD; 37% in childhood) (7), anxiety disorders (approximately 35% in childhood and adolescence) (7), psychotic symptoms (57% in adolescence and young adulthood) (11, 12), and psychotic spectrum disorders (around 41% in adulthood) (7, 13, 14). These typically occur at different developmental stages, making the clinical phenotype of 22q11.2DS highly heterogeneous not only between carriers, but also within affected individuals over time.

Some evidence suggests that the complex clinical phenotypes associated with 22q11.2DS represent distinct clinical outcomes that are underpinned by separable neurobiological mechanisms. For example, it has been shown that interindividual variability in brain structure accompanies the occurrence and severity of positive psychotic symptoms in 22q11.2DS (15). Yet, it remains largely unknown whether the neuropsychiatric symptoms that are commonly observed in 22q11.2DS are also mediated by the same neural mechanisms that underpin these symptoms in individuals without the microdeletion. This particularly applies to ASD symptomatology, which compared to psychotic symptomatology, remains currently underexplored. Despite the high prevalence, only three neuroimaging studies to date have examined the neuroanatomical underpinnings of ASD in the brains of 22q11.2DS individuals. Two of these studies report differences in right amygdala volume between 22q11.2DS individuals with and without ASD symptomatology, but there is no consensus yet with regards to the direction of the effect (i.e. enlarged or reduced in ASD) (9, 10). A recent study by our group also reported differences in regional cortical volume (rCV) and surface area (SA) between 22q11.2DS individuals with and without ASD symptomatology. These differences were predominantly observed in parieto-temporal regions as well as in the posterior cingulate and dorsolateral prefrontal cortices, brain regions that have previously been linked to wider autistic symptoms and traits (16). Preliminary evidence therefore suggests that 22q11.2DS individuals with ASD symptomatology are neuroanatomically distinct from those without ASD, and may represent a distinct neurobiological subgroup. None of these studies, however, have included a comparison to individuals with idiopathic ASD and it therefore remains unknown how closely the neurobiological phenotype of ASD in 22q11.2DS resembles the ASD phenotype in those without the microdeletion. Further, if we are to better identify how microdeletions impact on the phenotype of ASD, we need to understand if abnormalities in ASD individuals with and without 22q11.2DS are shared (or not).

This study aimed to examine the neuroanatomical underpinnings of ASD symptomatology across disorders using a categorical approach that allowed us to establish the extent to which 22q11.2DS modulates the neuroanatomy of ASD. Based on prior evidence (16), it was hypothesized that ASD symptomatology in 22q11.2DS is not simply due to a higher neuroanatomical 'load' or affection status (i.e. more severe behavioral impairments associated with more pronounced neuroanatomical differences), but instead significantly interacts with the microdeletion to give rise to a distinct neuroanatomical brain phenotype. Moreover, in a second analysis step, we aimed to consolidate the results of the categorical approach, where ASD is treated as a 'fixed-effect' variable based on diagnostic labels, with a multivariate dimensional approach using canonical correlation analysis (CCA), where ASD is considered a complex clinical construct or phenotypic trait spanned by multiple symptom domains

across disorders. This allowed us to link the complex clinical phenotype(s) of ASD with neuroanatomical variability in multiple brain regions across disorders, and to compare their multivariate association between groups.

Methods

Participants

The total sample consisted of 131 individuals between 6 and 25 years of age, including (1) 50 microdeletion carriers, where $n=25$ had a diagnosis of ASD (22q11.ASD) and $n=25$ individuals did not (22q11.nonASD); (2) 40 non-deletion carriers with a diagnosis of ASD (i.e. idiopathic ASD), and (3) 41 typically developing (TD) controls without the microdeletion (see Table 1 and Supplementary Methods 1). The 22q11.2 microdeletion was confirmed by *in-situ* hybridization (FISH) or microarray. ASD was assessed using the Autism Diagnostic Interview-Revised (ADI-R) (17) and the Autism Diagnostic Observation Schedule (ADOS) (18, 19). In accordance with previously published studies examining ASD symptomatology in 22q11.2DS (9, 16), all individuals with ASD met diagnostic cut-offs in the reciprocal social interaction (cut-off=10) and communication domain (cut-off=8) of the ADI-R, but were allowed to fall below threshold in the repetitive behaviors domain (cut-off=3). The 22q11.2DS sample has previously been described in Gudbrandsen et al. (2019) (16). To capture autism along a continuum consisting of multiple symptom domains, we also administered the Social Responsiveness Scale (SRS) (20, 21) in all participants, including individuals without a diagnosis of ASD. Overall intellectual ability was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (22). All participants or parents for those under 18 years of age, gave informed written consent in accordance with ethics approval by the respective institutional ethics boards. For further details on demographics and exclusion criteria see Supplementary Methods 1.

MRI Data Acquisition

For image acquisition, we employed a contemporary MRI scanner operating at 3T (Siemens Trio in Frankfurt and UCLA, and a Signa GE Medical System at the IoPPN). High-resolution structural ADNI MPRAGE sequences were acquired with full head coverage. At the IoPPN, 166 contiguous slices (1.2mm thickness, with 1.2×1.2 mm in-plane resolution) were acquired using a repetition time/echo time (TR/TE) of 7/2.9ms (flip angle=8°, FOV=26cm). At UCLA, 160 contiguous slices (1.2mm thickness, with 1.2×1.2 mm in-plane resolution) were acquired using a TR/TE of 2300/2.9ms (flip angle=8°, FOV=26cm). In Frankfurt, 176 contiguous slices (1.0mm thickness, with 1.0×1.0 mm in-plane resolution) were acquired using a TR/TE of 2300/2.2ms (flip angle=9°, FOV=26cm). Consistent image quality was ensured by a semi-automated quality control procedure at all sites, including a stringent pre-processing pipeline.

Cortical Surface Reconstruction using FreeSurfer

FreeSurfer v6.0.0 software (<http://surfer.nmr.mgh.harvard.edu/>) was used to derive models of the cortical surface for each T_1 -weighted image. These well-validated and fully automated procedures have been

extensively described elsewhere (23-27). Measures of cortical thickness (CT) were computed as the closest distance from the grey-white matter boundary to the grey matter-cerebrospinal fluid boundary at each vertex on the tessellated surface (25). Vertex-based estimates of SA were derived as outlined by Winkler et al. (2012) (28). For each participant, we also computed mean CT across the entire brain, as well as total brain volume and total SA. To improve the ability to detect population changes, each parameter was smoothed using a 5-mm surface-based smoothing kernel. Details on quality assessments and manual editing of surface models are described in the Supplementary Methods 3.

Statistical analyses

Statistical analyses were conducted using the SurfStat toolbox (<http://www.math.mcgill.ca/keith/surfstat/>) for Matlab (R2017b; MathWorks). Between-group differences in age, full-scale IQ, ASD symptom severity, and total brain measures were assessed via analyses of variance (ANOVA) with group as categorical fixed-effect factor. Pair-wise differences between subgroups were examined post hoc using Scheffé test to correct for multiple comparisons in R (R3.5.2). Parameter estimates for vertex-based measures of rCV, SA, and CT were estimated by regression of a general linear model (GLM) for each vertex i , with (1) group membership (i.e. having the microdeletion and/or having a diagnosis of ASD), gender, and site as categorical fixed-effect factors; (2) a 22q11.2DS-by-ASD interaction term; and (3) full-scale IQ, a linear and a quadratic age term, and a total brain measure (total brain volume for rCV, total SA for SA, and mean CT for CT) as continuous covariates, so that

See Formula 1 in supplementary information.

where ε_i is the residual error at vertex i . All included continuous covariates were mean centered across groups to improve interpretability of the coefficients. We examined between-group differences for the main effect of 22q11.2DS, estimated from the corresponding coefficient β_1 , as well as the main effect of ASD, estimated from the corresponding coefficient β_2 , normalized by the corresponding standard error respectively. We further examined the interaction effect between 22q11.2DS and ASD (coefficient β_3) across groups. Corrections for multiple comparisons across the whole brain were performed using 'random field theory' (RFT)-based cluster analysis for non-isotropic images using a cluster based significance threshold of $p < 0.05$ (2-tailed) (29).

Canonical Correlation Analysis (CCA)

In a second analysis step, we examined differences in the neural systems mediating autistic symptoms in 22q11.2DS individuals and individuals without the microdeletion (abbreviated as non22q11.2DS) within the dimensional framework of Canonical Correlation Analysis (CCA). Here, ASD was not treated as a categorical fixed effect across groups, but as multivariate latent trait construct that is spanned by interindividual differences in symptom profile. The general framework of CCA is well described elsewhere ((30); see also Supplementary Methods 4). In the present study, we examined the relationship between neuroanatomical variability in rCV, SA, and CT as predictors (X), and the five SRS subdomain scores in (1) social awareness (SAW), (2) social cognition (SCG), (3) social communication (SCM), (4) social

motivation (SM), and (5) restricted and repetitive behaviors (RRB) as clinical outcomes (Y) (see Supplementary Fig. S1 for schematic illustration). To reduce the large number of vertex-based neuroanatomical features to a smaller subset of regions, we initially computed bivariate Pearson correlation coefficients between each of the five SRS subdomains and each morphometric feature in 34 cortical regions per hemisphere using the Desikan-Killiany cortical parcellation atlas (31), after correcting the data for linear and quadratic age effects, gender, site, full-scale IQ, and total brain measures across groups. The resulting correlation matrices were then thresholded using an absolute threshold of 0.2 (i.e. small to moderate effect according to Cohen, 1988 (32)), and all brain regions associated with at least one of the clinical variables were included in the CCA. This resulted in a set of neuroanatomical features in and thus a total of canonical variates (CVs).

CCA was initially applied to the non22q11.2DS individuals to establish the relationship between neuroanatomical variability and inter-individual differences in autistic symptom profiles. The RV-coefficient (33) was firstly examined to test for the overall statistical significance of the multivariate association between and . Moreover, the significance of the full canonical model was evaluated using Wilks's lambda ((34)) and Pillai's Trace (35). A dimension reduction analysis was then performed to identify the number of significant CVs for the subsequent comparison between groups. Here, we explored the percentage of variance explained by each CV and tested for their statistical significance using Wilks's and Rao's F-test (36). Only CVs that explained sufficient clinical variance were retained for further analysis. The same canonical model was then fitted to the group of 22q11.2DS individuals. To make the factor structure comparable across groups, CVs were sorted in descending order based on the fraction of total clinical variance explained by each CV (i.e. canonical variate adequacies for clinical data). Last, *Tucker's congruence coefficient* (37) was used to compare the spatially distributed patterns of neuroanatomical variability associated with the retained canonical correlations (CCs) across groups. Here, a congruence coefficient of 0.90 is generally interpreted as indicating a high degree of factor similarity. All statistical analyses were performed using RStudio Version 1.2 (<https://www.rstudio.com/products/rstudio/>) using the *yacca: Yet Another Canonical Correlation Analysis Package* toolbox (<https://CRAN.R-project.org/package=yacca>).

Data availability

Further details on the data and utilized software are available upon request from the corresponding author. The full set of raw data is not currently publicly available due to ethical restrictions. However, a subset of the sample can be made available upon request.

Results

Participant Demographics, Diagnostic Group, and Global Brain Measures

There were no significant between-group differences in participants' age. However, groups differed significantly in gender distribution ($\chi^2(3)=2.26, p=0.016$), with a lower percentage of females in the idiopathic ASD group relative to the other subgroups, and in full-scale IQ ($F(3)=21.01, p<0.001$), with TD

controls scoring higher than all other groups, and individuals with 22q11.2DS having a lower IQ than individuals with idiopathic ASD. Further, we found a significant effect of group for total brain volume ($F(3)=10.56, p<0.001$) and total SA ($F(3)=12.41, p<0.001$), with both 22q11.2DS groups having a significantly lower total volume and area compared to both idiopathic ASD and TD controls ($p<0.05$ for all pair-wise comparisons). Last, there was a significant effect of group for mean CT ($F(3)=3.74, p<0.05$) across the cortex, with idiopathic ASD individuals having a trend towards reduced CT compared to 22q11.nonASD individuals ($p=0.088$), while no other pair-wise comparison was significant (see Table 1 and Supplementary Tables 1 for all pair-wise comparisons). We thus co-varied for gender, full-scale IQ, and respective total brain measure in all subsequent analyses.

Results of the categorical fixed-effects analyses

Main Effect of 22q11.2DS on rCV, SA, and CT

Significant neuroanatomical differences between 22q11.2 deletion carriers (i.e. 22q11.2DS with and without ASD) and non-carriers (i.e. idiopathic ASD and TD controls) were observed in several large clusters distributed across the cortex. More specifically, rCV was increased in 22q11.2DS in the bilateral superior frontal cortex, the lateral and medial orbitofrontal cortex, the pre- and postcentral gyrus, the insula, and the supramarginal gyrus, with increases being driven by a commensurate increase in SA. Increased rCV in 22q11.2DS was also observed in the left middle temporal gyrus, while increased SA was further observed in the left superior temporal gyrus and the left posterior cingulate cortex (PCC). In contrast, rCV was decreased in 22q11.2DS in a large cluster centered on the bilateral medial occipital and temporal lobes, as well as in the bilateral anterior cingulate cortex, and the pre- and postcentral gyrus, accompanied by commensurate decreases in SA. Further decreases in SA were observed in the bilateral dorsal anterior cingulate area and inferior temporal gyri. Last, we identified increased CT in 22q11.2DS in some scattered regions, including the bilateral lateral occipital cortex, the right postcentral gyrus, and the left supramarginal gyrus, whereas decreases in CT were observed in the bilateral superior temporal lobes, the parahippocampal gyri, and the posterior cingulate cortex (see Fig. 1, Supplementary Fig. S2, and Supplementary Table S2).

Main Effect of ASD on rCV, SA, and CT

For the main effect of ASD, we established that individuals with ASD symptomatology (i.e. individuals with idiopathic ASD and 22q11.ASD) were neuroanatomically distinct from those without (i.e. compared to TD controls and 22q11.nonASD), with significantly increased rCV in the left insula and left superior temporal gyrus, accompanied by a more widespread increase in SA, also spanning the fusiform, parahippocampal, lingual, and supramarginal gyri. rCV was further increased in the right inferior parietal cortex in ASD. In contrast, decreases in rCV in ASD were observed in the left entorhinal cortex, accompanied by a commensurate decrease in SA, that was more pronounced and also implicated the left fusiform gyrus. For measures of CT, individuals with ASD showed significant increases in the right isthmus cingulate cortex and the right superior temporal gyrus (see Fig. 1, Supplementary Fig. S2, and Supplementary Table S3).

Significant Interactions between 22q11.2DS and ASD

In addition to the main effects, we observed significant interactions between 22q11.2DS and ASD for measures of rCV and SA. These were located in the left dorsolateral prefrontal cortex (DLPFC) for both, rCV and SA, as well as in the right precentral gyrus for rCV only, and in the left PCC for SA only (see Fig. 1, Supplementary Fig. S2, and Supplementary Table S4). In significant clusters, ASD was associated with increased rCV and/or SA in 22q11.2DS (i.e. 22q11.ASD > 22q11.nonASD), but reduced rCV and/or SA in individuals without the microdeletion (i.e. idiopathic ASD < TD controls). In the DLPFC and PCC, individuals with 22q11.nonASD were the most affected on the neuroanatomical level (i.e. had the most reduced rCV and/or SA relative to all other groups), while both ASD groups were comparable in terms of their mean rCV and/or SA (22q11.nonASD 22q11.ASD = ASD TD controls). In the precentral cluster exclusively, 22q11.ASD individuals had the largest mean rCV compared to all other groups, with the mean of 22q11.nonASD individuals being between idiopathic ASD and TD controls (see Supplementary Fig. S3). As the 22q11.ASD and idiopathic ASD groups differed in symptom severity in the repetitive behavior domain, we also performed the analysis covarying for the SRS Restricted Interests and Repetitive Behavior subscale. However, the patterns of significant 22q11.2DS-by-ASD interactions remained unchanged overall (see Supplementary Fig. S4).

Results of the CCA

Initially, CCA was performed across individuals without the microdeletion. Here, we observed a significant multivariate association between the 19 regional measures of brain anatomy (see Methods) and the five symptom domains of the SRS ($R_{V_{coef}}=0.196$, $p<0.001$). Based on the number of clinical predictors, the CCA yielded five canonical variates (CVs) with correlations of 0.665, 0.632, 0.502, 0.427, and 0.368 for each successive canonical pair, respectively (see Fig. 2A). Collectively, the full model including all CCs was also statistically significant at $p<0.1$ using Wilk's $\Lambda=0.176$ ($F(95,281)=1.27$, $p<0.01$) and Pillai's trace=1.41 ($F(95,305)=1.26$, $p<0.07$). As Wilk's Λ indicates the variance unaccounted for by the model, the R-square type (r^2) effect size of the model was 0.823 (i.e. $1-\Lambda$), indicating that the full model explained about 82.35% of the variance shared between measures of neuroanatomy and clinical symptom profile. Moreover, the total variance in clinical symptoms that could be explained by neuroanatomical variation was 40.38%, to which only the first two CVs contributed significantly (27.81% and 10.1%, respectively; see Fig. 2A). Out of those, only the 1st CV was statistically significant (Bartlett's $\chi^2(95)=117.04$, $p<0.065$) and explained a total of 62.88% of variability within the set of clinical variables on its own (clinical canonical variate adequacy, see Fig. 2B). Thus, given the r^2 effects for each CV, only the first canonical variate was considered noteworthy in the context of the present study. This first CV was also sufficient to attain a good discrimination between individuals with and without ASD (see Fig. 2C). Figure 2D shows the canonical loadings (l_c) for each neuroanatomical predictor on the cortical surface, which highlights the set of brain regions maximally correlated with the 1st canonical variate. As expected, high positive loadings (i.e. >3) were observed in many regions of the social brain including the right medial orbitofrontal lobe (CT, $l_{CT}=0.47$), the rostral middle frontal gyrus (CT, $l_{CT}=0.51$), the left insula (rCV,

$I_{CV1}=0.41$), and the right superior temporal gyrus (rCV, $I_{CV1}=0.38$). High negative loadings were observed in the left precuneus (CT, $I_{CV1}=-0.38$), the bilateral superior parietal lobes (CT, bilateral: $I_{CV1}=-0.38$; rCV, left: $I_{CV1}=-0.30$, right: $I_{CV1}=-0.36$), and the right lateral orbitofrontal cortex (CT, $I_{CV1}=-0.34$). Detailed information on canonical loadings (I_C) for all CVs can be found in the neuroanatomical canonical loading plot in the Supplementary Fig. S5. In individuals without the microdeletion, clinical variability across the five subdomains of the SRS can therefore be reduced to a single latent trait variable that is (1) highly predictive of group membership (i.e. ASD vs. controls; see Fig. 2C), and that is (2) significantly associated with neuroanatomical variability across multiple morphometric features in a specific set of brain regions (see Fig. 2D).

In 22q11.2DS individuals, the multivariate association between autistic symptoms and neuroanatomical variability in the investigated set of brain regions was considerably reduced relative to non22q11.2DS individuals ($RV_{coef}=0.06$, $p<0.7$), and the full model did not reach statistical significance (Wilk's $\Lambda=0.065$, $F(95,131)=10.4$, $p<0.5$; Pillai's trace=1.92, $F(95,150)=0.98$, $p<0.6$). While canonical correlations were high overall (0.832, 0.704, 0.624, 0.444, 0.379, respectively, see Fig. 3A), only 24.74% of the clinical variance could be explained by the set of neuroanatomical features examined, with anatomical CVs 3 and 5 explaining the largest percentage of clinical variability (8.20% and 7.43%, respectively; see Fig. 3A). To identify the CV in 22q11.2DS that is comparable to CV1 in non22q11.2DS, clinical CVs were sorted based on the percentage of clinical variability explained (i.e. clinical variate adequacies). As shown in Figure 3B, CV5 in the 22q11.2DS group was the clinically most relevant variate, accounting for more than 50% of the clinical variance on its own, followed by CVs 3 and 4, which explained 21% and 17% of the clinical variance, respectively. Moreover, CV5 displayed a clinical loading profile that closely resembled the profile of CV1 in the non22q11.2DS individuals (i.e. high positive loadings across all five SRS subdomains; see Fig. 3B) with a congruence coefficient of 0.99 (high degree of factor similarity). CV5 in the 22q11.2DS group was therefore considered the equivalent of CV1 in the non22q11.2DS individuals and also showed a good discrimination between individuals with and without ASD (see Fig. 3C).

However, while these CVs displayed a high degree of clinical factor similarity across groups, they were mediated by different neuroanatomical substrates between groups (see Fig. 2D, Fig. 3D, and Fig. 4). When comparing the neuroanatomical underpinnings of CV1 in non22q11.2DS and CV5 in 22q11.2DS based on their loadings, we established that there was a low level of congruence overall (congruence coefficient=0.64). Largest differences in CV loadings (i.e. >0.3) were observed for CT in the right lateral and medial orbitofrontal cortex (DI=-0.56 and 0.46, respectively), in the right rostral middle frontal cortex (DI=0.38), and in the left precuneus and superior parietal cortex (DI=-0.35 and -0.30, respectively; see Fig. 4). Thus, while the complex clinical phenotype of ASD may be reduced to a single continuous variable in both 22q11.2DS and non22q11.2DS individuals, this latent clinical factor seems to be mediated by different neuroanatomical substrates.

Discussion

This study aimed to determine whether ASD symptomatology in individuals with 22q11.2DS is underpinned by similar neuroanatomical substrates that mediate ASD symptoms in non22q11.2DS. We utilized both a categorical and a dimensional approach to (1) establish the extent to which the neuroanatomy of 22q11.2DS is modulated by (i.e. significantly interacts with) having a diagnosis of ASD, and to (2) compare the patterns of neuroanatomical variability that mediate the complex (i.e. multi-dimensional) clinical phenotype of ASD across disorders. Within the categorical framework, we initially established that it is possible to separate the effect of 22q11.2DS from the effect of ASD on the level of neuroanatomy as characterized by regional variability in rCV, SA, and CT. Notably, we also observed significant 22q11.2DS-by-ASD interactions suggesting that, 22q11.2DS individuals who also have ASD, may represent a subgroup that is neuroanatomically distinct from 22q11.2DS non-ASD individuals, and from individuals without the microdeletion. These results were confirmed by the dimensional approach, which further highlighted that, while the complex clinical phenotype of ASD might be reduced to the same underlying (i.e. latent trait) construct across disorders, the neuroanatomical substrates associated with this clinical construct were different between carriers and non-carriers of the 22q11.2 microdeletion.

Neuroanatomical differences associated with the 22q11.2 microdeletion are well documented in the literature and include spatially distributed differences in rCV, SA, and CT in parietotemporal and cingulate regions, as well as the bilateral insula, parahippocampal gyrus, and DLPFC (15, 16, 38). Here, we examined the neuroanatomy of 22q11.2DS initially within a 2x2 factorial design that included (1) 22q11.2DS individuals with and without ASD, (2) individuals with idiopathic ASD, and (3) TD controls. While it remains a topic of debate whether ASD should be considered a categorical 'fixed-effect' variable, this design allowed us to identify a set of brain regions where neuroanatomical variability in rCV, SA, and CT were uniquely attributable to either the microdeletion or having ASD. By examining the main effects of groups, we were able to demonstrate that it is possible to separate the effect of 22q11.2DS from the main effect of ASD on the neuroanatomical level based on patterns of neuroanatomical differences that included extensive and spatially distributed neuroanatomical differences across all four lobes of the cortex for the effect of 22q11.2DS, and more localized atypicalities in predominantly temporal regions for the main effect of ASD. More specifically, having ASD was linked to neuroanatomical abnormalities in the superior temporal gyrus (STG), fusiform gyrus, parahippocampal gyrus, isthmus cingulate cortex, and entorhinal cortex. Many of these brain regions have previously been reported to be integral parts of the neural systems that mediate autistic symptoms and traits. For example, the STG has been implicated in both language and social cognition in ASD (39-41). Further, the parahippocampal gyrus, isthmus cingulate cortex, and entorhinal cortex, are all part of the limbic system, which has been associated with impaired socioemotional and face processing in ASD (42-45). Overall, there is a strong spatial correspondence between the set of brain regions we identified as being neuroanatomically different in individuals with ASD symptomatology, including those with 22q11.2DS, and the set of brain regions mediating autistic symptoms in idiopathic ASD.

The results reported in the present study also extend the findings of a previous neuroimaging study by our group, which was conducted in a subset of this sample, where we compared 22q11.2DS individuals with ASD symptomatology to 22q11.2DS without, and to TD controls (16). Notably, the main effect of

22q11.2DS was associated predominantly with significant reductions in SA, which have been shown to contribute more significantly to commensurate differences in rCV than measures of CT (46), and is also in line with previous findings in 22q11.2DS (15, 38, 47). However, as our comparison group for the main effect of 22q11.2DS in the present study consisted of both TD controls and individuals with idiopathic ASD, the sum of squares associated with each model term were partitioned differently across studies with regards to their main effects allocation (22q11.2DS while covarying for ASD and *vice versa*), which may explain why the pattern of neuroanatomical variability associated with the main effect of 22q11.2DS is not identical to the pattern reported previously (16). Taking together the findings of the present study and previous reports, however, there is strong evidence to suggest that 22q11.2DS is associated with significant structural brain abnormalities, which in turn may impact on the various clinical phenotypes associated with the syndrome. Our findings indicate that 22q11.2DS and ASD have separable neuroanatomical underpinnings, but further, it suggests that, given the increased prevalence of ASD in 22q11.2DS relative to the normative population, the effects of 22q11.2DS on brain development might impact on the risk of ASD, but in itself are not sufficient to cause the condition.

Within the factorial design, it was also possible to determine to what extent the neuroanatomy of ASD is significantly modulated by 22q11.2DS (i.e. differs from individuals with 22q11.2DS and from individuals with idiopathic ASD). For example, we observed significant 22q11.2DS-by-ASD interactions in the left dorsolateral prefrontal cortex, the left posterior cingulate cortex, and in the right precentral gyrus. In these brain regions, individuals with 22q11.2DS without ASD symptomatology were the most affected, followed by 22q11.2DS individuals with ASD, individuals with idiopathic ASD, and TD controls in terms of affection status. While these interactions are complex and difficult to interpret, it seems that ASD in 22q11.2DS is not simply due to an exacerbation of the 22q11.2DS brain phenotype *per se*, i.e. more severe behavioral impairments associated with more pronounced neuroanatomical atypicalities. Instead, ASD symptoms in 22q11.2DS seem to be associated with a pattern of neuroanatomical differences that cannot be explained by either the microdeletion or a diagnosis of ASD alone. This implies that individuals with 22q11.2DS and ASD constitute a distinct neuroanatomical subgroup that is neuroanatomically different from 22q11.2DS individuals without ASD, and from individuals with idiopathic ASD. Thus, although 22q11.2DS individuals with ASD share the same clinical phenotype as idiopathic ASD individuals, the neuroanatomical underpinnings appear to differ between groups, and 22q11.2DS in itself is not sufficient to cause ASD.

Notably, while the factorial design allowed us to disentangle the effect of ASD from the main effect of 22q11.2DS, and to explore their interaction, there has been some debate whether ASD should be considered a uniform clinical construct that is common (i.e. invariant) across idiopathic and 'syndromic' forms of ASD, and can hence be encoded as a categorical main effect across groups. For example, while all individuals with ASD met cut-offs in the social and communication domains of the ADI-R, not all individuals with 22q11.2DS met cut-offs in the repetitive domain (see ref(16) for discussion). Although our results remain stable when covarying for repetitive symptoms, it remains unclear whether the distinct neuroanatomical phenotype of 22q11.2DS with ASD is the cause or the consequence of a potentially unique clinical profile (see (48, 49)). In a second analysis step, we therefore also employed a dimensional

approach using CCA, which allowed us to treat ASD as a continuous clinical construct spanned by multiple symptom domains, and to examine the multivariate association between inter-individual clinical profiles and neuroanatomical variability between 22q11.2 deletion carriers and non-carriers. Our findings imply that while it is possible to reduce the complex clinical ASD phenotype to a single dominant latent-trait factor with a comparable clinical factor structure in both carriers and non-carriers, the set of brain regions that explained maximal clinical variance in non22q11.2DS individuals was only loosely correlated with clinical variability in 22q11.2 deletion carriers. Thus, both approaches converge in suggesting that ASD symptomatology is mediated by different neuroanatomical substrates in individuals with and without the 22q11.2 microdeletion, even when taking inter-individual variability in clinical ASD phenotypes into account.

Limitations

Our result should be interpreted in the light of several methodological limitations. First, we employed a multicenter design to overcome single-site recruitment limitations. However, FreeSurfer derived measures of surface anatomy have been shown to be highly reliable across scanner platforms and field-strengths', when MRI instrument and data processing factors are controlled for (50). In our study, all surface reconstructions were also subjected to the same stringent type of quality assessment and pre-processing pipeline, and inter-site effects were accounted for in the statistical model. Moreover, due to the parametric nature, the dimensional approach is less biased by effects of categorical variables such as site and gender. To address the differing gender distribution between the idiopathic ASD individuals and the other groups, we also controlled for gender in the categorical fixed-effects analysis. Notably, while there is a male-biased prevalence with an estimated gender distribution of 4:1 (males to females) in idiopathic ASD (51), within 22q11.2 deletion carriers the distribution of males and females with ASD is estimated to be roughly equal (52). Thus, the gender distribution in our sample reflects the gender distribution in the respective populations, which adds to the generalizability of our results. Last, we included individuals with a relatively wide age range (i.e. from 6-25 years). Even though groups were matched in terms of their respective mean, and we corrected for linear and quadratic age effects, the nature and severity of autistic symptoms and their related neuroanatomical variability might vary across the lifespan. Hence, it will be crucial in the future to examine the multivariate correlation between the clinical ASD phenotype and neuroanatomical variability in more well-defined age groups, and to characterize their association across development.

Conclusions

Our findings indicate that brain mechanisms underlying ASD, associated with specific genetic etiology, diverge from those in idiopathic ASD.

Declarations

Ethics Approval and consent to participate

All participants, and accompanying parents for those under 18 years of age, gave informed written consent in accordance with ethics approval by the Ethics Committee of the Faculty of Medicine of the Goethe University Frankfurt, the National Research Ethics Service (NRES) Committee South Central (study reference: 12/SC/0576), or the UCLA Institutional Review Board (IRB).

Consent for publication

Not applicable

Availability of data and materials

Further details on the data and utilized software are available upon request from the corresponding author. The full set of raw data is not currently publicly available due to ethical restrictions. However, a subset of the sample can be made available upon request.

Competing Interests

Prof. Murphy sat on an advisory board for Roche and received an honorarium.

No other authors reported any financial interests or conflicts of interests.

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Author contributions

MG, AB, CM, and LK completed recruitment and data collection. ED, CB, and VS assisted in data collection, data entry, and sample preparation. AB and MG analysed data with support from CE. CM, CB, DGM, and MC contributed to the revisions of the manuscript. MG, AB, and CE wrote the manuscript. All authors have provided critical input into the revisions of the manuscript and approved final version.

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Abbreviations

22q11.2DS – *22q11.2 Deletion Syndrome*

ASD – *Autism Spectrum Disorder*

ADHD – *Attention Deficit Hyperactivity Disorder*

rCV – *regional Cortical Volume*

SA – *Surface Area*

Non22q11.2DS – *Individuals without the microdeletion (i.e. idiopathic ASD and TD controls)*

CCA - *Canonical Correlation Analysis*

CC – *Canonical Correlation*

CV - *Canonical Variate*

22q11.ASD – *Individuals with 22q11.2DS AND ASD*

22q11.nonASD - *Individuals with 22q11.2DS but no ASD*

Non22q11.ASD - *Individuals with idiopathic ASD but no microdeletion*

TD – *Typically Developing (controls)*

ADI-R – *Autism Diagnostic Interview-Revised*

ADOS – *Autism Diagnostic Observation Schedule*

SRS - *Social Responsiveness Scale*

WASI - *Wechsler Abbreviated Scale of Intelligence*

CT – *Cortical Thickness*

SAW – *Social Awareness subscale of the SRS*

SCG – *Social Cognition subscale of the SRS*

SCM – *Social Communication subscale of the SRS*

SM – *Social Motivation subscale of the SRS*

RBB – *Restricted and Repetitive Behaviours subscale of the SRS*

PCC – *Posterior Cingulate Cortex*

DLPFC - *Dorsolateral Prefrontal Cortex*

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Tables

Table 1: Participant Demographics and Global Brain Measures

	22q11.nonASD (n = 25 [11♂, 14♀])		22q11.ASD (n = 25 [13♂, 12♀])		ASD (n = 40 [32♂, 8♀])		Controls (n = 41 [23♂, 18♀])		Test Statistic F p	
Age [years]	14 ± 6	(6-25)	15 ± 4	(7-23)	15 ± 2	(11-18)	14 ± 4	(7-24)	0.18	0.91
Full-scale IQ	86 ± 15	(60-116)	81 ± 12	(61-112)	96 ± 13	(64-116)	104 ± 11	(76-123)	21.01	<0.001
ADOS-R <i>Social</i> ¹	5 ± 3	(1-9)	19 ± 5	(9-28)	17 ± 4	(9-27)	n/a	n/a	95.93	<0.001
ADOS-R <i>Communication</i> ¹	6 ± 4	(0-16)	14 ± 4	(8-24)	13 ± 4	(5-23)	n/a	n/a	29.98	<0.001
ADOS-R <i>Repetitive</i> ¹	1 ± 2	(0-8)	3 ± 3	(0-10)	5 ± 2	(1-10)	n/a	n/a	16.80	<0.001
ADOS <i>CSS</i> ¹	3 ± 2	(1-8)	6 ± 3	(1-10)	6 ± 3	(1-10)	n/a	n/a	9.30	<0.001
ADOS <i>Total Score</i>	55 ± 26	(16-103)	101 ± 33	(41-174)	95 ± 29	(42-159)	23 ± 19	(0-75)	69.38	<0.001
ADOS <i>Repetitive</i>	9 ± 6	(1-22)	17 ± 7	(7-32)	16 ± 7	(0-34)	2 ± 3	(0-10)	49.31	<0.001
Mean Cortical Volume [L]	0.66 ± 0.08	(0.41 - 0.89)	0.68 ± 0.07	(0.52 - 0.78)	0.75 ± 0.07	(0.60 - 0.92)	0.73 ± 0.07	(0.59 - 0.90)	10.56	<0.001
Mean Cortical Surface Area [m ²]	0.20 ± 0.02	(0.13 - 0.25)	0.21 ± 0.02	(0.17 - 0.24)	0.23 ± 0.02	(0.18 - 0.27)	0.22 ± 0.02	(0.19 - 0.27)	12.41	<0.001
Mean Cortical Thickness [mm]	2.78 ± 0.13	(2.59 - 3.06)	2.77 ± 0.10	(2.60 - 2.96)	2.71 ± 0.10	(2.51 - 2.93)	2.71 ± 0.10	(2.48 - 3.01)	3.74	<0.05

Values are expressed as mean ± standard deviation (range); 1) Data based on 89 individuals.

Figures

Figure 1

Categorical Results for Main Effect of 22q11.2DS, Main Effect of ASD, and 22q11.2DS-by-ASD Interaction Effect. (A) Significant differences in regional cortical volume (rCV), (B) surface area (SA), and (C) cortical thickness (CT) for the main effect of 22q11.2DS (left panel), the main effect of ASD (middle panel), and for the 22q11.2DS-by-ASD interaction (right panel). Displayed are the random field theory (RFT)-based cluster corrected ($p < 0.05$, 2-tailed) difference maps following multiple comparisons, where increased parameter estimates in 22q11.2DS (or ASD) are marked in red to yellow, and decreased parameters are marked in blue to cyan.

Figure 2

CCA Results for individuals without the 22q11.2 microdeletion. (A) Canonical correlations (subplot) and canonical variates (CVs) sorted in descending order, and based on the percentage of clinical variance explained; (B) clinical canonical loadings plot depicting correlations between each of the five clinical CVs and each of the five SRS subdomain scores in social awareness (SAW), social cognition (SCG), social communication (SCM), social motivation (SM), and restricted and repetitive behaviors (RRB). CVs are sorted in descending order based on the percentage of explained clinical variance as indicated in shades of green; (C) scatter plots depicting individual observations based on their scores on the first CV, which explained the largest percentage of clinical variance. Data points are coloured by group (ASD vs. controls) and sized by the individual's total SRS score; (D) canonical loadings of each neuroanatomical predictor (i.e. regional cortical volume (rCV), surface area (SA), and cortical thickness (CT)) on the 1st (significant) CV.

Figure 3

CCA Results for 22q11.2DS individuals. (A) Canonical correlations (subplot) and canonical variates (CVs) sorted in descending order, and based on the percentage of clinical variance explained; (B) clinical canonical loadings plot depicting correlations between each of the five clinical CVs and each of the five SRS subdomain scores in social awareness (SAW), social cognition (SCG), social communication (SCM), social motivation (SM), and restricted and repetitive behaviors (RRB). CVs are sorted in descending order based on the percentage of explained clinical variance as indicated in shades of green; (C) scatter plots depicting individual observations based on their scores on the 5th CV, which explained the largest percentage of clinical variance. Data points are coloured by group (22q11.ASD vs. 22q11.nonASD) and sized by the individual's total SRS score; (D) canonical loadings of each neuroanatomical predictor (i.e. regional cortical volume (rCV), surface area (SA), and cortical thickness (CT)) on the 5th CV.

Figure 4

Comparison of Brain Loadings between carriers and non-carriers of the 22q11.2 microdeletion. (A) Neuroanatomical loadings for measures of regional cortical volume (rCV), surface area (SA), and/or cortical thickness (CT) on the 1st and 5th CV, which explained the largest percentage of clinical variance in each group, i.e. CV1 for the non22q11.2DS group (first row) and CV5 for the 22q11.2DS group (second row). The third row shows the difference in loadings between the groups for each region. (B) Canonical loadings displayed on the cortical surface highlighting the set of brain regions where the multivariate association between neuroanatomical and clinical CVs differed between groups.

Supplementary Files

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