

Beyond the Global Brain Differences: Intraindividual Variability Differences in 1q21.1 Distal and 15q11.2 BP1-BP2 Deletion Carriers

Rune Boen, Tobias Kaufmann, Dennis van der Meer, Oleksandr Frei, Ingrid Agartz, David Ames, Micael Andersson, Nicola J. Armstrong, Eric Artiges, Joshua R. Atkins, Jochen Bauer, Francesco Benedetti, Dorret I. Boomsma, Henry Brodaty, Katharina Brosch, Randy L. Buckner, Murray J. Cairns, Vince Calhoun, Svenja Caspers, Sven Cichon, Aiden P. Corvin, Benedicto Crespo-Facorro, Udo Dannlowski, Friederike S. David, Eco J.C. de Geus, Greig I. de Zubicaray, Sylvane Desrivieres, Joanne L. Doherty, Gary Donohoe, Stefan Ehrlich, Else Eising, Thomas Espeseth, Simon E. Fisher, Andreas J. Forstner, Lidia Fortaner-Uyà, Vincent Frouin, Masaki Fukunaga, Tian Ge, David C. Glahn, Janik Goltermann, Hans J. Grabe, Melissa J. Green, Nynke A. Groenewold, Dominik Grotegerd, Gøril Rolfseng Grøntvedt, Tim Hahn, Ryota Hashimoto, Jayne Y. Hehir-Kwa, Frans A. Henskens, Avram J. Holmes, Asta K. Håberg, Jan Haavik, Sebastien Jacquemont, Andreas Jansen, Christiane Jockwitz, Erik G. Jönsson, Masataka Kikuchi, Tilo Kircher, Kuldeep Kumar, Stephanie Le Hellard, Costin Leu, David E. Linden, Jingyu Liu, Robert Loughnan, Karen A. Mather, Katie L. McMahon, Allan F. McRae, Sarah E. Medland, Susanne Meinert, Clara A. Moreau, Derek W. Morris, Bryan J. Mowry, Thomas W. Mühleisen, Igor Nenadić, Markus M. Nöthen, Lars Nyberg, Roel A. Ophoff, Michael J. Owen, Christos Pantelis, Marco Paolini, Tomas Paus, Zdenka Pausova, Karin Persson, Yann Quidé, Tiago Reis Marques, Perminder S. Sachdev, Sigrid B. Sando, Ulrich Schall, Rodney J. Scott, Geir Selbæk, Elena Shumskaya, Ana I. Silva, Sanjay M. Sisodiya, Frederike Stein, Dan J. Stein, Benjamin Straube, Fabian Streit, Lachlan T. Strike, Alexander Teumer, Lea Teutenberg, Anbupalam Thalamuthu, Paul A. Tooney, Diana Tordesillas-Gutierrez, Julian N. Trollor, Dennis van 't Ent, Marianne B.M. van den Bree, Neeltje E.M. van Haren, Javier Vázquez-Bourgon, Henry Völzke, Wei Wen, Katharina Wittfeld, Christopher R.K. Ching, Lars T. Westlye, Paul M. Thompson, Carrie E. Bearden, Kaja K. Selmer, Dag Alnæs, Ole A. Andreassen, and Ida E. Søndersby, for the ENIGMA-CNV Working Group

ABSTRACT

BACKGROUND: Carriers of the 1q21.1 distal and 15q11.2 BP1-BP2 copy number variants exhibit regional and global brain differences compared with noncarriers. However, interpreting regional differences is challenging if a global difference drives the regional brain differences. Intraindividual variability measures can be used to test for regional differences beyond global differences in brain structure.

METHODS: Magnetic resonance imaging data were used to obtain regional brain values for 1q21.1 distal deletion ($n = 30$) and duplication ($n = 27$) and 15q11.2 BP1-BP2 deletion ($n = 170$) and duplication ($n = 243$) carriers and matched noncarriers ($n = 2350$). Regional intra-deviation scores, i.e., the standardized difference between an individual's regional difference and global difference, were used to test for regional differences that diverge from the global difference.

RESULTS: For the 1q21.1 distal deletion carriers, cortical surface area for regions in the medial visual cortex, posterior cingulate, and temporal pole differed less and regions in the prefrontal and superior temporal cortex differed more than the global difference in cortical surface area. For the 15q11.2 BP1-BP2 deletion carriers, cortical thickness in regions in the medial visual cortex, auditory cortex, and temporal pole differed less and the prefrontal and somatosensory cortex differed more than the global difference in cortical thickness.

CONCLUSIONS: We find evidence for regional effects beyond differences in global brain measures in 1q21.1 distal and 15q11.2 BP1-BP2 copy number variants. The results provide new insight into brain profiling of the 1q21.1 distal and 15q11.2 BP1-BP2 copy number variants, with the potential to increase understanding of the mechanisms involved in altered neurodevelopment.

<https://doi.org/10.1016/j.biopsych.2023.08.018>

Carriers of certain rare recurrent copy number variants (CNVs), i.e., deletions or duplications of a segment of the genome, have a higher risk of developing psychiatric and neurodevelopmental disorders, including schizophrenia and autism spectrum disorder (1–5). Several rare recurrent CNVs have moderate to large effects on structural brain measures derived from magnetic resonance imaging (MRI) (6,7). The effects of CNVs on brain structure have been suggested to occur primarily during early neurodevelopment (8), and some rare recurrent CNVs have been associated with altered cellular function, composition, and size derived from cortical organoids that model fetal and early neurodevelopment (9–12). The 1q21.1 distal and 15q11.2 BP1-BP2 deletions are two of the most common recurrent CNVs (1,13,14). They yield a higher risk of psychiatric and neurodevelopmental disorders (1–5) and show moderate to large effects on brain structure (15,16). Thus, studying 1q21.1 distal and 15q11.2 BP1-BP2 deletion carriers offers a promising genetics-first approach to study deviations in neurodevelopment and brain structure, which may underlie the increased risk of developing psychiatric and neurodevelopmental disorders (5,8).

To date, neuroimaging studies on CNVs have focused on conventional mean comparisons between carriers and non-carriers, which have been informative for brain profiling of CNV carriers. For instance, several CNVs have shown global effects on the brain, as demonstrated by group differences in mean cortical thickness, total cortical surface area, and total subcortical volume, in addition to widespread regional differences (6,7). However, brain profiling may be challenging if an overall global difference in the brain drives many of the regional mean differences or if regional differences are driven by distinct subgroups in each comparison, rendering inter-regional brain profiles difficult to interpret. To overcome this challenge, detecting brain regions that diverge from the global difference could benefit from intraindividual variability measures, in which regional values represent the relative position within an individualized brain profile. Identification of brain regions that diverge from the overall global difference of the CNV may provide valuable insights into the regional penetrance, brain organization, and functional consequences in CNV carriers. Indeed, as has been demonstrated in other fields, such as cognitive science and neuropsychology (17–22), novel scientific and clinical insights can be achieved by looking beyond mean group differences through investigating intraindividual variability.

Both 1q21.1 distal and 15q11.2 BP1-BP2 deletion carriers exhibit global differences in brain structure, with the former displaying a lower total cortical surface area (15) and the latter showing a higher mean cortical thickness and lower total

cortical surface area (16). Additionally, these deletions exhibit regional differences across the cortex (15,16). However, the regional differences vary across the brain as indicated by variation in effect sizes across brain regions. This could indicate that the carriers of the 1q21.1 distal and 15q11.2 BP1-BP2 deletions exhibit higher variability in brain structure, along with systematic interregional differences in brain structure as measured by MRI-derived features.

In both 1q21.1 distal and 15q11.2 BP1-BP2 CNV carriers, the largest regional differences are typically found in frontal regions, associated with higher cognitive processing. In contrast, the posterior brain regions, associated with primary sensory processing, typically do not show significant differences (15,16). Insight into variation in brain structure may be useful for understanding differences in brain function, as cortical morphology overlaps with the functional hierarchical gradient of the brain (23). This functional hierarchical gradient reflects a sensorimotor (i.e., involved in unimodal and functional specific processes) to association (i.e., involved in higher-order cognitive processes) axis in the human brain (23–25), which has been supported by anatomical, functional, and evolutionary data (24). Thus, a more fine-grained brain profile of the structural differences in 1q21.1 distal and 15q11.2 BP1-BP2 CNV carriers may aid understanding of their phenotypic profile.

Brain structural differences in 1q21.1 distal and 15q11.2 BP1-BP2 CNV carriers indicate global mean differences (i.e., cortical thickness and cortical surface area) as well as regional group differences in primarily frontal brain regions. The regional group differences indicate that some brain regions are more affected than others. Here, we define more affected brain regions as regions that differ more than the global mean difference and less affected brain regions as regions that differ less than the global mean difference. To measure this, we used an intraindividual variability measure to detect brain regions that diverge from the global difference, where the regional values represent its position within an individualized brain profile. We expected that anterior regions within the association cortices would be more affected, whereas posterior regions within the primary sensorimotor cortices would be less affected in carriers of the 1q21.1 distal and 15q11.2 BP1-BP2 CNVs.

METHODS AND MATERIALS

Sample

Individuals carrying a 1q21.1 distal or 15q11.2 CNV and a matched noncarrier group were obtained from the Enhancing Neuroimaging Genetics through Meta Analysis (ENIGMA) CNV

Working Group core dataset and the UK Biobank across 61 scanner sites. Each CNV carrier was matched with 5 non-carriers based on age, sex, scanner site, and intracranial volume using the MatchIt package in R (26). This resulted in 4 subsets (sample characteristics are presented in Tables 1 and 2; see also Note 1 in Supplement 1).

MRI-Derived Features, CNVs, and Quality Control

Neuroimaging data were obtained from the UK Biobank, as described elsewhere (27), and from the ENIGMA-CNV core dataset. The ENIGMA-CNV neuroimaging measures were collected from several sites (see Appendix 1 in Supplement 2 for details) and analyzed using the standardized ENIGMA protocol (<https://enigma.ini.usc.edu/protocols/imaging-protocols/>). Details of the quality control of MRI are provided in Note 2 in Supplement 1. Briefly, the MRI data from the ENIGMA-CNV Working Group were subjected to the ENIGMA cortical quality control procedures (<https://enigma.ini.usc.edu/protocols/imaging-protocols/>), where the 68 cortical and 14 subcortical regions were extracted using the Desikan-Killiany atlas. For the UK Biobank sample, we used the Euler number as a proxy for image quality (28) and removed all participants with Euler numbers below minus 4 standard deviations from downstream analyses ($n = 437$). To account for site effects in the samples, we ran each of the 4 subsets through ComBat, an instrument for data harmonization (29). CNV calling in ENIGMA-CNV was based on previous publications (15,16). For the UK Biobank sample, we identified CNVs based on the returned dataset from Crawford *et al.* (30). All participants with a CNV as defined in previous publications (15,16,30) were removed from downstream analyses except for the individuals flagged with the 1q21.1 distal or the 15q11.2 BP1-BP2 CNV.

Derivation of Dependent Variables

We adjusted for the effect of age, age², sex, and intracranial volume on every brain regional value using linear regression across the carriers and the noncarriers. The residualized brain regional values were used to calculate the mean and standard deviation for the noncarriers only. We estimated 1) z scores per region [similar calculations as in (31)] and created 2) global index and 3) intraindividual standard deviation [similar calculations as in (21)] as well as 4) regional intra-deviation (RID) score.

z Scores. Specifically, z scores for CNV carriers and noncarriers were calculated based on the mean and

standard deviation from the noncarriers as shown in equation 1:

$$Z_{if} = \frac{(X_{if} - M_{if})}{SD_{if}} \quad (1)$$

where Z_{if} is the standardized value for brain region i using feature f (i.e., cortical thickness, surface area, or subcortical volume), X_{if} is the regional value for brain region i for feature f , and M_{if} and SD_{if} represent the mean and standard deviation, respectively, for brain region i using feature f across the noncarriers. Thus, for every individual, we obtained a vector of standardized z scores across 68 cortical regions for cortical thickness and cortical surface area and 14 subcortical regions.

Global Index. We created an individualized global index for cortical thickness, cortical surface area, and subcortical volume, respectively, by calculating the mean z score across the cortical and subcortical regions as shown in equation 2:

$$Gl_f = \frac{1}{n_f} \sum_{i=1}^{n_f} Z_{if} \quad (2)$$

where Gl_f is the global index for feature f , n is the total number of brain regions for feature f , and Z_{if} is the standardized value for the brain region i for feature f derived from equation 1.

Intraindividual Standard Deviation. We also calculated the intraindividual standard deviation across the z scores for cortical thickness, cortical surface area, and subcortical volume to obtain measures of within-individual variability, as shown in equation 3:

$$iSD_f = \sqrt{\frac{\sum_{i=1}^{n_f} (Z_{if} - Gl_f)^2}{n_f - 1}} \quad (3)$$

where iSD_f is the intraindividual standard deviation for feature f , n_f is total number of brain regions for feature f , Z_{if} is the standardized value for brain region i for feature f , and Gl_f is the global index for feature f (i.e., mean z score across brain regions for an individual) as derived from equation 2. A low intraindividual standard deviation indicates that an individual's z scores across brain regions are relatively consistent and do not vary much across brain regions, while

Table 1. Sample Characteristics for 1q21.1 Distal CNVs and Noncarrier Comparison Groups

	1q21.1 Distal Deletion, $n = 30$	1q21.1 Distal Deletion Comparison Group, $n = 150$	1q21.1 Distal Duplication, $n = 27$	1q21.1 Distal Duplication Comparison Group, $n = 135$
Age, Years, Mean	41.6	44.6	56.4	53.7
Age, Years, Range	7.7–68.7	9.2–76.2	18.7–73.1	9.5–77.2
Females, n (%)	14 (46.7%)	73 (48.7%)	15 (55.6%)	77 (57.0%)
Intracranial Volume, mm ³ × 10 ⁶ , Mean (SD)	1.25 (0.23)	1.26 (0.25)	1.59 (0.16)	1.56 (0.30)

CNV, copy number variant.

Table 2. Sample Characteristics for 15q11.2 BP1-BP2 CNVs and Noncarrier Comparison Groups

	15q11.2 BP1-BP2 Deletion, <i>n</i> = 170	15q11.2 BP1-BP2 Deletion Comparison Group, <i>n</i> = 850	15q11.2 BP1-BP2 Duplication, <i>n</i> = 243	15q11.2 BP1-BP2 Duplication Comparison Group, <i>n</i> = 1215
Age, Years, Mean	55.9	55.9	55.8	55.9
Age, Years, Range	7.1–77.7	6.8–90.0	7.83–88.5	3.75–89.8
Females, <i>n</i> (%)	90 (52.9%)	428 (50.4%)	127 (52.3%)	608 (50.0%)
Intracranial Volume, mm ³ × 10 ⁶ , Mean (SD)	1.48 (0.20)	1.50 (0.20)	1.46 (0.19)	1.46 (0.20)

CNV, copy number variant.

a high intraindividual standard deviation indicates that the *z* scores across brain regions are relatively inconsistent, indexing a more variable brain.

Regional Intra-deviation Score. Finally, to identify regions that diverge more than expected from an individual’s global index and intraindividual standard deviation, we created an RID score calculated using equation 4 for every brain region across feature *f*:

$$RID_{if} = \frac{(Z_{if} - G_{if})}{iSD_f} \tag{4}$$

where *RID_{if}* is the RID score for brain region *i* using feature *f*, *Z_{if}* is the standardized value for brain region *i* for feature *f*, and *G_{if}* is the global index for feature *f* as shown in equation 2. The *iSD_f* reflects the intraindividual standard deviation for the *z* score across brain regions in feature *f* as formulated in equation 3. Here, we define regions that are less affected as those that do not follow the global tendency in the data, whereas the regions that exceed the global tendency of the data are considered to be more affected. To establish brain-cognition relationships between the brain measures and cognition, we tested for associations between RID and *z* scores and cognitive ability (Note 3 and Figure S1 in Supplement 1; Table S1).

Statistical Analyses

All statistical analyses were conducted in Rstudio (R version 4.0.0; <https://www.R-project.org/>), and brain visualizations were created using the ENIGMA toolbox (32). For the per-CNV analyses, we tested for group differences by including carrier status (i.e., either carrier or noncarrier) in a linear regression model. The deletion and duplication carriers were tested separately with their corresponding matched noncarrier group used as the reference. The estimated standardized beta values were extracted from the models and are presented in the results as a measure of effect size. The *p* values underwent a false discovery rate (FDR) (33) adjustment to account for multiple comparisons for each of the 4 CNV groups. Corrected *p* values < .05 were considered statistically significant. Three main analyses were performed: First, in line with the conventional mass-univariate analysis approach, we performed group comparisons on the *z* scores across all the regions of interest (ROIs) for cortical thickness, cortical surface area, and subcortical volume (FDR corrected for 150 comparisons). Second, we compared the global index and intraindividual standard deviation and mean corrected intraindividual standard deviation values between

carriers and noncarriers (FDR corrected for 12 comparisons). The mean corrected intraindividual standard deviation represents the intraindividual standard deviation after regressing out the global index, as the mean values tend to be correlated with the standard deviation. Third, for the RID scores, group comparisons were computed between carriers and noncarriers for all ROIs for cortical thickness, cortical surface area, and subcortical volume (FDR corrected for 150 comparisons). Due to missing values in some brain regions, the analyses were restricted to individuals with complete observations for the feature that was analyzed (i.e., cortical thickness, cortical surface area, and subcortical volume). Sensitivity analyses were conducted for the significant RID score differences by adjusting for affection status (i.e., known psychiatric or neurological diagnoses). In addition, we examined the interaction term between carrier status and affection status and between carrier status and cognitive ability. Finally, we compared the brain profile of significant differences in RID scores with the significant differences in *z* scores adjusted for the global index.

RESULTS

Global Measures

The group differences in the global index and the intraindividual standard deviation measures are presented in Table 3 with reference values for the noncarrier groups in Table S2. The 1q21.1 distal deletion carriers had a lower global index for surface area, whereas the 15q11.2 BP1-BP2 deletion carriers had a lower global index for surface area and a higher global index for cortical thickness. In addition, the 15q11.2 BP1-BP2 duplication carriers had a lower global index for cortical thickness. Furthermore, there was a higher intraindividual standard deviation for cortical surface for both the 1q21.1 distal duplication carriers (both for the mean corrected measure and for the uncorrected measure) and the 15q11.2 BP1-BP2 deletion carriers (only for the mean corrected measure) as well as a higher intraindividual standard deviation for cortical thickness in the 15q11.2 BP1-BP2 deletion carriers (both for the mean corrected measure and for the uncorrected measure). With one exception, correlations between the intraindividual standard deviation measures across CNV groups did not show any significant differences (Note 4 and Figure S2 in Supplement 1).

1q21.1 Distal CNV

1q21.1. Distal Deletion. The 1q21.1. distal deletion carriers showed widespread lower cortical surface area with significant differences in 63 ROIs using *z* scores (Figure 1A, B,

Table 3. Group Differences in Global Index and Intraindividual Standard Deviation

	1q21.1 Distal Deletion	1q21.1 Distal Duplication	15q11.2 BP1-BP2 Deletion	15q11.2 BP1-BP2 Duplication
Global Index				
Cortical surface area	−1.29 (0.18) ^d	0.40 (0.22)	−0.22 (0.09) ^b	−0.09 (0.07)
Cortical thickness	0.39 (0.21)	−0.04 (0.22)	0.35 (0.09) ^d	−0.24 (0.07) ^b
Subcortical volume	−0.15 (0.20)	−0.48 (0.22) ^a	−0.17 (0.09) ^a	0.02 (0.07)
Intraindividual Standard Deviation, Mean Uncorrected				
Cortical surface area	−0.20 (0.21)	0.73 (0.22) ^c	0.15 (0.09)	−0.02 (0.07)
Cortical thickness	0.37 (0.21)	0.44 (0.22) ^a	0.20 (0.09) ^b	0.00 (0.07)
Subcortical volume	−0.08 (0.20)	0.22 (0.22)	0.04 (0.09)	0.02 (0.07)
Intraindividual Standard Deviation, Mean Corrected				
Cortical surface area	0.24 (0.21)	0.62 (0.22) ^b	0.23 (0.09) ^b	0.06 (0.07)
Cortical thickness	0.37 (0.21)	0.46 (0.22) ^a	0.19 (0.08) ^b	0.00 (0.07)
Subcortical volume	−0.06 (0.20)	0.30 (0.22)	0.08 (0.09)	0.02 (0.07)

Values represent the standardized beta coefficient between carriers and noncarriers, with noncarriers as the reference. Standard error is presented in parentheses.

p_{FDR} , false discovery rate–corrected p .

^a $p < .05$

^b $p_{FDR} < .05$

^c $p_{FDR} < .01$

^d $p_{FDR} < .001$.

top; Table S3) and exhibited a higher RID score for cortical surface area in regions within the occipital, superior parietal, temporal pole, and posterior cingulate cortex as well as lower RID scores in regions within the superior temporal and frontal regions (Figure 1A–C, bottom; Table S4). Further, 1q21.1 distal deletion carriers showed higher cortical thickness compared with noncarriers in 19 ROIs using z scores (Figure 2A, B, top; Table S3), in addition to lower RID scores for regions within the occipital lobe and paracentral lobule and higher RID scores for regions within the superior temporal and inferior frontal cortex (Figure 2A–C, bottom; Table S4). The 1q21.1 distal deletion carriers also exhibited lower subcortical volume in left thalamus and right nucleus accumbens (Table S3) and lower RID score for the left thalamus (Table S4). All significant RID score differences survived adjustment for affection status. The interaction term between carrier status and affection status was not associated with the significant RID scores (Note 5 in Supplement 1; Table S5). A subset of the significant RID scores were implicated in the brain-cognition RID map (Figure S1 in Supplement 1). However, we did not observe any significant interactions between carrier status and cognitive ability on any of the significant RID scores (Note 6 in Supplement 1; Table S6). The results yielded more significant group differences in RID scores (i.e., 24) compared with z scores adjusted for the global index between 15q11.2 BP1-BP2 deletion carriers and noncarriers (i.e., 13) (Supplementary Note 7 and Figure S3 in Supplement 1; Table S7).

1q21.1 Distal Duplication. The 1q21.1 distal duplication carriers showed higher cortical surface area in the right pars opercularis and right superior frontal gyrus and lower volume in the right and left hippocampus compared with noncarriers (Table S8). Using RID scores, no significant differences in the ROIs were found (Table S9).

15q11.2 BP1-BP2 CNV

15q11.2 BP1-BP2 Deletion. The 15q11.2 BP1-BP2 deletion carriers showed lower cortical surface area in 10 ROIs

using z scores (Figure 3A and B, top; Table S10) and higher RID scores for the left frontal pole and right pars opercularis surface area, but lower RID scores for the left and right pars orbitalis surface area compared with noncarriers (Figure 3A–C, bottom; Table S11). For cortical thickness, the 15q11.2 BP1-BP2 deletion carriers showed higher cortical thickness in 30 regions using z scores (Figure 4A, B, top; Table S10). The RID scores for cortical thickness were lower in regions within occipital and temporal regions and higher in motor and frontal regions compared with noncarriers (Figure 4A–C, bottom; Table S11). The 15q11.2 BP1-BP2 deletion carriers also showed lower z scores for left caudate, right pallidum, and right nucleus accumbens (Table S10). All significant RID scores remained significant after adjustment for affection status. No significant interactions between carrier status and affection status (Table S12; Note 5 in Supplement 1) or between carrier status and cognitive ability for the 15q11.2 BP1-BP2 deletion carriers were observed (Table S13; Note 6 in Supplement 1). The results yielded more significant group differences in RID scores (i.e., 14) compared with z scores adjusted for global index (i.e., 12) between 15q11.2 BP1-BP2 deletion carriers and noncarriers (Note 7 and Figure S4 in Supplement 1; Table S14).

15q11.2 BP1-BP2 Duplication. The 15q11.2 BP1-BP2 duplication carriers showed lower cortical thickness in 11 ROIs and higher right superior frontal cortical surface area using z scores (Table S15), but showed no significant differences in the ROIs using RID scores (Table S16).

DISCUSSION

To our knowledge, the current study is the first to identify intraindividual variability differences in brain structure in CNV carriers. Using the intraindividual standard deviation measure, we observed higher variability in the regional effects for cortical surface area in both 1q21.1 distal duplication and 15q11.2 BP1-BP2 deletion carriers and higher variability in the regional effects for cortical thickness for the 15q11.2 BP1-BP2 deletion

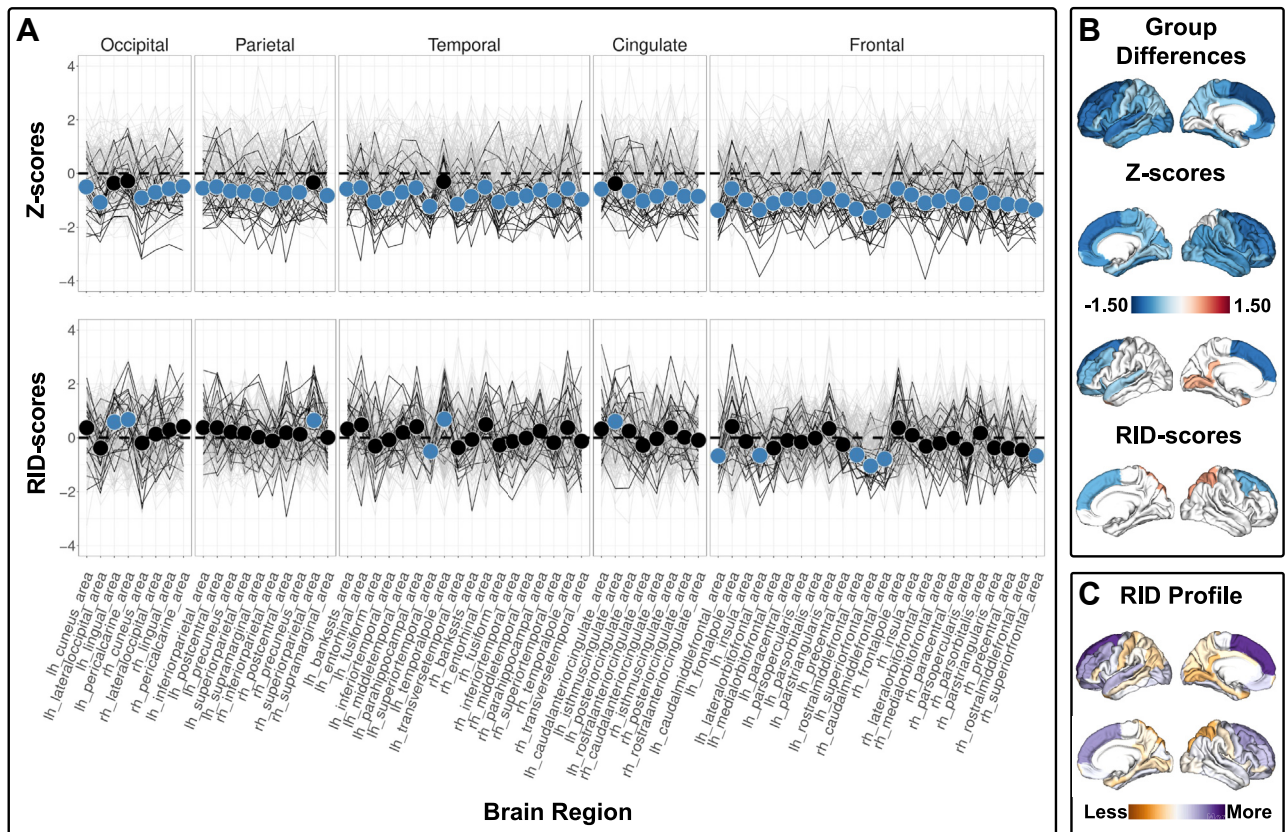


Figure 1. Cortical surface area comparison between 1q21.1 distal deletion carriers and noncarriers. **(A)** Top panel shows z scores, i.e., group differences in regional cortical surface area. Bottom panel shows regional intra-deviation (RID) scores, i.e., group differences in regional cortical surface area that are scaled to the individual's own global index. Noncarriers are represented by gray lines, and 1q21.1 distal deletion carriers are represented by black lines. Blue dots indicate significant differences. The insular cortex is included under the frontal cortex for visualization purposes. **(B)** Top panel shows the significant differences in z scores, and bottom panel shows the significant differences in RID scores. Blue-red diverging maps represent the effect size. **(C)** Spatial distribution of all the mean differences in RID scores. All values are shown regardless of significance. Yellow-purple diverging maps represent the direction of the mean differences. Increased yellow intensity represents values that are less deviant than the overall global mean difference in cortical surface area, and increased purple intensity represents values that are more deviant than the overall global mean difference in cortical surface area. The z scores and RID scores are based on raw values adjusted for age, age², sex, and intracranial volume on site harmonized data.

carriers compared with noncarriers. Using RID scores, we found that a subset of brain regions diverged significantly from noncarriers for both the 1q21.1 distal and the 15q11.2 BP1-BP2 deletion carriers. We also found a higher number of significant regional differences using RID scores compared with the conventional global covariation approach. The current results hold promise for identifying specific CNV-associated brain profiles by targeting regional differences using an individualized approach, which are overlooked in studies applying conventional brain MRI measures.

In line with previous results (15), the 1q21.1 distal deletion carriers showed lower global cortical surface area compared with noncarriers. The observed differences in z scores indicate widespread lower cortical surface area, whereas the RID scores indicate that the cortical surface area in posterior and primary sensory regions (i.e., lingual, pericalcarine, superior parietal, isthmus of the cingulate gyrus) is less affected, and frontal and association cortices (i.e., caudal middle frontal, lateral orbitofrontal, rostral middle frontal, superior frontal cortex) are more affected. Thus, the observed regional z score

group differences along lateral and medial parietal to lateral inferior temporal and motor cortex appear to be largely reflective of the global effect. A subset of the significant RID scores (i.e., the superior temporal gyri and left supramarginal gyrus cortical thickness and left lateral orbitofrontal and left lateral superior temporal gyrus cortical surface area) were associated with cognitive ability in noncarriers. However, the effect sizes are low, and the current sample size of CNV carriers is too small to reliably detect such brain-cognition associations.

The 15q11.2 BP1-BP2 deletion showed a higher global cortical thickness compared with noncarriers, primarily concentrated in the frontal cortex, recapitulating previously reported group differences in cortical thickness (16). We complement these findings by showing group differences in RID scores, which indicates that the cortical thickness in sensory cortices (i.e., cuneus and pericalcarine area) is less affected, and the association cortices (i.e., rostral middle frontal and superior frontal cortex) are more affected by the deletion. The association cortices that show cortical thickness

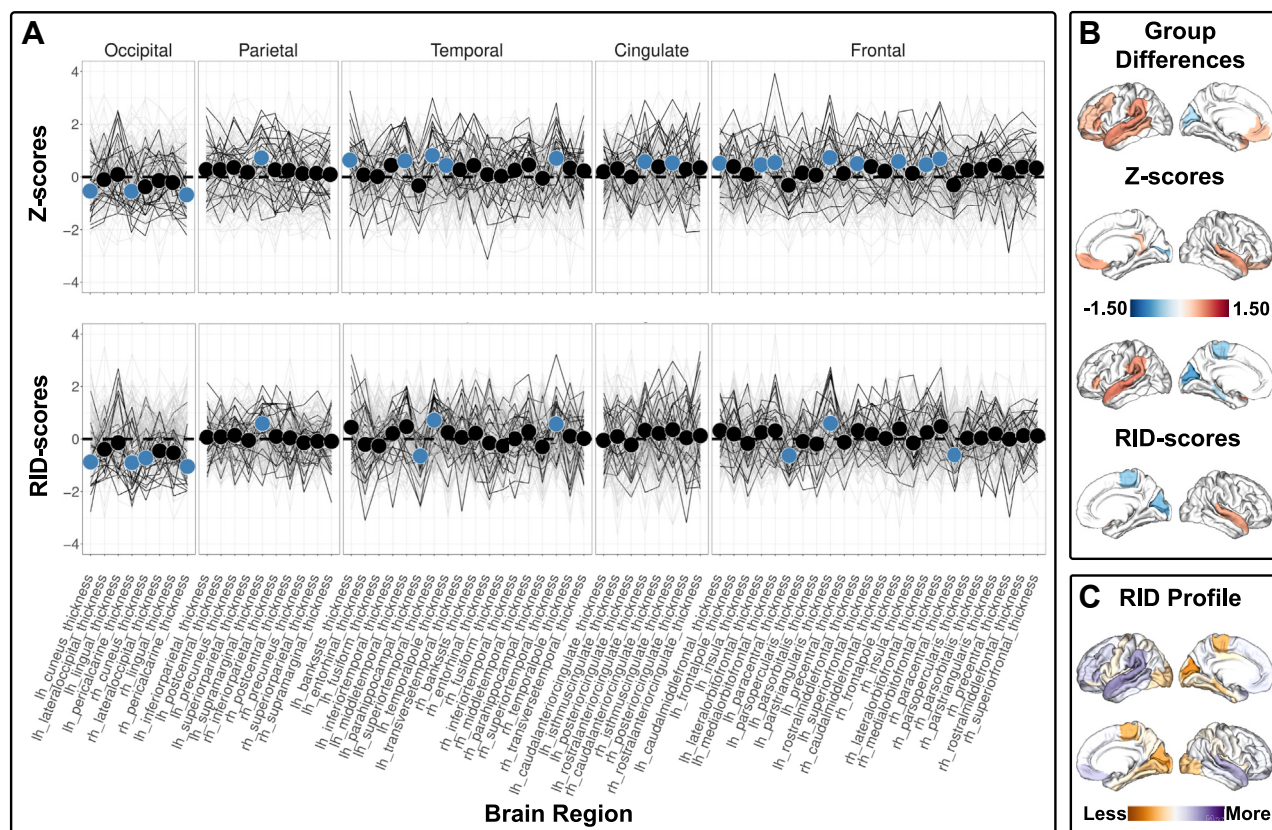


Figure 2. Cortical thickness comparison between 1q21.1 distal deletion carriers and noncarriers. **(A)** Top panel shows z scores, i.e., group differences in regional cortical thickness. Bottom panel shows regional intra-deviation (RID) scores, i.e., group differences in regional cortical thickness that are scaled to the individual's own global index. Noncarriers are represented by gray lines, and 1q21.1 distal deletion carriers are represented by black lines. Blue dots indicate significant differences. The insular cortex is included under the frontal cortex for visualization purposes. **(B)** Top panel shows the significant differences in z scores, and bottom panel shows the significant differences in RID scores. Blue-red diverging maps represent the effect size. **(C)** Spatial distribution of all the mean differences in RID scores. All values are shown regardless of significance. Yellow-purple diverging maps represent the direction of the mean differences. Increased yellow intensity represents values that are less deviant than the overall global mean difference in cortical thickness, and increased purple intensity represents values that are more deviant than the overall global mean difference in cortical thickness. The z scores and RID scores are based on raw values adjusted for age, age², sex, and intracranial volume on site harmonized data.

differences using RID scores are regions that underlie complex cognitive functions (23–25) and may subserve the lower cognitive performance in 15q11.2 BP1-BP2 deletion carriers compared with control individuals (14,34).

Notably, some findings deviated from the interpretation of a less affected sensorimotor cortex and a more affected association cortex. Both the 1q21.1 distal and the 15q11.2 BP1-BP2 deletion carriers showed evidence for a relatively less affected cortical surface area and cortical thickness, respectively, in the left temporal pole. We also found that the cortical thickness of the postcentral gyri, a primary somatosensory region, is more affected in the 15q11.2 BP1-BP2 deletion carriers. To speculate, this may be associated with the motor delay observed in clinically affected 15q11.2 BP1-BP2 deletion carriers (35). For cortical surface area in the 15q11.2 BP1-BP2 deletion carriers, we found inconsistent effects for frontal regions: although we observed a relatively more different bilateral pars orbitalis, we also found evidence for a less different left frontal pole and right pars opercularis. Furthermore, we did not find significant differences in RID scores in the 15q11.2

BP1-BP2 duplication carriers or in the 1q21.1 distal duplication carriers. The results complement previous findings of lower effect sizes in brain measures for duplication versus deletion carriers (6,7) and thus may support that carrying the deletion distorts the anatomical relationships in the brain more than carrying the duplication.

Global and frontal regional group differences in cortical thickness are prominent brain features of several neurodevelopmental disorders, including autism spectrum disorder (36) and schizophrenia (37). Thus, group differences in brain structure may be confounded by individuals with neurodevelopmental or psychiatric disorders. Here, all the significant RID score differences in 1q21.1 distal and 15q11.2 BP1-BP2 deletions survived adjustment for affection status, and there were no interaction effects between carrier status and affection status on the significant RID scores.

The current results implicate novel mechanisms in neurodevelopment. Compelling candidates for the changes in the 1q21.1 distal CNV are the human specific *NOTCH2NL* genes, which have been linked to the evolutionary expansion of the

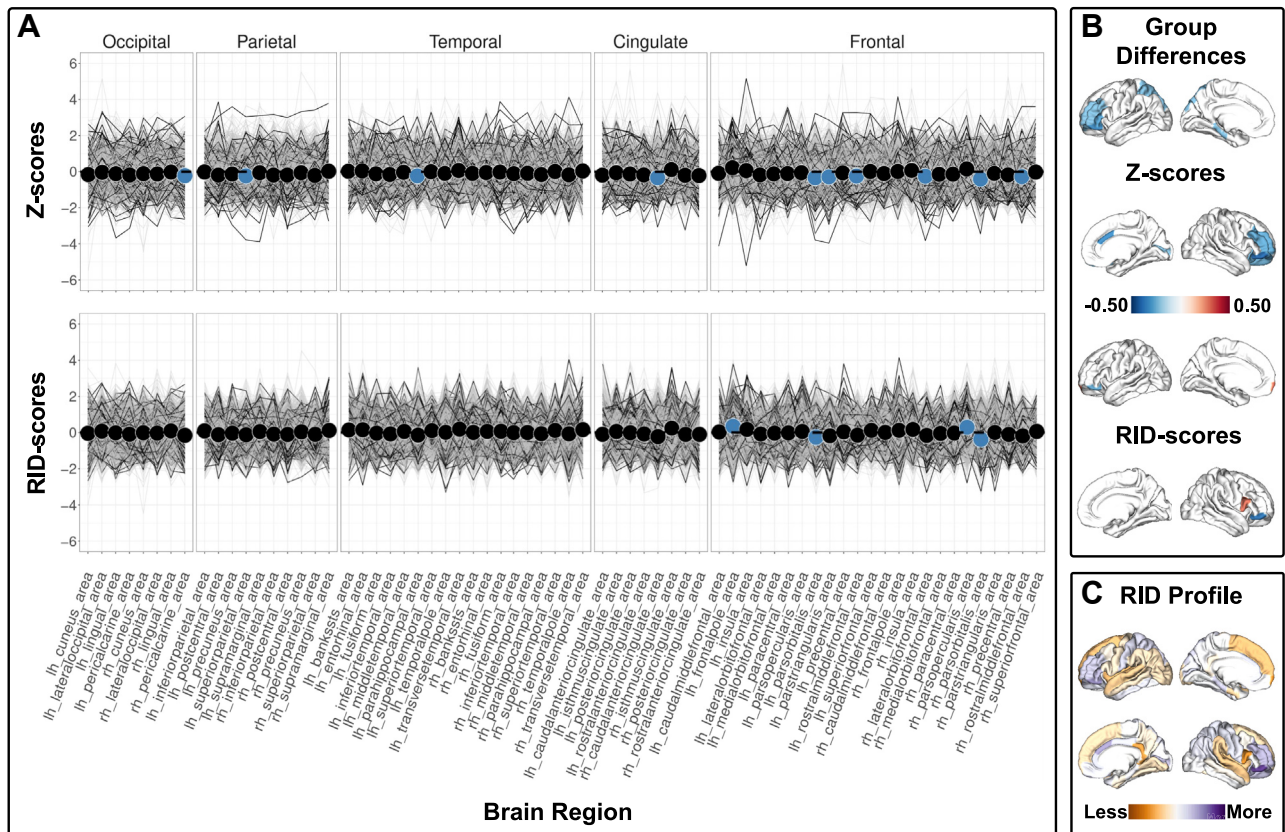


Figure 3. Cortical surface area comparison between 15q11.2 BP1-BP2 deletion carriers and noncarriers. **(A)** Top panel shows z scores, i.e., group differences in regional cortical surface area. Bottom panel shows regional intra-deviation (RID) scores, i.e., group differences in regional cortical surface area that are scaled to the individual's own global index. Noncarriers are represented by gray lines, and 15q11.2 BP1-BP2 deletion carriers are represented by black lines. Blue dots indicate significant differences. The insular cortex is included under the frontal cortex for visualization purposes. **(B)** Top panel shows the significant differences in z scores, and bottom panel shows the significant differences in RID scores. Blue-red diverging maps represent the effect size. **(C)** Spatial distribution of all the mean differences in RID scores. All values are shown regardless of significance. Yellow-purple diverging maps represent the direction of the mean differences. Increased yellow intensity represents values that are less deviant than the overall global mean difference in cortical surface area, and increased purple intensity represents values that are more deviant than the overall global mean difference in cortical surface area. The z scores and RID scores are based on raw values adjusted for age, age², sex, and intracranial volume on site harmonized data.

human neocortex (38,39). NOTCH signaling is important for outer radial glial cell self-renewal, which is thought to contribute to cortical expansion (40). Deletion of the *NOTCH2NL* genes in human cortical organoids yields smaller organoids compared with control organoids (38), and *NOTCH2NL* increases the number of cycling basal progenitors in the mouse embryonic neocortex (41). Thus, *NOTCH2NL* could yield a potential mechanistic link between the assumed lower gene expression levels in 1q21.1 distal deletion carriers and the lower cortical surface area, which is possibly important for the expansion of frontal regions.

Among the 4 genes in the 15q11.2 BP1-BP2 loci (42), *CYFIP1* has gained considerable interest due to its association with schizophrenia (43,44) and autism (45–47). *Cyfp1* exhibits high expression levels in the developing mouse brain (47). *CYFIP1* has also been linked to variation in cortical surface area (48) as well as various cellular phenotypes, including myelination (49), neurite length and branch number, cell size (50), dendritic spine formation (51), and regulation of radial glial cells (52). Notably, *Cyfp1* haploinsufficiency reduces

myelination thickness in rats (49). Cortical thickness, as estimated with MRI, has been suggested to be influenced by myelination (53). Thus, the higher cortical thickness observed in 15q11.2 BP1-BP2 deletion carriers may be due to altered myelination in the brain, possibly with somatosensory cortex being particularly sensitive to these alterations. *Cyfp1* deficiency has also been associated with functional connectivity deficits in motor cortices as well as aberrant motor coordination in mice (54). Finally, it should be noted that the 1q21.1 distal and the 15q11.2 BP1-BP2 loci span several genes, and genes within CNVs are likely to be involved in multifaceted genetic interactions (55). More research is needed to identify the causative biological mechanisms of the brain structural phenotypes.

This study has strengths and limitations. We used an intraindividual variability approach to examine brain metrics that are related to an individual's own interregional brain profile. By examining metrics that consider the variation within individuals, it is possible to map the heterogeneity and deviations in CNV carriers compared with noncarriers. However,

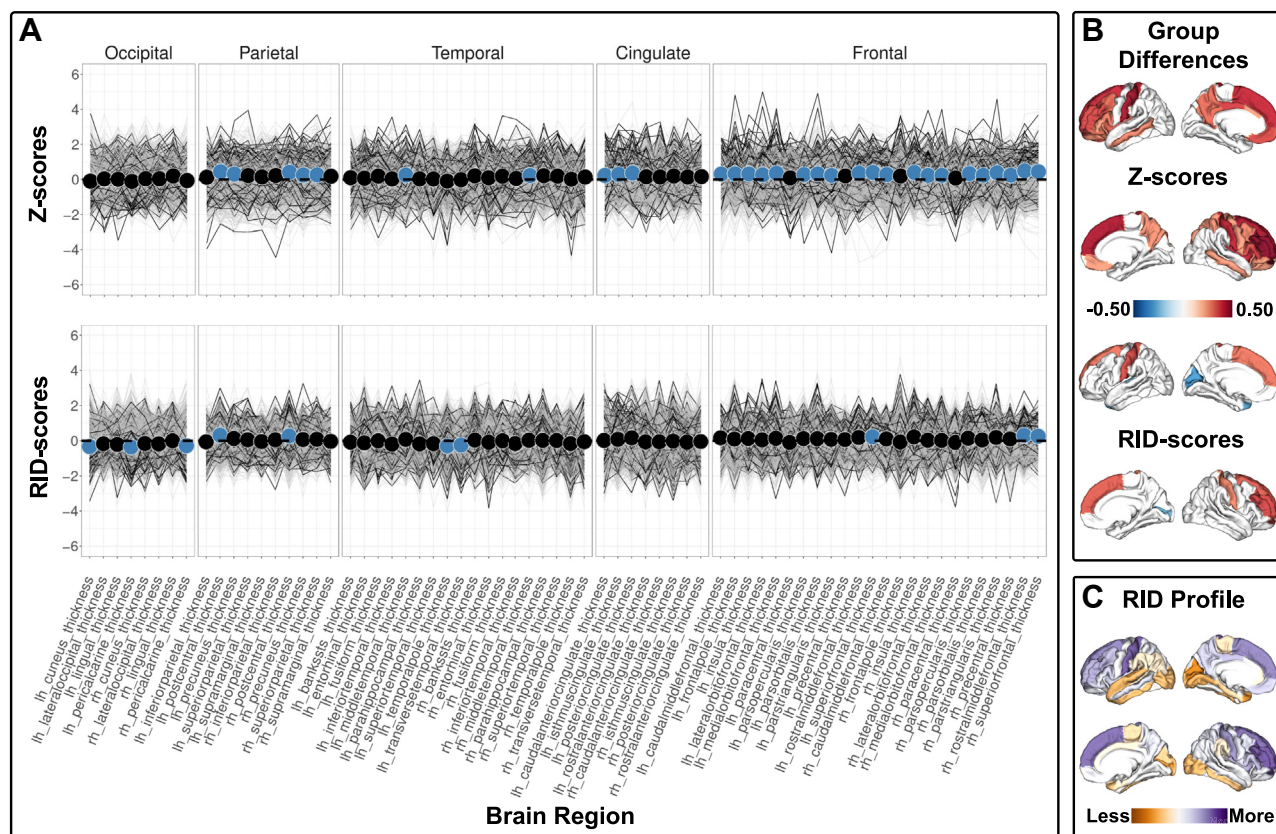


Figure 4. Cortical thickness comparison between 15q11.2 BP1-BP2 deletion carriers and noncarriers. **(A)** Top panel shows z scores, i.e., group differences in regional cortical thickness. Bottom panel shows regional intra-deviation (RID) scores, i.e., group differences in regional cortical thickness that are scaled to the individual's own global index. Noncarriers are represented by gray lines, and 15q11.2 BP1-BP2 deletion carriers are represented by black lines. Blue dots indicate significant differences. The insular cortex is included under the frontal cortex for visualization purposes. **(B)** Top panel shows the significant differences in z scores, and bottom panel shows the significant differences in RID scores. Blue-red diverging maps represent the effect size. **(C)** Spatial distribution of all the mean differences in RID scores. All values are shown regardless of significance. Yellow-purple diverging maps represent the direction of the mean differences. Increased yellow intensity represents values that are less deviant than the overall global mean difference in cortical thickness, and increased purple intensity represents values that are more deviant than the overall global mean difference in cortical thickness. The z scores and RID scores are based on raw values adjusted for age, age², sex, and intracranial volume on site harmonized data.

variability measures should be interpreted with caution, as some effects on the brain may be so extreme that further deviations are unlikely to be observed. That is, CNVs may yield large effects on brain structure, but only to a certain extent due to biological constraints. Thus, we urge caution when interpreting intraindividual standard deviation in brain measures, as ceiling and floor effects may bias the variability metrics. Still, we identified structures that are significantly less different or more different relative to the mean difference, indicating sufficient variability in the individualized brain metrics. About one half (1q21.1 distal) and two thirds (15q11.2 BP1-BP2) of the carriers are derived from the UK Biobank, which has a healthy volunteer bias (56), possibly yielding underestimations of brain structural differences. However, this is somewhat counterbalanced by the ENIGMA-CNV dataset that likely increases the heterogeneity in the study sample (although some datasets are likely to have similar bias toward healthy individuals as the UK Biobank). Indeed, the variability observed in brain structure within individuals underscores the heterogeneity between and within individuals in the sample. Future studies with larger

sample sizes are needed to examine the phenotypic heterogeneity observed in CNV carriers.

The results of the current study aid understanding of 1q21.1 distal and 15q11.2 BP1-BP2 CNV brain profiles by identifying regional differences using intraindividual variability metrics, which has the potential to give better insight into the neuronal mechanisms in neurodevelopment and risk for psychiatric diseases. We find evidence for regional differences beyond the global differences in brain structure, where the spatial effects partly support the hypothesis of less affected sensorimotor cortex and more affected association cortex in both 1q21.1 distal and 15q11.2 BP1-BP2 deletion carriers.

ACKNOWLEDGMENTS AND DISCLOSURES

1000BRAINS. This work was supported by the Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, European Union's Horizon 2020 Research and Innovation Programme (Grant No. 945539 [HBP SGA3; SCJ]), and Joint Lab Supercomputing and Modeling for the Human Brain.

We thank the Heinz Nixdorf Foundation for the generous support of the Heinz Nixdorf Study. We also thank the scientists and the study staff of the

Heinz Nixdorf Recall Study and 1000BRAINS. We gratefully acknowledge the computing time granted through JARA-HPC on the supercomputer JURECA at Forschungszentrum Jülich.

TOP: This work was supported by Research Council of Norway (Grant Nos. 23273 (Centre of Excellence, Norwegian Centre for Mental Disorders, NORMENT), Grant Nos. 324252 and 226971).

ENIGMA-CNV Working Group. This work was supported by the Research Council of Norway (Grant No. 223273 [to OAA]), South-Eastern Norway Regional Health Authority (Grant No. 2020060 [to IES, RB]), European Union's Horizon 2020 Research and Innovation Programme (CoMorment project; Grant No. 847776 [to IES]), Kristian Gerhard Jebsen Stiftelsen (Grant No. SKGJ-MED-021 [to IES]), and National Institute of Mental Health (NIMH) (Grant Nos. U01MH119736, R21MH116473, R01MH085953 [to CEB]), and 1R01MH129858-01A1 [to SJ].

This work was performed on Services for Sensitive Data, University of Oslo, with resources provided by UNINETT Sigma2, the national infrastructure for high performance computing and data storage in Norway.

Australian Schizophrenia Research Bank: This work was supported by the Australian National Health and Medical Research Council (NHMRC) (Enabling Grant No. 386500, L3 Investigator Grant No. 1196508 [to CP]), and Program Grant No. APP1150083 [to CP]), Pratt Foundation, Ramsay Health Care, Viertel Charitable Foundation, and Schizophrenia Research Institute. Chief Investigators for the Australian Schizophrenia Research Bank were Vaughan Carr, US, RJS, Assen Jablensky, BJM, Patricia Michie, Stanley Catts, FAH, and CP.

ECHO-DEFINE: This work was supported by the Wellcome Trust (Institutional Strategic Support Fund [to MBMvdB]) and Clinical Research Training Fellowship Grant No. 102003/Z/13/Z [to JLD]), Waterloo Foundation (Grant No. WF 918-1234 [to MBMvdB]), Baily Thomas Charitable Fund (Grant No. 2315/1 [to MBMvdB]), NIMH (Grant Nos. 5U01MH101724 and U01MH119738 [to MBMvdB]), IMAGEN-ID and IMAGEN-2 studies (funded by Medical Research Council Grant Nos. MR/N022572/1 and MR/T033045/1 [to MBMvdB]), and Medical Research Council (Centre Grant No. MR/P005748/1 [to MJO]). The DEFINE study was supported by a Wellcome Trust Strategic Award (Grant No. 100202/Z/12/Z [to MJO]).

FOR2107 Marburg and Münster: This work is part of the German multicenter consortium "Neurobiology of Affective Disorders: A Translational Perspective on Brain Structure and Function," supported by the German Research Foundation (Deutsche Forschungsgemeinschaft; Forschungsgruppe/Research Unit FOR2107). Principal investigators with respective areas of responsibility in the FOR2107 consortium: Work Package WP1, FOR2107/MACS cohort and brainimaging: TK (speaker FOR2107; DFG Grant Nos. KI 588/14-1, KI 588/14-2, KI 588/20-1, and KI 588/22-1), UD (co-speaker FOR2107; Grant Nos. DA 1151/5-1, DA 1151/5-2, and DA 1151/6-1), Axel Krug (Grant Nos. KR 3822/5-1 and KR 3822/7-2), IN (Grant Nos. NE 2254/1-2, NE 2254/3-1, and NE 2254/4-1), Carsten Konrad (Grant No. KO 4291/3-1). WP5, genetics: Marcella Rietschel (Grant Nos. RI 908/11-1 and RI 908/11-2), MMN (Grant Nos. NO 246/10-1 and NO 246/10-2), Stephanie Witt (Grant Nos. WI 3439/3-1 and WI 3439/3-2). WP6, multi-method data analytics: AJ (Grant Nos. JA 1890/7-1 and JA 1890/7-2), TH (Grant No. HA 7070/2-2).

We are deeply indebted to all study participants and staff. A list of acknowledgments can be found at: www.for2107.de/acknowledgements.

UCLA-Utrecht: This work was supported by the NIMH (Grant No. R01 MH090553 [to RAO]). The NIMH had no further role in study design, in the collection, analysis, and interpretation of the data, in the writing of the report, and in the decision to submit the paper for publication.

QTIM: This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant No. R01 HD050735) and the NHMRC (Grant Nos. 486682 and 1009064). Genotyping was supported by the NHMRC (Grant No. 389875).

BETULA: This work was supported by the Knut and Alice Wallenberg Foundation (scholar grant [to LN]).

Freesurfer calculations were enabled by resources provided by the Swedish National Infrastructure for Computing at HPC2N, Umeå.

SHIP (Study of Health in Pomerania): This work is part of the Community Medicine Research net of the University of Greifswald, Germany, which is supported by the Federal Ministry of Education and Research (Grant Nos. 01ZZ9603, 01ZZ0103, and 01ZZ0403), Ministry of Cultural Affairs, and Social Ministry of the Federal State of Mecklenburg-West

Pomerania. Genome-wide data in SHIP have been supported by the Federal Ministry of Education and Research (Grant No. 03ZIK012) and a joint grant from Siemens Healthineers and the Federal State of Mecklenburg-West Pomerania. MRI scans in SHIP and SHIP-TREND have been supported by a joint grant from Siemens Healthineers and the Federal State of Mecklenburg-West Pomerania.

PAFIP (Programa de Atención a las Fases Iniciales de Psicosis): This work was supported by the Instituto de Salud Carlos III (Grant Nos. 00/3095, 01/3129, PI020499, PI14/00639, PI17/01056, and PI14/00918), SENY Fundació (Research Grant No. CI2005 0308007), and Fundación Marqués de Valdecilla Instituto de Investigación Sanitaria Valdecilla (Grant Nos. A/02/07, NCT0235832, and NCT02534363).

Osaka: This work was supported by the Japan Agency for Medical Research and Development (Grant Nos. JP21wm0425012, JP18dm0307002, JP22wm0525019, and JP22dk0207060) and Japan Society for the Promotion of Science KAKENHI (Grant Nos. JP20H03611, JP22H04926, and 20K15778).

Some computations were performed at the Research Center for Computational Science, Okazaki, Japan (Project: NIPS, 18-IMS-C162, 19-IMS-C181, 20-IMS-C162, 21-IMS-C179, 22-IMS-C195).

IMAGEN: This work was supported by the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-Related Behavior in Normal Brain Function and Psychopathology) (Grant No. LSHM-CT-2007-037286), Horizon 2020-funded ERC Advanced Grant STRATIFY (Brain Network Based Stratification of Reinforcement-Related Disorders) (Grant No. 695313), Medical Research Foundation and Medical Research Council (Grants Nos. MR/R00465X/1 and MRF-058-0004-RG-DESRI [Neurobiological Underpinning of Eating Disorders: Integrative Biopsychosocial Longitudinal Analyses in Adolescents] and MR/S020306/1 and MRF-058-0009-RG-DESRI-C0759 [Establishing Causal Relationships Between Biopsychosocial Predictors and Correlates of Eating Disorders and Their Mediation by Neural Pathways]), National Institutes of Health (NIH) (Consortium Grant No. U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence, and Grant No. 1R56AG058854-01), National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, ERANID (Understanding the Interplay Between Cultural, Biological and Subjective Factors in Drug Use Pathways) (Grant No. PR-ST-0416-10004), BRIDGET (JPND: Brain Imaging, cognition Dementia and next generation Genomics) (Grant No. MR/N027558/1), Human Brain Project (HBP SGA 2) (Grant No. 785907), FP7 project MATRICS (Grant No. 603016), Medical Research Council Grant Consortium on Vulnerability to Externalizing Disorders and Addictions (Grant No. MR/N000390/1), Bundesministerium für Bildung und Forschung (Grant Nos. 01GS08152, 01EV0711, Forschungsnetz AERIAL 01EE1406A, and 01EE1406B), Deutsche Forschungsgemeinschaft (Grant Nos. SM 80/7-2, SFB 940/2, and NE 1383/14-1), Agence Nationale de la Recherche (ANR) (Grant Nos. ANR-12-SAMA-0004 and AAPG2019 [GeBra]), Erant Neuron (Grant Nos. AF12-NEUR0008-01 [WM2NA], ANR-18-NEUR00002-01 [ADORE], and ANR-12-SAMA-0004), Fondation de France (Grant No. 00081242), Fondation pour la Recherche Médicale (Grant No. DPA20140629802), Mission Interministérielle de Lutte contre les Drogues et les Conduites Addictives, Assistance Publique Hôpitaux de Paris and Institut National de la Santé et de la Recherche Médicale (Interface Grant), Paris Sud University IDEX 2012, Fondation de l'Avenir (Grant No. AP-RM-17-013), and Fédération pour la Recherche sur le Cerveau.

MCIC (Mind Clinical Imaging Consortium): This work was supported by the NIH (NIH/National Center for Research Resources Grant No. P41RR14075 [to VC] and Grant No. R01EB005846 [to VC]), Department of Energy (Grant No. DE-FG02-99ER62764), Mind Research Network, Morphometry Biomedical Informatics Research Network (Grant Nos. 1U24 and RR021382A), Function Biomedical Informatics Research Network (Grant No. U24RR021992-01 [to VC]), NIH/National Center for Research Resources Grant No. MO1 RR025758-01 [to VC], and NIMH Grant No. 1RC1MH089257 [to VC]), Deutsche Forschungsgemeinschaft (research fellowship [to SE]), and Brain and Behavior Research Foundation (NARSAD Young Investigator Award [to SE]).

NTR (Netherlands Twin Register): This work was supported by the Netherlands Organization for Scientific Research (NWO) and Netherlands

Organisation for Health Research and Development (Grant Nos. 904-61-090, 985-10-002, 912-10-020, 904-61-193, 480-04-004, 463-06-001, 451-04-034, 400-05-717, Addiction-31160008, 016-115-035, 481-08-011, 056-32-010, Middelgroot-911-09-032, OCW_NWO Gravity programme—024.001.003, and NWO-Groot 480-15-001/674), Center for Medical Systems Biology (NWO Genomics), NBIC/BioAssist/RK (Grant No. 2008.024), Biobanking and Biomolecular Resources Research Infrastructure The Netherlands (Grant Nos. 184.021.007 and 184.033.111), Spinozapremie (Grant No. NWO-56-464-14192), Royal Netherlands Academy of Arts and Sciences Academy Professor Award (Grant No. PAH/6635) and University Research Fellow grant (to DIB), Amsterdam Public Health research institute (former EMGO+ Institute for Health and Care Research), Amsterdam Neuroscience (former Neuroscience Campus Amsterdam), European Science Foundation (Grant No. EU/QLRT-2001-01254), European Community's Seventh Framework Programme (FP7- HEALTH-F4-2007-2013, Grant Nos. 01413: ENGAGE and 602768: ACTION), European Research Council (Grant Nos. ERC Starting 284167, ERC Consolidator 771057, and ERC Advanced 230374), Rutgers University Cell and DNA Repository (NIMH Grant No. U24 MH068457-06), NIH (Grant Nos. R01D0042157-01A1, R01MH58799-03, MH081802, DA018673, and R01 DK092127-04 and Grand Opportunity Grant Nos. 1RC2 MH089951 and 1RC2 MH089995), and Avera Institute for Human Genetics.

The genotyping and analyses were partly funded by the Genetic Association Information Network of the Foundation for the National Institutes of Health. Computing was supported by NWO (Grant No. 2018/EW/00408559), BiG Grid, Dutch e-Science Grid, and SURFSara.

OATS (Older Australian Twins Study): This work was supported by the NHMRC and Australian Research Council Strategic Award Grant of the Ageing Well, Ageing Productively Program (Grant No. 401162), NHMRC project (seed) grants (Grant Nos. 1024224 and 1025243), NHMRC project grants (Grant Nos. 1045325 and 1085606), and NHMRC program grants (Grant Nos. 568969 and 1093083).

The OATS Study was facilitated through access to Twins Research Australia, a national resource supported by a Centre of Research Excellence Grant (Grant No. 1079102) from the NHMRC. We thank the participants for their time and generosity in contributing to this research. We acknowledge the contribution of the OATS research team (<https://cheba.unsw.edu.au/project/older-australian-twins-study/>) to this study.

PING (Pediatric Imaging, Neurocognition, and Genetics): This work was supported by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant Nos. RC2DA029475 and R01 HD061414).

EPIGEN-London/University College London: The work was partly undertaken at University College London Hospitals NHS Foundation Trust/University College London, which received a proportion of funding from the UK Department of Health National Institute for Health Research Biomedical Research Centres funding scheme.

We thank the Wolfson Trust and the Epilepsy Society for supporting the Epilepsy Society MRI scanner.

OSR (Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Raffele)-Milan: This work was supported by the European Union H2020 (EU.3.1.1 Grant No. 754740 MOODSTRATIFICATION.EU), Italian Ministry of Health (Grant No. RF-2018-12367249) and Italian Ministry of University and Scientific Research (Grant No. A_201779W93T).

Dublin: This work was supported by the European Research Council (Grant No. ERC-2015-STG-677467 [to GD]) and Science Foundation Ireland (Grant No. SFI-16/ERCS/3787 [to GD]).

Brain Imaging Genetics (BIG): This work makes use of the BiG database, first established in Nijmegen, the Netherlands, in 2007. This resource is now part of Cognomics (www.cognomics.nl), a joint initiative by researchers from the Donders Centre for Cognitive Neuroimaging, Human Genetics and Cognitive Neuroscience departments of Radboud University Medical Centre, and Max Planck Institute for Psycholinguistics in Nijmegen. The Cognomics Initiative is supported by the participating departments and centers and Biobanking and Biomolecular Resources Research Infrastructure (Netherlands), Hersentstichting Nederland, and NWO. The research leading to these results also receives funding from the NWO (Gravitation Grant No. 024.001.006 Language in Interaction), European Community's Seventh Framework Programme (FP7/2007-2013) (Grant Nos. 602450

IMAGEMEND, 278948 TACTICS, and 602805 Aggrosotype), European Community's Horizon 2020 programme (Grant Nos. 643051 MiND, and ERC-2010-AdG 268800-NEUROSCHEMA). In addition, the work was supported by the ENIGMA Consortium (Grant No. U54 EB020403) from the BD2K Initiative of a cross-NIH partnership.

UK Biobank: This research has been conducted using the UK Biobank Resource under Application Number 27412.

OAA has received speaker's honorarium from Lundbeck, Janssen, and Sunovion and is a consultant to Coretechs.ai. TRM reports personal fees from Pfizer, Lundbeck, Astellas, Janssen, and Angelini outside the submitted work. He is an employee and shareholder of Pasithea Therapeutics. CRKC has received partial research support from Biogen for work unrelated to the topic of this article (principal investigator, PMT). PMT has received partial research support from Biogen for work unrelated to the topic of this article. MBMvdB and MJO report grants from Takeda Pharmaceuticals outside the submitted work. MJO reports a grant from Akkrivia Health outside the submitted work. HJG has received travel grants and speaker's honoraria from Fresenius Medical Care, Neuraxpharm, Servier, and Janssen as well as research funding from Fresenius Medical Care. GS has received honoraria for participating at advisory board meetings from Roche and Biogen regarding new Alzheimer's disease drugs. KKS has received consultant and speaker's honoraria from Roche and OrionPharma, reimbursement of travel and accommodation costs at a meeting from Kolpharma, and sponsorships for arranging conferences from Desitin and Eisai AB. IG has received speaker's honorarium from Lundbeck. MMN has received fees for membership in an advisory board from HMG Systems Engineering GmbH, for membership in the Medical-Scientific Editorial Office of the Deutsches Ärzteblatt, and for serving as a consultant for Everis Belgium in a project of the European Commission (REFORM/SC2020/029). MMN also receives salary payments from Life & Brain GmbH and holds shares in Life & Brain GmbH. All these concerned activities outside the submitted work. CP received honoraria for talks from Lundbeck, Australia Pty Ltd. outside the submitted work. DJS has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen. JH has received speaker's honorarium from Medice and Takeda outside the submitted work. KP reports work with Novo Nordisk and Roche clinical trials outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Medical Genetics, Oslo University Hospital, Oslo, Norway (RB, IES); Norwegian Centre for Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway (RB, TKa, DvdM, OF, LTW, DAI, OAA, IES); Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health, University of Tübingen, Germany (TKa); German Center for Mental Health (DZPG), partner site Tübingen, Tübingen, Germany (TKa); School of Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands (DvdM); Centre for Bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway (OF); Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (IA, EGJ, OAA); Department of Clinical Research, Diakonhjemmet Hospital, Oslo, Norway (IA); Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm, Sweden (IA); University of Melbourne Academic Unit for Psychiatry of Old Age, St George's Hospital, Kew, Victoria, Australia (DAm); National Ageing Research Institute, Parkville, Victoria, Australia (DAm); Department of Integrative Medical Biology and Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden (MA); Department of Mathematics and Statistics, Curtin University, Perth, Western Australia, Australia (NJA); Institut National de la Santé et de la Recherche Médicale U1299, École Normale Supérieure Paris-Saclay, Université Paris Saclay, Gif-sur-Yvette, France (EA); Établissement public de santé (EPS) Barthélemy Durand, Etampes, France (EA); School of Biomedical Sciences and Pharmacy, College of Medicine, Health and Wellbeing, University of Newcastle, Callaghan, New South Wales, Australia (JRA, MJ, RJS, PAT); Precision Medicine Research Program, Hunter Medical Research Institute, Newcastle, New South Wales, Australia (JRA, MJ); Cancer Epidemiology

Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (JRA); University Clinic for Radiology, University of Münster, Münster, Germany (JB); Psychiatry and Clinical Psychobiology Unit, Division of Neuroscience, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute, Milan, Italy (FB, LF-U, MP); Division of Neuroscience, Psychiatry and Clinical Psychobiology Unit, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy (FB, LF-U, MP); Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (DIB, EJCdG, DvE); Centre for Healthy Brain Ageing, School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia (HB, KAM, PSS, ATTh, WW); Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany (KB, AJ, TKi, IN, FSte, BS, LT); Department of Psychology and Center for Brain Science, Harvard University, Cambridge, Massachusetts (RLB); Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts (RLB); Tri-institutional Center for Translational Research in Neuroimaging and Data Science, Georgia State University/Georgia Institute of Technology/Emory University, Atlanta, Georgia (VC); Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany (SCa, SCi, AJF, CJ, TWM); Institute for Anatomy I, Medical Faculty & University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany (SCa, CJ, TWM); Department of Biomedicine, University of Basel, Basel, Switzerland (SCi); University Hospital Basel, Institute of Medical Genetics and Pathology, Basel, Switzerland (SCi); Department of Psychiatry, Trinity College Dublin, Dublin, Ireland (APC); Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/Centro superior de investigaciones científicas (CSIC), Sevilla, Spain (BC-F); Centro de Investigación Biomédica en Red Salud Mental, Sevilla, Spain (B-CF, JV-B); Department of Psychiatry, University of Sevilla, Sevilla, Spain (BC-F); Institute for Translational Psychiatry, University of Münster, Münster, Germany (UD, JG, DG, TH, SM); Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany (FSD, AJF, MMN); School of Psychology and Counselling, Queensland University of Technology, Brisbane, Queensland, Australia (GldZ); Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (SD); Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom (JLD, MJO); Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, United Kingdom (JLD); School of Psychology and Center for Neuroimaging, Cognition and Genomics, University of Galway, Galway, Ireland (GD); Translational Developmental Neuroscience Section, Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany (SE); Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands (EE, SEF); Department of Psychology, University of Oslo, Oslo, Norway (TE, LTW); Department of Psychology, Oslo New University College, Oslo, Norway (TE); Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands (SEF, ES); Neurospin, Commissariat à l'Energie Atomique (CEA), Université Paris-Saclay, Gif-sur-Yvette, France (VF); Section of Brain Function Information, National Institute for Physiological Sciences, Okazaki, Japan (MF); Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts (TG); Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (TG); Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Boston, Massachusetts (DCG); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (DCG); Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany (HJG, ATe, KW); Discipline of Psychiatry and Mental Health, School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia (MJG); Neuroscience Research Australia, Sydney, New South Wales, Australia (MJG, YQ); Department of Psychiatry and Mental Health, Neuroscience Institute, University of Cape Town, Cape Town, South Africa (NAG); Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan (RH); Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands (JYH-K); School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales,

Australia (FAH); Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle, New South Wales, Australia (FAH); Department of Psychiatry, Rutgers University, New Brunswick, New Jersey (AJH); Brain Health Institute, Rutgers University, Piscataway, New Jersey (AJH); Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway (GRG, AKH, SBS); Department of Radiology and Nuclear Medicine, St. Olav's Hospital, Trondheim, Norway (AKH); Department of Biomedicine, University of Bergen, Bergen, Norway (JH); Division of Psychiatry, Haukeland University Hospital, Bergen, Norway (JH); Sainte Justine Hospital Research Center, Montreal, Quebec, Canada (SJ); Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada (SJ); Core-Facility Brainimaging and Department of Psychiatry, Faculty of Medicine, Philipps-University Marburg, Marburg, Germany (AJ); Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm Region, Stockholm, Sweden (EGJ); Department of Genome Informatics, Graduate School of Medicine, Osaka University, Osaka, Japan (MK); Department of Computational Biology and Medical Sciences, Graduate School of Frontier Science, The University of Tokyo, Chiba, Japan (MK); Sainte Justine Hospital Research Center, Montreal, Quebec, Canada (KK); Norwegian Centre for Mental Disorders Research, Department of Clinical Science, University of Bergen, Bergen, Norway (SLH); Dr. Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway (SLH); Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom (CL, SMS); Department of Neurology, McGovern Medical School, UTHealth Houston, Houston, Texas (CL); Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, United Kingdom (DEL, AIS); School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands (DEL); Department of Computer Science and Center for Translational Research in Neuroimaging and Data Science, Georgia State University, Atlanta, Georgia (JL); Department of Cognitive Science and Population Neuroscience and Genetics Lab, University of California San Diego, La Jolla, California (RL); School of Clinical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia (KLM); Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia (AFM); Psychiatric Genetics, Queensland Institute of Medical Research (QIMR) Berghofer Medical Research Institute, Brisbane, Queensland, Australia (SEM, LTS); University of Queensland, Brisbane, Queensland, Australia (SEM); Queensland University of Technology, Brisbane, Queensland, Australia (SEM); Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Marina del Rey, California (CAM, CRKC, PMT); Centre for Neuroimaging, Cognition and Genomics, School of Biological and Chemical Sciences, University of Galway, Galway, Ireland (DWM); Queensland Brain Institute and Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia (BJM); Department of Biomedicine, University of Basel, Basel, Switzerland (TWM); Departments of Radiation Sciences, Integrative Medical Biology and Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden (LN); Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom (MJO); Departments of Psychiatry and Neuroscience, Faculty of Medicine and Sainte Justine Hospital Research Center, University of Montreal, Montreal, Quebec, Canada (TP); Departments of Psychiatry and Psychology, University of Toronto, Toronto, Ontario, Canada (TP); The Hospital for Sick Children, Toronto, Ontario, Canada (ZP); Department of Physiology, University of Toronto, Toronto, Ontario, Canada (ZP); Department of Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands (RAO); Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway (KP, GS); School of Psychology, University of New South Wales, Sydney, New South Wales, Australia (YQ); Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Carlton South, Victoria, Australia (CP); Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (TRM); Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, New South Wales, Australia

(PSS); Department of Neurology and Clinical Neurophysiology, University Hospital of Trondheim, Trondheim, Norway (GRG, SBS); Hunter Medical Research Institute, Newcastle, New South Wales, Australia (US, RJS, PAT); Division of Molecular Medicine, New South Wales Health Pathology, Newcastle, New South Wales, Australia (RJS); National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway (KP, GS); Faculty of Medicine, University of Oslo, Oslo, Norway (GS); Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands (ES); Chalfont Centre for Epilepsy, Chalfont St Peter, United Kingdom (SMS); SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa (DJS); Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany (FStr); School of Psychology and Counselling, Faculty of Health, Queensland University of Technology, Brisbane, Australia (LTS); Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany (ATe); German Centre for Cardiovascular Research, Greifswald, Germany (ATe, HV); Instituto de Física de Cantabria UC-CSIC, Santander, Spain (DT-G); Department of Radiology, Marqués de Valdecilla University Hospital, Valdecilla Biomedical Research Institute, Instituto de Investigación Sanitaria Valdecilla, Santander, Spain (DT-G); Department of Developmental Disability Neuropsychiatry and Centre for Healthy Brain Ageing, School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia (JNT); Western Centre for Health Research and Education, Sunshine Hospital, St Albans, Victoria, Australia (CP); Institute of Psychological Medicine and Clinical Neurosciences and Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom (MBMvdB); Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre, Rotterdam, the Netherlands (NEMvH); Department of Psychiatry, University Medical Centre Utrecht, Utrecht, the Netherlands (NEMvH); Department of Psychiatry, University Hospital Maqués de Valdecilla, Instituto de Investigación Sanitaria Valdecilla, Santander, Spain (JV-B); Departamento de Medicina y Psiquiatría, Universidad de Cantabria, Santander, Spain (JV-B); Greifswald University Hospital, Greifswald, Germany (HV); KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway (LTW, OAA, IES); Semel Institute for Neuroscience and Human Behavior, Departments of Psychiatry and Biobehavioral Sciences and Psychology, University of California Los Angeles, Los Angeles, California (RAO, CEB); Department of Research and Innovation, Division of Clinical Neuroscience, Oslo University Hospital and the University of Oslo, Oslo, Norway (KKS); Kristiania University College, Oslo, Norway (DAI); and Institute for Translational Neuroscience, University of Münster, Münster, Germany (SM, MBMvdB).

Address correspondence to Rune Boen, M.Phil., at boenrune@gmail.com.

Received Apr 11, 2023; revised Jul 25, 2023; accepted Aug 21, 2023.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.biopsych.2023.08.018>.

REFERENCES

- Calle Sánchez X, Helenius D, Bybjerg-Grauholm J, Pedersen C, Hougaard DM, Børglum AD, *et al.* (2022): Comparing copy number variations in a Danish case cohort of individuals with psychiatric disorders. *JAMA Psychiatry* 79:59–69.
- Stefansson H, Rujescu D, Cichon S, Pietiläinen OPH, Ingason A, Steinberg S, *et al.* (2008): Large recurrent microdeletions associated with schizophrenia. *Nature* 455:232–236.
- Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, *et al.* (2017): Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet* 49:27–35.
- Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, *et al.* (2022): Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature* 604:509–516.
- Mollon J, Almasly L, Jacquemont S, Glahn DC (2023): The contribution of copy number variants to psychiatric symptoms and cognitive ability. *Mol Psychiatry* 28:1480–1493.
- Modenato C, Martin-Brevet S, Moreau CA, Rodríguez-Herreros B, Kumar K, Draganski B, *et al.* (2021): Lessons learned from neuroimaging studies of copy number variants: A systematic review. *Biol Psychiatry* 90:596–610.
- Sønderby IE, Ching CRK, Thomopoulos SI, van der Meer D, Sun D, Villalon-Reina JE, *et al.* (2022): Effects of copy number variations on brain structure and risk for psychiatric illness: Large-scale studies from the ENIGMA working groups on CNVs. *Hum Brain Mapp* 43:300–328.
- Moreau CA, Ching CR, Kumar K, Jacquemont S, Bearden CE (2021): Structural and functional brain alterations revealed by neuroimaging in CNV carriers. *Curr Opin Genet Dev* 68:88–98.
- Chapman G, Alsaqati M, Lunn S, Singh T, Linden SC, Linden DEJ, *et al.* (2022): Using induced pluripotent stem cells to investigate human neuronal phenotypes in 1q21.1 deletion and duplication syndrome. *Mol Psychiatry* 27:819–830.
- Urresti J, Zhang P, Moran-Losada P, Yu NK, Negraes PD, Trujillo CA, *et al.* (2021): Cortical organoids model early brain development disrupted by 16p11.2 copy number variants in autism. *Mol Psychiatry* 26:7560–7580.
- Khan TA, Revah O, Gordon A, Yoon SJ, Krawisz AK, Goold C, *et al.* (2020): Neuronal defects in a human cellular model of 22q11.2 deletion syndrome. *Nat Med* 26:1888–1898.
- Sundberg M, Pinson H, Smith RS, Winden KD, Venugopal P, Tai DJC, *et al.* (2021): 16p11.2 deletion is associated with hyperactivation of human iPSC-derived dopaminergic neuron networks and is rescued by RHOA inhibition in vitro. *Nat Commun* 12:2897.
- Smajlagić D, Lavrichenko K, Berland S, Helgeland Ø, Knudsen GP, Vaudel M, *et al.* (2021): Population prevalence and inheritance pattern of recurrent CNVs associated with neurodevelopmental disorders in 12,252 newborns and their parents. *Eur J Hum Genet* 29:205–215.
- Kendall KM, Rees E, Escott-Price V, Einon M, Thomas R, Hewitt J, *et al.* (2017): Cognitive performance among carriers of pathogenic copy number variants: Analysis of 152,000 UK Biobank subjects. *Biol Psychiatry* 82:103–110.
- Sønderby IE, van der Meer D, Moreau C, Kaufmann T, Walters GB, Ellegaard M, *et al.* (2021): 1q21.1 distal copy number variants are associated with cerebral and cognitive alterations in humans. *Transl Psychiatry* 11:1–16.
- Writing Committee for the ENIGMA-CNV Working Group, van der Meer D, Sønderby IE, Kaufmann T, Walters GB, Abdellaoui A, *et al.* (2020): Association of copy number variation of the 15q11.2 BP1-BP2 region with cortical and subcortical morphology and cognition. *JAMA Psychiatry* 77:420–430.
- Anderson AE, Jones JD, Thaler NS, Kuhn TP, Singer EJ, Hinkin CH (2018): Intra-individual variability in neuropsychological performance predicts cognitive decline and death in HIV. *Neuropsychology* 32:966–972.
- Dykert D, Der G, Starr JM, Deary IJ (2012): Sex differences in reaction time mean and intraindividual variability across the life span. *Dev Psychol* 48:1262–1276.
- Hilborn JV, Strauss E, Hultsch DF, Hunter MA (2009): Intraindividual variability across cognitive domains: Investigation of dispersion levels and performance profiles in older adults. *J Clin Exp Neuropsychol* 31:412–424.
- MacDonald SWS, Nyberg L, Bäckman L (2006): Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends Neurosci* 29:474–480.
- Roalf DR, Quarmley M, Mechanic-Hamilton D, Wolk DA, Arnold SE, Moberg PJ, *et al.* (2016): Within-individual variability: An index for subtle change in neurocognition in mild cognitive impairment. *J Alzheimers Dis* 54:325–335.
- Tammes CK, Fjell AM, Westlye LT, Østby Y, Walhovd KB (2012): Becoming consistent: Developmental reductions in intraindividual variability in reaction time are related to white matter integrity. *J Neurosci* 32:972–982.
- Keller AS, Sydnor VJ, Pines A, Fair DA, Bassett DS, Satterthwaite TD (2023): Hierarchical functional system development supports executive function. *Trends Cogn Sci* 27:160–174.
- Sydnor VJ, Larsen B, Bassett DS, Alexander-Bloch A, Fair DA, Liston C, *et al.* (2021): Neurodevelopment of the association cortices:

- Patterns, mechanisms, and implications for psychopathology. *Neuron* 109:2820–2846.
25. Yeo BTT, Krienen FM, Eickhoff SB, Yaakub SN, Fox PT, Buckner RL, *et al.* (2015): Functional specialization and flexibility in human association cortex. *Cereb Cortex* 25:3654–3672.
 26. Ho D, Imai K, King G, Stuart EA (2011): MatchIt: Nonparametric pre-processing for parametric causal inference. *J Stat Softw* 42:1–28.
 27. Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, *et al.* (2018): Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* 166:400–424.
 28. Monereo-Sánchez J, de Jong JJA, Drenth GS, Beran M, Backes WH, Stehouwer CDA, *et al.* (2021): Quality control strategies for brain MRI segmentation and parcellation: Practical approaches and recommendations—insights from the Maastricht study. *Neuroimage* 237:118174.
 29. Radua J, Vieta E, Shinohara R, Kochunov P, Quidé Y, Green MJ, *et al.* (2020): Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *Neuroimage* 218:116956.
 30. Crawford K, Bracher-Smith M, Owen D, Kendall KM, Rees E, Pardiñas AF, *et al.* (2019): Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. *J Med Genet* 56:131–138.
 31. Kochunov P, Huang J, Chen S, Li Y, Tan S, Fan F, *et al.* (2019): White matter in schizophrenia treatment resistance. *Am J Psychiatry* 176:829–838.
 32. Larivière S, Paquola C, Park BY, Royer J, Wang Y, Benkarim O, *et al.* (2021): The ENIGMA Toolbox: Multiscale neural contextualization of multisite neuroimaging datasets. *Nat Methods* 18:698–700.
 33. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol* 57:289–300.
 34. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnúsdóttir B, Morgen K, Arnarsdóttir S, *et al.* (2014): CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature* 505:361–366.
 35. Cox DM, Butler MG (2015): The 15q11.2 BP1–BP2 microdeletion syndrome: A review. *Int J Mol Sci* 16:4068–4082.
 36. van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, Busatto GF, *et al.* (2018): Cortical and subcortical brain morphometry differences between patients with autism spectrum disorder and healthy individuals across the lifespan: Results from the ENIGMA ASD Working Group. *Am J Psychiatry* 175:359–369.
 37. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, *et al.* (2018): Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Consortium. *Biol Psychiatry* 84:644–654.
 38. Fiddes IT, Lodewijk GA, Mooring M, Bosworth CM, Ewing AD, Mantalas GL, *et al.* (2018): Human-specific NOTCH2NL genes affect Notch signaling and cortical neurogenesis. *Cell* 173:1356–1369.e22.
 39. Suzuki IK, Gacquer D, Heurck RV, Kumar D, Wojno M, Bilheu A, *et al.* (2018): Human-specific NOTCH2NL genes expand cortical neurogenesis through Delta/Notch regulation. *Cell* 173:1370–1384.e16.
 40. Hansen DV, Lui JH, Parker PRL, Kriegstein AR (2010): Neurogenic radial glia in the outer subventricular zone of human neocortex. *Nature* 464:554–561.
 41. Florio M, Heide M, Pinson A, Brandl H, Albert M, Winkler S, *et al.* (2018): Evolution and cell-type specificity of human-specific genes preferentially expressed in progenitors of fetal neocortex. *Elife* 7:e32332.
 42. Chai JH, Locke DP, Greally JM, Knoll JHM, Ohta T, Dunai J, *et al.* (2003): Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. *Am J Hum Genet* 73:898–925.
 43. Tam GWC, van de Lagemaat LN, Redon R, Strathdee KE, Croning MDR, Malloy MP, *et al.* (2010): Confirmed rare copy number variants implicate novel genes in schizophrenia. *Biochem Soc Trans* 38:445–451.
 44. Nebel RA, Zhao D, Pedrosa E, Kirschen J, Lachman HM, Zheng D, *et al.* (2016): Reduced CYFIP1 in human neural progenitors results in dysregulation of schizophrenia and epilepsy gene networks. *PLoS One* 11:e0148039.
 45. Wang J, Tao Y, Song F, Sun Y, Ott J, Saffen D (2015): Common regulatory variants of CYFIP1 contribute to susceptibility for autism spectrum disorder (ASD) and classical autism. *Ann Hum Genet* 79:329–340.
 46. Toma C, Torricio B, Hervás A, Valdés-Mas R, Tristán-Noguero A, Padillo V, *et al.* (2014): Exome sequencing in multiplex autism families suggests a major role for heterozygous truncating mutations. *Mol Psychiatry* 19:784–790.
 47. Zwaag B van der, Staal WG, Hochstenbach R, Poot M, Spierenburg HA, de Jonge MV, *et al.* (2010): A co-segregating microduplication of chromosome 15q11.2 pinpoints two risk genes for autism spectrum disorder. *Am J Med Genet B Neuropsychiatr Genet* 153B:960–966.
 48. Woo YJ, Wang T, Guadalupe T, Nebel RA, Vito A, Bene VAD, *et al.* (2016): A common CYFIP1 variant at the 15q11.2 disease locus is associated with structural variation at the language-related left supramarginal gyrus. *PLoS One* 11:e0158036.
 49. Silva AI, Haddon JE, Ahmed Syed Y, Trent S, Lin TCE, Patel Y, *et al.* (2019): Cyfip1 haploinsufficient rats show white matter changes, myelin thinning, abnormal oligodendrocytes and behavioural inflexibility. *Nat Commun* 10:3455.
 50. Oguro-Ando A, Rosensweig C, Herman E, Nishimura Y, Werling D, Bill BR, *et al.* (2015): Increased CYFIP1 dosage alters cellular and dendritic morphology and dysregulates mTOR. *Mol Psychiatry* 20:1069–1078.
 51. De Rubeis S, Pasciuto E, Li KW, Fernández E, Di Marino D, Buzzi A, *et al.* (2013): CYFIP1 coordinates mRNA translation and cytoskeleton remodeling to ensure proper dendritic spine formation. *Neuron* 79:1169–1182.
 52. Yoon KJ, Nguyen HN, Ursini G, Zhang F, Kim NS, Wen Z, *et al.* (2014): Modeling a genetic risk for schizophrenia in iPSCs and mice reveals neural stem cell deficits associated with adherens junctions and polarity. *Cell Stem Cell* 15:79–91.
 53. Natu VS, Gomez J, Barnett M, Jeska B, Kirilina E, Jaeger C, *et al.* (2019): Apparent thinning of human visual cortex during childhood is associated with myelination. *Proc Natl Acad Sci U S A* 116:20750–20759.
 54. Domínguez-Iturza N, Lo AC, Shah D, Armendáriz M, Vannelli A, Mercaldo V, *et al.* (2019): The autism- and schizophrenia-associated protein CYFIP1 regulates bilateral brain connectivity and behaviour. *Nat Commun* 10:3454.
 55. Jensen M, Girirajan S (2019): An interaction-based model for neuropsychiatric features of copy-number variants. *PLoS Genet* 15:e1007879.
 56. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, *et al.* (2017): Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 186:1026–1034.