Lessons Learned From Neuroimaging Studies of Copy Number Variants: A Systematic Review

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Review

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ABSTRACT

Pathogenic copy number variants (CNVs) and aneuploidies alter gene dosage and are associated with neurodevelopmental psychiatric disorders such as autism spectrum disorder and schizophrenia. Brain mechanisms mediating genetic risk for neurodevelopmental psychiatric disorders remain largely unknown, but there is a rapid increase in morphometry studies of CNVs using T1-weighted structural magnetic resonance imaging. Studies have been conducted one mutation at a time, leaving the field with a complex catalog of brain alterations linked to different genomic loci. Our aim was to provide a systematic review of neuroimaging phenotypes across CNVs associated with developmental psychiatric disorders including autism and schizophrenia. We included 76 structural magnetic resonance imaging studies on 20 CNVs at the 15q11.2, 22q11.2, 1q21.1 distal, 16p11.2 distal and proximal, 7q11.23, 15q11-q13, and 22q13.33 (*SHANK3*) genomic loci as well as aneuploidies of chromosomes X, Y, and 21. Moderate to large effect sizes on global and regional brain morphometry are observed across all genomic loci, which is in line with levels of symptom severity reported for these variants. This is in stark contrast with the much milder neuroimaging effects observed in idiopathic psychiatric disorders. Data also suggest that CNVs have independent effects on global versus regional measures as well as on cortical surface versus thickness. Findings highlight a broad diversity of regional morphometry patterns across genomic loci. This heterogeneity of brain patterns provides insight into the weak effects reported in magnetic resonance imaging studies of cognitive dimension and psychiatric conditions. Neuroimaging studies across many more variants will be required to understand links between gene function and brain morphometry.

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A BRIEF HISTORY OF COPY NUMBER VARIANTS

Copy number variants (CNVs) are defined as either the gain or loss of a stretch of DNA >1000 bp. Trisomy 21, discovered in 1959, was the first example of altered gene dosage across an entire chromosome. It was followed in the 1980s to 1990s by discoveries of CNVs associated with clinically defined syndromes such as the 7q11.23 (Williams-Beuren syndrome) (1) and 22q11.2 (velocardiofacial syndrome) (2) deletions. The rate of discovery accelerated by several orders of magnitude around 2010 with the advent of high-throughput chromosomal microarrays, which allowed for genome-wide interrogation of CNVs. Approximately 15%, 9%, and 2% to 8% of individuals referred to the clinic for motor delay and intellectual disabilities (3), autism spectrum disorder (ASD) (4), and schizophrenia (SCZ) (5,6), respectively, carry a pathogenic CNV.

There are two major classes of CNVs: 1) recurrent rare CNVs (the focus of this review) that generally arise by nonallelic homologous recombination during meiosis (7), leading to CNVs with identical size and gene content in unrelated individuals; or 2) nonrecurrent CNVs occurring at random positions in the genome, which are thus, individually, extremely rare.

Carriers of recurrent pathogenic CNVs are at increased risk for malformations, neurodevelopmental disorders (8) (Table 1), and other medical conditions (9–11). In comparison with the highest odds ratios (ORs) observed for individual single nucleotide polymorphisms in ASD, SCZ, attention-deficit/hyperactivity disorder, or major depressive disorder (ORs, ~1.05–1.25) (12–15), deleterious CNVs are associated with substantially higher risk (OR often >10) (15) (Table 1). Ultra-rare nonrecurrent CNVs are distributed across the genome and cannot be studied individually, but burden analyses have shown that they are, as a group, overrepresented in SCZ (15) and ASD, and that they decrease intelligence irrespective of a diagnosis of a neuropsychiatric disorder (16). Models estimate that the vast majority of 1-Mb deletions or duplications containing coding elements increase ASD risk (17) and that approximately 10,000 genes negatively affect intelligence when deleted (18).

CNVs have spurred considerable interest because they allow for the investigation of mechanisms and biological risk underlying neurodevelopmental disorders irrespective of clinical symptomatology (19,20). This approach is typically referred to as genotype-first or genetic-first.

A steadily increasing number of morphometry studies using T1-weighted structural magnetic resonance imaging (MRI) in CNV carriers have highlighted robust and large effects on brain structures that partially overlap with those previously observed in idiopathic psychiatric disorders (21–23). These studies were

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Table 1. Effects of CNVs on IQ and Risk for ASD and SCZ

CNV (Hg19-Mb)	BPs Hg19	Deletions			Duplications		
		IQ *z* Score	ASD OR	SCZ OR	IQ *z* Score	ASD OR	SCZ OR
Trisomy 21 (Down Syndrome)	–	–	–	–	−3.3	Male: 6.83; Female: 17.60	Male: 3.67; Female: 0.49
X (Turner Syndrome)	–	−0.5	3%–5%[a]	NA	–	–	–
XXX	–	–	–	–	−0.5	5.6	17.86
XXY	–	–	–	–	−0.6	4	17.86
XYY	–	–	–	–	−0.2	4.6	–
XXYY	–	–	–	–	−0.88	1.92	–
7q11.23 (WBS)	72.7–74.1	−2.09	32	NA	−0.93[b]	30[b]	23[b]
1q21.1 Distal (*CHD1L*)	145.3–147.5	−1.01	1.56	6	−0.08	8.03	3
15q11.2 BP1–BP2	22.7–23.2	−0.6	1.30	1	−0.05	1.80	1
15q11-q13 AS	23.6–28.4	< −4	NA	NA	−1.5[b]	50[b]	12[b]
15q11-q13 PWS	23.6–28.4	−3	NA	NA	−1.5[b]	50[b]	12[b]
16p11.2 Proximal (*TAOK2*)	29.6–30.30	−1.61	9.50	1	−0.81	11.81	12
16p11.2 Distal (*SH2B1*)	28.3 or 28.7–28.9	−0.81	1.73	4	−0.2	1.15	1
22q11.2 (*TBX1*)	18.89–21.9	−1.9	32.37	92	−1.51	3.28	0.15
22q13.33 (*SHANK3*)	Variable	−4.5	∞	1	NA	NA	NA

Genes in parentheses are provided to help recognize the CNV, not because the gene plays a major role in brain phenotypes. Breakpoints for *SHANK3* deletions are variable. ORs from previously published case-control association studies (15,17,27,137–140) and effect sizes on IQ from previously published studies (18,73,136,141–143) are noted.

AS, Angelman syndrome; ASD, autism spectrum disorder; BP, breakpoint; CNV, copy number variant; NA, no data or has not been identified in case control association studies; OR, odds ratio; PWS, Prader-Willi syndrome; SCZ, schizophrenia; WBS, Williams-Beuren syndrome.

[a]For Turner syndrome, there are no ORs and we report the prevalence in %.

[b]No neuroimaging studies were available to include in this review.

conducted one mutation at a time, thus providing a complex catalogue of brain anatomy patterns linked to different genomic loci.

OBJECTIVES

We reviewed the morphometric MRI findings of 20 recurrent CNVs commonly identified in the neurodevelopmental disorder clinic. We aimed at understanding 1) potential general principles of gene dosage on global and regional brain morphometry and 2) what neuroimaging studies of CNVs have taught us about brain dimensions underlying neurodevelopmental psychiatric disorders such as ASD and SCZ.

To do so, we identified and reviewed data from 76 structural MRI studies on 20 CNVs at the 15q11.2, 22q11.2, 1q21.1 distal, 16p11.2 distal and proximal, 7q11.23, 15q11-q13, and 22q13.33 (*SHANK3*) genomic loci as well as aneuploidies of chromosomes X, Y, and 21. This represents the most comprehensive review of neuroimaging studies on rare variants published to date.

METHODS

Eligibility Criteria, Information Source, and Study Selection

A total of 58 genomic variants were selected because of their formal association with ASD or SCZ based on large case-control association studies (5,15,17,24–27). Down syndrome (DS), sex aneuploidies, and 15q11-q13 and 7q11.23 deletions were added because of the link to ASD or because of the extensive number of neuroimaging studies (Table 1). For these 58 variants, neuroimaging articles were selected according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (http://www.prisma-statement.org/) from January 2000 until April 2020 (Figure 1). Search keywords on PubMed included the names of all genomic loci, name of syndrome, and aneuploidy detailed in Table 2. Those search terms were used in combination with the following words: “neuroimaging” OR "brain volume" OR "voxel-based morphometry" OR "surface-based morphometry" OR "cortical thickness" OR "surface area." The 775 studies that resulted from this search went through three screening steps, as detailed in Figure 1. We removed articles without whole-brain analyses and with sample size <12 participants per group of CNVs to provide 80% of power to detect the largest effect sizes for global metrics (*z* score = 1.2).

In the third step, we removed articles reporting findings that could not be included in any of the result sections for one or more reasons: e.g., alternative outcome measures, no explicit data for global measures, no case-control contrast. Finally, the 76 articles on CNVs and aneuploidies listed in Table 2 were included in this review.

Variables

Outcome measures included total brain volume (TBV), mean cortical thickness (Mean-CT), total cortical surface area (Total-SA), and regional gray matter volumes, SA, and CT.

We performed a meta-analysis of the effect size of each CNV on three global metrics (TBV, Mean-CT, and Total-SA) using the R package *rmeta* (R v4.0.2, rmeta package v3.0; R Foundation for Statistical Computing). For this specific analysis on global metrics, we only included studies that explicitly reported sample size and mean and SD for carriers (M_1, SD_1)

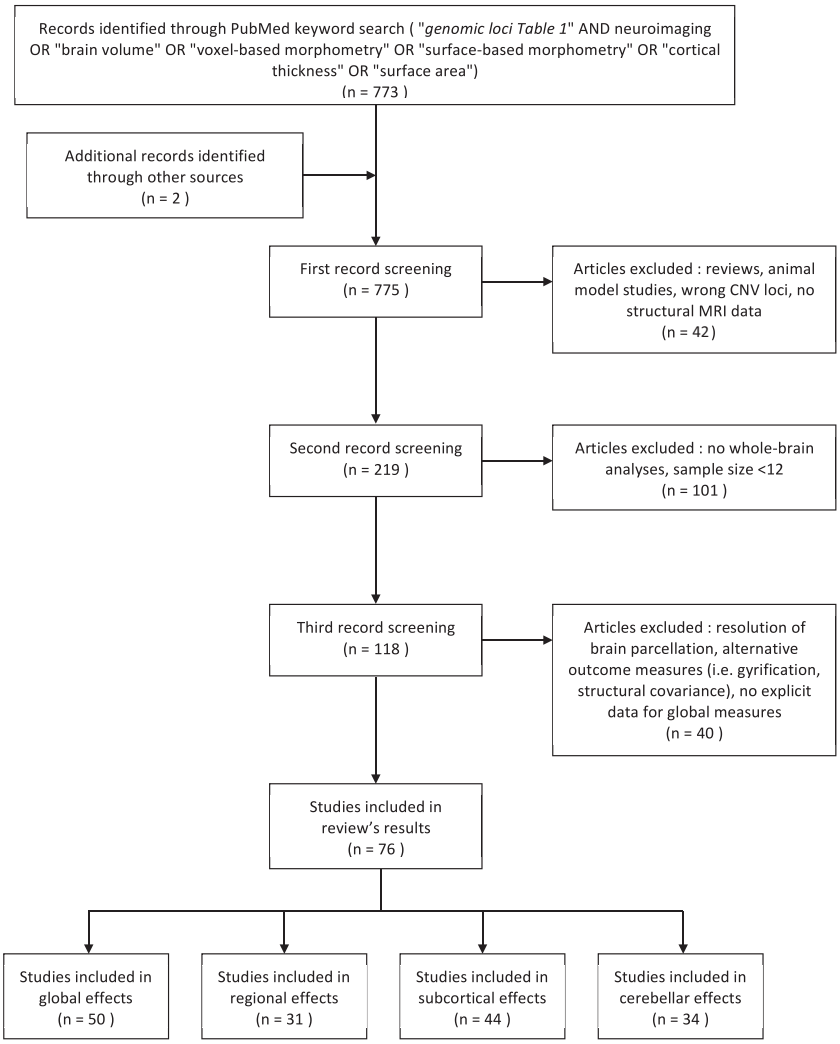

Figure 1. Flow diagram of systematic review according to PRISMA guidelines (144). CNV, copy number variant; MRI, magnetic resonance imaging.

and for noncarriers (M_2, SD_2). For each study, we computed the Cohen's *d*—also known as standardized mean difference—and its 95% confidence interval with the following formula: Cohen's $d = (M_1 - M_2) / SD_{pooled}$ where $SD_{pooled} = \sqrt{((SD_1^2 + SD_2^2)/2)}$. A summary estimate of the effect size of each CNV was calculated as a weighted average of the effects estimated in the individual studies (Figure 2).

Because CNVs have large effects on global metrics, in sections reporting regional cortical, subcortical, and cerebellar effects, we only included studies that adjusted regional effects for global brain metrics, to allow direct comparison. Moreover, given the extensive number of publications on 22q11.2, we decided to add an additional threshold of >50 carriers in order to select only well-powered studies for regional cortical effects.

RESULTS

Global Brain Effects

Meta-analysis showed that almost all reviewed CNVs and aneuploidies altered global brain metrics, but the directionality of their effects varied from one locus to another (Figure 2; Figure S1). Mirror dose responses have been demonstrated for 16p11.2 proximal and 1q21.1 distal CNVs, corroborating previous reports on head size measurements in humans and zebrafish (21,28,29). 22q11.2 and 16p11.2 distal CNVs showed a trend for mirror dose responses, but duplication sample sizes are too small to provide definitive answers (21,30). Additional X chromosomes decreased TBV, while additional Y chromosomes tend to increase TBV (31).

TBV and Total-SA alterations show comparable effect sizes and the same directionality for each given CNV (Figure 2A, B). On the other hand, effects on Mean-CT are inconsistently observed across CNVs (Figure 2C). For instance, mirror gene dosage response for 16p11.2 proximal CNVs was present for TBV and Total-SA but not for Mean-CT (28). Likewise, increasing the dosage of the X chromosome significantly reduced TBV and Total-SA, while Mean-CT was relatively unaltered (31).

These findings may shed light on results published for idiopathic conditions that are clinically more—or equally—severe than most CNVs selected in this review. Individuals

Table 2. Publications Selected for the 20 CNVs-Aneuploidies Included in the Review

Search Keywords	Number of Studies	Studies	Sample Size (Cases and Controls)
Trisomy 21 (Down Syndrome)	12	Pinter JD, *et al.*, 2001 (92)	16 DS, 15 control
		Lee NR, *et al.*, 2016 (93)	31 DS, 45 control
		Carducci F, *et al.*, 2013 (94)	21 DS, 27 control
		Annus T, *et al.*, 2017 (95)	46 DS, 30 control
		Bletsch A, *et al.*, 2018 (96)	26 DS, 23 control
		Menghini D, *et al.*, 2011 (70)	12 DS, 12 control
		Teipel SJ, *et al.*, 2004 (72)	27 DS age correlation
		Koran MEI, *et al.*, 2014 (71)	14 DS, 41 WBS, 82 control
		Carter JC, *et al.*, 2008 (97)	30 DS, 22 control
		Lee NR, *et al.*, 2020 (98)	17 DS with parent-reported sleep problems, 9 DS, 22 control
		Romano A, *et al.*, 2016 (99)	84 DS correlation with age
		Tarui T, *et al.*, 2020 (49)	10 fetuses DS, 12 fetuses control
Chromosome Aneuploidy, Aneuploidy, Klinefelter's Syndrome, Turner Syndrome, XXX, XXY, XYY, XXYY	22	Xenophontos A, *et al.*, 2020 (100)	169 euploid, 132 aneuploid (28 XXX, 58 XXY, 26 XYY, 20 XXYY)
		Nadig A, *et al.*, 2018 (101)	28 XXX, 56 XXY, 25 XYY, 19 XXYY, 79 XY
		Mankiw C, *et al.*, 2017 (102)	28 XXX, 56 XXY, 25 XYY, 19 XXYY, 88 XY
		Fish AM, *et al.*, 2017 (103)	24 XXX, 52 XXY, 26 XYY, 19 XXYY, 5 XXXXY, 65 XX, 73 XY
		Raznahan A, *et al.*, 2016 (31)	28 XXX, 56 XXY, 26 XYY, 20 XXYY, 89 XY
		Reardon PK, *et al.*, 2016 (81)	23 XXX, 38 XXY, 19 XYY, 15 XXYY, 97 XY
		Skakkebæk A, *et al.*, 2013 (69)	65 XXY, 65 XY
		Hanley AP, *et al.*, 2015 (104)	25 XXYY, 92 XY
		Lenroot RK, *et al.*, 2014 (105)	35 XXX, 70 control
		Lentini E, *et al.*, 2013 (106)	38 XXY, 86 control
		Bryant DM, *et al.*, 2011 (107)	31 XXY, 36 control
		Giedd JN, *et al.*, 2007 (108)	42 XXY, 87 control
		O'Donoghue S, *et al.*, 2020 (37)	55 X, 53 control
		Davenport ML, *et al.*, 2020 (57)	26 X, 86 control
		Xie S, *et al.*, 2015 (109)	34 X, 21 control
		Hong DS, *et al.*, 2014 (38)	42 X, 31 XXX, 56 control
		Lepage J-F, *et al.*, 2013 (40)	40 X, 27 control
		Lepage J-F, *et al.*, 2013 (110)	46 X, 45 control
		Bray S, *et al.*, 2011 (41)	30 X, 15 control
		Marzelli MJ, *et al.*, 2011 (111)	13 X, 13 control
		Raznahan A, *et al.*, 2010 (112)	24 X, 19 control
		Good CD, *et al.*, 2003 (113)	21 X, 42 control
7q11.23, WBS, Williams Syndrome	9	Green T, *et al.*, 2016 (56)	44 WBS, 49 control
		Meda SA, *et al.*, 2012 (114)	31 WBS, 50 control
		Menghini D, *et al.*, 2011 (70)	12 WBS, 13 control
		Sampaio A, *et al.*, 2010 (115)	15 WBS, 13 control
		Campbell LE, *et al.*, 2009 (116)	15 WBS, 15 control
		Chiang M-C, *et al.*, 2007 (117)	41 WBS, 39 control
		Reiss AL, *et al.*, 2004 (118)	43 WBS, 40 control
		Pinter JD, *et al.*, 2001 (92)	14 WBS, 14 control
		Fan CC, *et al.*, 2017 (66)	22 WBS, 16 control
1q21.1 Distal	2	Sønderby IE, *et al.*, 2021 (36)	33 deletion, 25 duplication, 37,917 control
		Modenato C, *et al.*, 2020 (29)	29 1q21.1 deletion, 19 1q21.1 duplication, 72 15q11.2 deletion, 76 15q11.2 duplication, 83 16p11.2 deletion, 73 16p11.2 deletion, 74 22q11.2 deletion, 22 22q11.2 duplication, 331/965 control
15q11.2	2	van der Meer D, *et al.*, 2020 (47)	203 deletion, 306 duplication, 45247 control
		Modenato C, *et al.*, 2020 (29)	29 1q21.1 deletion, 19 1q21.1 duplication, 72 15q11.2 deletion, 76 15q11.2 duplication, 83 16p11.2 deletion, 73 16p11.2 deletion, 74 22q11.2 deletion, 22 22q11.2 duplication, 331/965 control

Table 2. Continued

Search Keywords	Number of Studies	Studies	Sample Size (Cases and Controls)
16p11.2	6	Cárdenas-de-la-Parra A, *et al.*, 2019 (50)	56 deletion, 19 duplication, 105 control
		Martin-Brevet S, *et al.*, 2018 (28)	78 deletion, 71 duplication, 212 control
		Hippolyte L, *et al.*, 2016 (64)	14 deletion, 17 duplication, 23 control
		Qureshi AY, *et al.*, 2014 (58)	25 deletion, 17 duplication, 62 control
		Maillard AM, *et al*., 2015 (119)	14 deletion, 17 duplication, 23 control
		Modenato C, *et al.*, 2020 (29)	29 1q21.1 deletion, 19 1q21.1 duplication, 72 15q11.2 deletion, 76 15q11.2 duplication, 83 16p11.2 deletion, 73 16p11.2 deletion, 74 22q11.2 deletion, 22 22q11.2 duplication, 331/965 control
16p11.2 Distal	1	Sønderby IE, *et al.*, 2020 (21)	12 deletion, 12 duplication, 6882 control
22q11.2	16	Sun D, *et al.*, 2020 (48)	386 deletion, 315 control
		Lin A, *et al.*, 2017 (30)	66 deletion, 21 duplication, 56 control
		Eliez S, *et al.*, 2001 (120)	18 deletion, 18 control
		Gudbrandsen M, *et al.*, 2019 (121)	62 deletion, 57 control
		Campbell LE, *et al.*, 2006 (122)	39 deletion, 26 control
		Jalbrzikowski M, *et al.*, 2017 (51)	116 deletion, 55 control
		Shashi V, *et al.*, 2010 (123)	22 deletion, 16 control
		Antshel KM, *et al.*, 2008 (124)	92 deletion, 59 control
		Ching CRK, *et al.*, 2020 (22)	533 deletion, 330 control
		Gothelf D, *et al.*, 2011 (61)	19 deletion, 18 control longitudinal
		Kates WR, *et al.*, 2011 (53)	44 deletion, 25 control
		Chow EWC, *et al.*, 2011 (125)	29 deletion, 34 control
		Ramanathan S, *et al.*, 2017 (54)	75 deletion, 60 control longitudinal
		Schaer M, *et al.*, 2010 (126)	27 deletion patients with congenital heart disease, 26 deletion patients with cardiac normal status, 80 control
		Bearden CE, *et al.*, 2009 (59)	21 deletion,13 control
		Modenato C, *et al.*, 2020 (29)	29 1q21.1 deletion, 19 1q21.1 duplication, 72 15q11.2 deletion, 76 15q11.2 duplication, 83 16p11.2 deletion, 73 16p11.2 deletion, 74 22q11.2 deletion, 22 22q11.2 duplication, 331/965 control
22q13.33 (*SHANK3*)	2	Liu C, *et al.*, 2021 (127)	14 *SHANK3* deletion, 26 ASD, 32 control
		Jesse S, *et al.*, 2020 (128)	12 *SHANK3* deletion, 14 control
15q11-q13, 15q11-13, PWS, AS	2 AS	Yoon HM, *et al.*, 2020 (129)	14 AS, 28 control
		Aghakhanyan G, *et al.*, 2016 (130)	16 AS, 21 control
	5 PWS	Azor AM, *et al.*, 2019 (131)	20 PWS, 40 control
		Manning KE, *et al.*, 2018 (132)	20 PWS, 40 control
		Lukoshe A, *et al.*, 2013 (133)	12 PWS deletion, 12 PWS maternal uniparental disomy, 11 control
		Honea RA, *et al.*, 2012 (134)	15 PWS deletion, 8 PWS maternal uniparental disomy, 25 control
		Ogura K, *et al.*, 2011 (135)	12 PWS, 13 control

38 CNVs With No or Insufficient Data: 7q11.23 duplication; 15q11.2-13.1 duplication; 2p16.3 (*NRXN1*) deletion; 3q29 deletion; 15q13.3 deletion; 16p13.11 deletion and duplication; distal Xq28 duplication; 9q24.3 *DMRT1* deletion and duplication; 8q22.2 *VPS13B* deletion; 7q36.3 *VIPR2 WDR60* deletion and duplication; 16p12.1 deletion; 1p36.33 duplication; 9p24.2 (*SLC1A1*) deletion; 15q21.3 (*CGNL1*) duplication; 17q12 deletion; 17p12 deletion; 10q11.21q11.23 duplication; 2q11.2 deletion; 16p13.2 duplication; 16q23.3 (*CDH13*) deletion; 15q13.2-q13.3 deletion and duplication; 4p16.3 duplication; 2q11.2 deletion; 2q12.2-q12.3 deletion; 2q21.1 deletion; 13q12.12 deletion; 15q13.1-q13.2 deletion and duplication; 15q13.3 deletion and duplication; 15q24 duplication; 17p11.2 deletion and duplication; 17q11.2 duplication

CNVs with no or insufficient neuroimaging data include all CNVs with studies including <12 cases or no structural neuroimaging studies.
AS, Angelman syndrome; ASD, autism spectrum disorder; CNV, copy number variant; DS, Down syndrome; PWS, Prader-Willi syndrome; WBS, Williams-Beuren syndrome.

with SCZ have decreased TBV and Total-SA with small effect sizes (Cohen's d = −0.12 and −0.25, respectively). In the largest meta-analyses of ASD, Total-SA and TBV were slightly increased (Cohen's d = 0.08 and 0.11, respectively) (32). The small effects in idiopathic conditions likely reflect etiological and mechanistic heterogeneity. On the other hand, Mean-CT is increased in ASD (Cohen's d = 0.22 and 0.41 in two recent large studies) (32,33) and decreased in SCZ (Cohen's d = −0.53) (34) with moderate effect sizes similar to those found for CNVs.

Regional Effects on the Cortex

Because large global effects have profound consequences on regional measures (Figure 3A), we only considered regional findings adjusted for global effects in the following sections

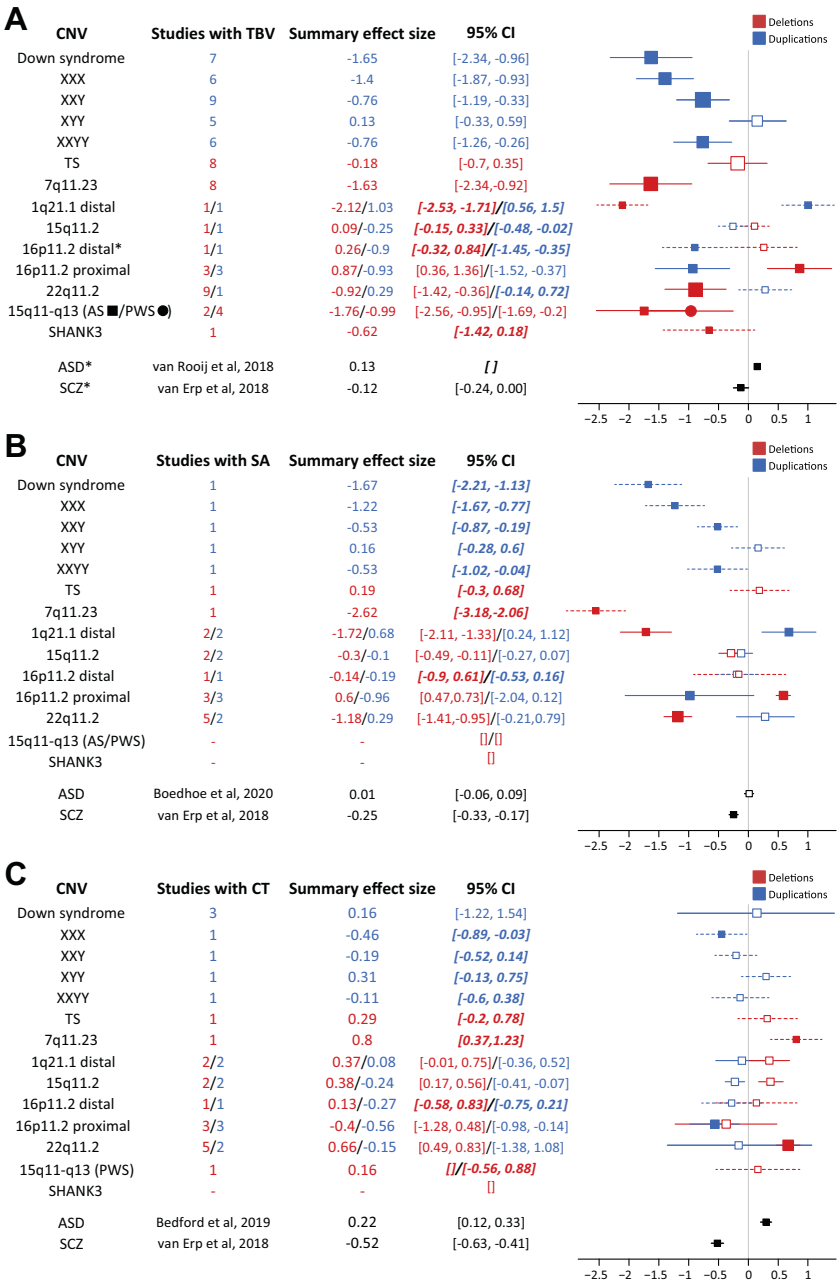

Figure 2. Forest plots of the summary estimates from the meta-analyses of the effects of 20 copy number variants (CNVs)—as well as idiopathic autism spectrum disorder (ASD) and schizophrenia (SCZ)—on three global metrics: **(A)** total brain volume (TBV), **(B)** total surface area (SA), and **(C)** mean cortical thickness (CT). Summary estimates of the effect size of each CNV were derived from meta-analyses including all neuroimaging studies reporting TBV, total SA, and mean CT data, respectively (see Table 2 and Figure S1). Data for idiopathic ASD and SCZ were obtained from the largest studies to date (32–34). 95% confidence intervals (CIs) provided by the meta-analyses are presented as solid error bars, whereas CNVs with only one available study show the 95% CI from that particular study as dotted error bars, together with bold italic font in the 95% CI column. The size of the square is proportional to the number of studies reporting data. Filled squares correspond to statistically significant effect sizes. CNV deletions are depicted in blue, duplications are depicted in red, and data on idiopathic psychiatric conditions are depicted in black. *Intracranial volume instead of TBV. AS, Angelman syndrome; PWS, Prader-Willi syndrome; TS, Turner syndrome.

(cortical, subcortical, and cerebellar results). All CNVs included in this review impact regional cortical volume, CT, or SA (Figure 3B). CNVs associated with the largest effect sizes on cognition (DS, 22q11.2, 7q11.23, and deletions overall) (18) show the highest proportion of significantly altered regions. CNVs without formal association to disease (15q11.2 or 16p11.2 distal duplications) show few or no alterations. There are no obvious patterns recurrently observed across all CNVs, but some regions appear to be more frequently affected: insula, cingulate, dorsolateral prefrontal cortex, inferior frontal gyrus, orbitofrontal cortex, supplementary motor cortex, postcentral gyrus, superior parietal area, fusiform gyrus, and superior temporal area. The few studies reporting Cohen's *d* for regional alterations showed moderate-to-large effect sizes (absolute Cohen's *d* ranging from 0.5 to 1.3 in 16p11.2 proximal and 22q11.2) (29,30,35,36), which is in stark contrast with the small effects (absolute Cohen's $d \leq 0.20$) (32,34) in SCZ and ASD.

Subcortical and Cerebellar Effects

Subcortical structures are invariably affected by CNVs with seemingly distinct patterns. Duplications mainly decrease

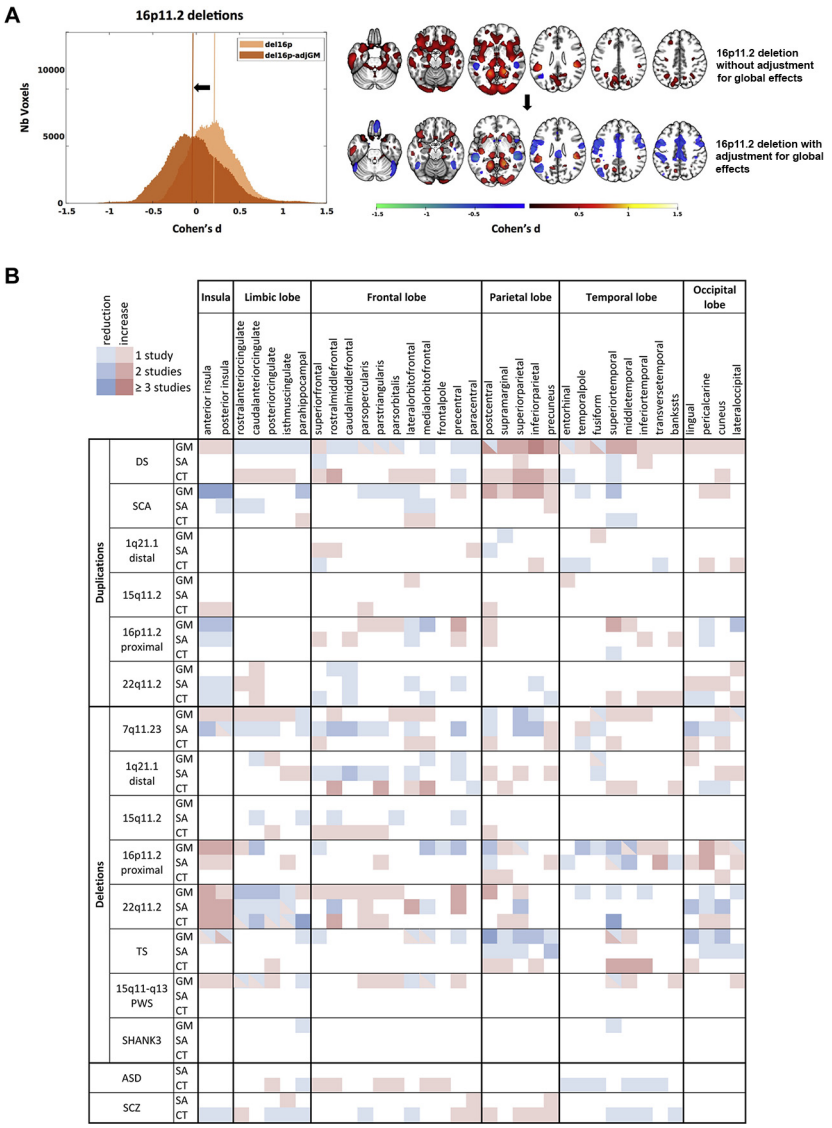

Figure 3. Impact of global effects on regional findings and regional cortical alterations adjusted for global effects (total brain volume/intracranial volume, total surface area, or mean cortical thickness) and summarized by cortical lobe. **(A)** Example of the impact of global effect on regional results: contrast between 16p11.2 deletions and control. On the left side, the density plots show the distribution of Cohen's *d* for all gray matter (GM) voxels before and after global adjustment for total GM volume. On the right, brain maps showing Cohen's *d* values surviving familywise error before (top) and after (bottom) adjustment for total GM volume. **(B)** Findings for each copy number variant are reported for three neuroimaging measures: GM volume, surface area (SA), and cortical thickness (CT). Blue indicates a reported decrease, while red indicates a reported increase. A darker color corresponds to an increasing number of studies reporting the same result. Triangles represent conflicting results. Data for 16p11.2 distal have not been published, and no adjusted data are available on 15q11-q13 Angelman syndrome. Data for autism spectrum disorder (ASD) and schizophrenia (SCZ) are from published meta-analyses (32,34). DS, Down syndrome; SCA, sex chromosome aneuploidy (XXX, XXY, XYY, XXYY); PWS, Prader-Willi syndrome; TS, Turner syndrome.

subcortical volumes (relative to intracranial volume [ICV]) and predominantly affect the striatum as well as the hippocampus. Deletions may affect subcortical structures more broadly. While both negative and positive moderate-to-large effects are observed across subcortical structures in CNVs, ASD and SCZ show exclusively negative small effects (Figure 4).

The cerebellum, predominantly the vermis lobule VIII to X and cerebellar cortex, was largely affected in CNV carriers: reductions are reported in most of the findings on duplications (DS, sex chromosome aneuploidy [XXY], 1q21.1 distal, 15q11.2) (37–40). In the deletions, some mirror increases in cerebellar volumes were observed (1q21.1 distal, Turner syndrome, and 7q11.23) whereas 16p11.2 proximal and 22q11.2 deletions showed a decreased volume of cerebellum (relative to ICV) (37–41). Reported effect sizes do not go beyond Cohen's $d = 1$.

While one study demonstrated a decrease in cerebellar volume in SCZ (42), the largest, most recent meta-analysis in ASD did not identify clear effects on the cerebellum (43).

Sex- and Age-Related Effects

Sex is a major factor influencing the way neurodevelopmental disorders present. An excess in males has been observed in ASD, intellectual disabilities, speech and language disorders, and attention-deficit/hyperactivity disorder (44). Overall, females are less likely to be referred to the clinic compared with males with the same genetic variants (45): e.g., there is a 2:1 male-to-female ratio for 16p11.2 proximal CNV carriers in the clinic (45,46) and an overrepresentation of deleterious CNVs in females compared with males with neurodevelopmental symptoms (45). In this review, about 20% of the selected studies investigated sex-related effects but were often

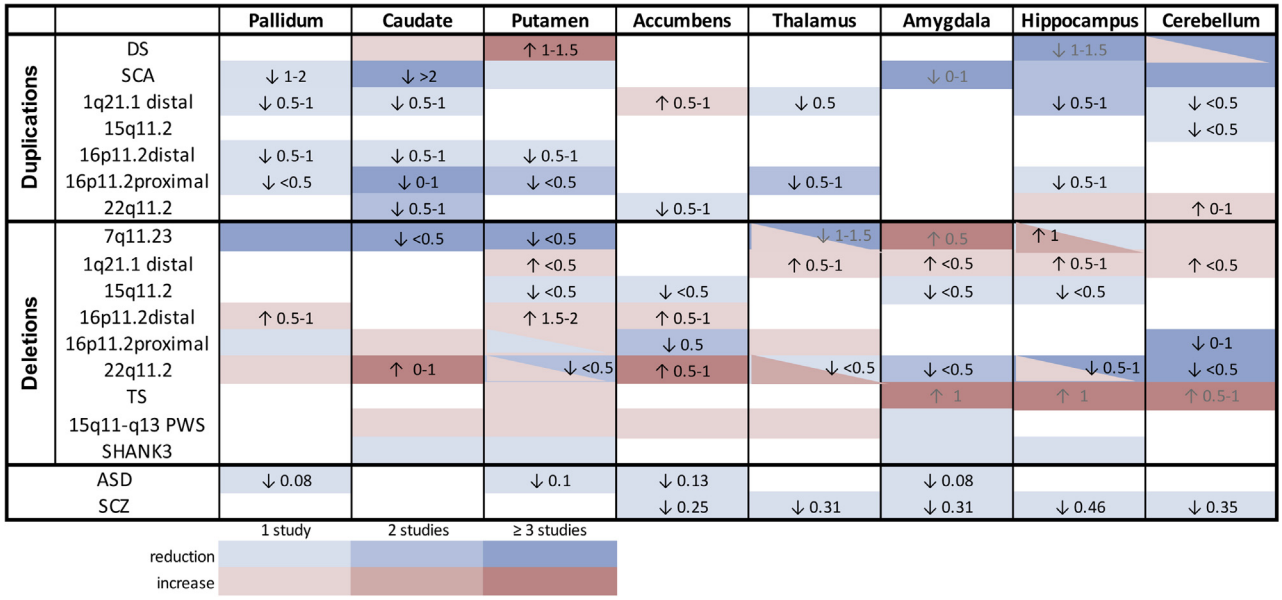

Figure 4. Volumetric alterations adjusted for global effects (total brain volume/intracranial volume, total cortical surface area, or mean cortical thickness) in subcortical and cerebellar structures. Blue and red indicate a reported significant decrease or increase, respectively, relative to control subjects (no distinction is made between right and left hemisphere results). A darker color represents more studies reporting the same result. Ranges of effect sizes (Cohen's *d*) are noted in the cells when reported and are written in gray when they are computed from the raw mean and SD values (not adjusted for total brain volume). Arrows indicate the direction of the effect (↓decrease; ↑increase), while triangles represent conflicting results. No adjusted data were available on 15q11-q13 Angelman syndrome. Data for autism spectrum disorder (ASD) and schizophrenia (SCZ) are from published meta-analyses, and exact effect sizes are reported (32,34,42). DS, Down syndrome; PWS, Prader-Willi syndrome; SCA, sex chromosome aneuploidy (XXX, XXY, XYY, XXYY); TS, Turner syndrome.

underpowered to do so, and none of the large datasets (e.g., 22q11.2, 15q11.2, and 16p11.2 studies) reported any effects (28,47,48), indicating that the sex bias observed in the neurodevelopmental disorder clinic (45) may not be linked to differences at the level of brain structure.

Adjusting for complex nonlinear age trajectories is a major challenge in neuroimaging research. Cohorts of individuals with rare genetic variants often have a broad age range and rarely include sufficient number of noncarrier control subjects to accurately model age effects. On the other hand, these cohorts offer unique opportunities to study the effects of the same molecular mechanisms across broad neurodevelopmental periods. Currently, age-related neuroimaging effects identified in children, adolescents, and adults ascertained for a clinical diagnosis such as ASD could instead reflect the shifting diagnostic criteria during the last decades.

For SA and cortical volumes, data suggest that CNV-associated alterations appear early on. Cortical, subcortical, and cerebellar growth trajectories are decreased in DS during the third trimester of pregnancy, and decreased cerebellar volume was reported as early as the second trimester (49). For 22q11.2 and 16p11.2 proximal deletions, neuroimaging alterations have been reported in individuals as young as 4.5 years of age (50–52) and do not seem to be influenced by age through adolescence and young adulthood (28,48,50,53,54), except for subcortical volumes for the 22q11.2 deletion carriers (22). Interestingly, MRI studies on 16p11.2 proximal deletion mice models have identified volume alterations in the insula and striatum at 7 days postnatal, equivalent to the human prenatal period (55). Similarly, 7q11.23 deletion carriers had smaller SA compared with control subjects in most brain regions—in both children and adults—suggesting that early reductions in SA may be driving the overall reduction in brain volume (56). In Turner syndrome, decreased gray matter volumes in premotor, somatosensory, and parieto-occipital cortex were already present at 1 year of age, suggesting a stable phenotype with origins in the prenatal or early postnatal period (57). In contrast, CT studies suggest that normative patterns of age-related thinning may be disrupted in some CNVs. 16p11.2 proximal duplication carriers showed a trend toward accelerated cortical thinning visible around 40 years of age in comparison with control subjects (58). Increased CT observed in adult 7q11.23 deletion carriers has been interpreted as delayed maturation (56). In 22q11.2 deletion, an overall thicker cortex appears to be associated with accelerated cortical thinning in the prefrontal and posterior regions (52,59,60). This may be driven by an increased proportion of 22q11.2 deletion carriers with psychosis (associated with decreased CT) in the older age groups (54,61,62).

LINKING NEUROIMAGING, COGNITION, AND BEHAVIOR

CNVs have moderate-to-large effect sizes on cognitive and behavioral effects, which are robust across studies. Early findings have highlighted remarkable phenotypic profiles such as social disinhibition, excessive empathy, and nonsocial anxiety described in Williams-Beuren syndrome (7q11.23 deletion) (63) as well as child apraxia of speech in 16p11.2 proximal deletion (64). With the growing number of CNVs under

investigation, data are also showing common effects. As an example, shared variance of behavioral impairments in 1q21.1 distal, 2p16.3, *NRXN1*, 9q34, Kleefstra syndrome, 15q11.2, 15q13.3, 16p11.2, and 22q11.2 CNVs appears much higher than variance explained by each CNV (65).

Do Brain Alterations Mediate Effects on Cognition and Behavior?

As opposed to idiopathic conditions, CNV effect sizes are similar across cognitive, behavioral, and neuroimaging alterations. The latter could imply that neuroimaging features may mediate cognitive and behavioral phenotypes. Preliminary analyses suggest that neuroimaging phenotypes may mediate some of the robust associations between CNVs and cognition. Neuroimaging features associated with 15q11.2 deletion may mediate between 4% and 10% of the cognitive effects of this CNV (47). Similarly, alterations of Total-SA and ICV accounted for 5% to 17% of some cognitive deficits in 1q21.1 distal carriers (36). In Williams-Beuren syndrome, a study on 22 CNV carriers suggested that the neuroanatomical profile mediated cognitive impairments and hypersociability (66). A study in 49 unaffected individuals carrying 12 different SCZ-associated CNVs suggested that the relationship between SCZ-CNVs and fluid intelligence was partially mediated by CNV-associated subcortical alterations (67). In the above-mentioned findings, the brain–cognition relationship showed the same directionality in CNVs and control groups. This is not always the case, as exemplified by 1q21.1 distal duplication and 16p11.2 proximal deletion that are both associated with increased TBV and SA while decreasing cognitive performance. The opposite albeit small relationship is observed in the general population (68), possibly explained by mechanisms affecting cognition with opposing effects on TBV and total SA. Likewise, many underpowered studies have reported similar deviations from normative brain–cognition association (28,30,69–73). Larger samples are required to confirm and further characterize these observations.

Neuroimaging Differences May Correlate With Phenotypic Variance Within CNV Groups

Although 22q11.2 deletion carriers show thicker cortex than control subjects, carriers with psychosis have a thinner cortex relative to carriers without psychosis. Effect sizes for regional CT alterations in 22q11.2 individuals with psychosis versus those without were significantly correlated with regional CT and subcortical alterations in idiopathic SCZ versus control subjects (22,48). These studies suggest that the additional brain differences present in 22q11.2 individuals with psychosis (compared with 22q11.2 individuals without psychosis) are similar to those associated with idiopathic psychiatric conditions. In other words, mechanisms associated with idiopathic SCZ are also present in 22q11.2 deletion carriers who develop SCZ. This may be partially explained by the higher polygenic risk for SCZ identified in groups of CNV carriers (in particular 22q11.2 deletions) with an SCZ diagnosis compared with carriers without SCZ (74,75). Whether this applies to other CNVs or other diagnoses—such as ASD—remains to be demonstrated.

QUESTIONS RAISED BY IMAGING RESULTS

Global Effects

CNVs have well-established and pervasive effects on TBV and Total-SA, which is in line with the highly polygenic nature of SA (76). Dosage effects on TBV and Total-SA have been interpreted as evidence of abnormal neurogenesis (77), presumably involving genes implicated in the control of cell size and proliferation (78–80). The seemingly differential effects of CNVs on SA and CT support recent genome-wide association studies (76) indicating that distinct neurodevelopmental mechanisms affect cortical SA expansion and CT increase.

Interestingly, the effect sizes on global brain metrics appear to be disconnected from the number of genes encompassed in CNVs, their intolerance to loss of function, and symptoms severity. Under additive assumptions, one may expect that very large CNVs encompassing many dosage-sensitive genes would have extreme impacts on global metrics (e.g., 3 or 4 SDs) similar to effects on cognition, but this is not the case: e.g., DS and 1q21.1 distal CNVs have similar effect sizes on TBV but encompass approximately 200 and 16 genes (50 and 2 dosage-sensitive genes), respectively, and have vastly different cognitive outcomes. The same observation holds for CNVs with similar effects on global brain metrics but with vastly different risk for SCZ (ORs were 60, 10, and 4 for 22q11.2, 16p11.2, and 1q21.1 distal, respectively) (15). It is plausible that large polygenic CNVs encompass genes with positive and negative effects on global metrics, thus cancelling out each other's effects. Alternatively, such CNVs may contain no gene modulating brain volume.

Regional Effects Are Independent From Global Effects

CNVs show a dissociation between global and regional effect sizes on brain morphometry. 1q21.1 distal deletion and duplication exemplify the contrast between very large global effects and smaller regional effects once adjusted for global measures. Dissociation is also observed between the directionalities of global and regional effects: deletions at the 22q11.2, 16p11.2 proximal, 1q21.1 distal, and 15q11.2 loci are associated with decreased cingulate and supplementary motor cortex volumes irrespective of their directional effects on TBV. Thus, global and adjusted regional effects might be mechanistically distinct as suggested by recent studies (29,35). Our review also highlights the heterogeneity of methods used across studies to adjust for global metrics: linear, allometric (81) using TBV, ICV, Total-SA, or Mean-CT as covariates. Some studies provide no adjustment at all, which may lead to inflation or cancellation of regional effect sizes.

General Principles of Gene Dosage at the Regional Level

An important question raised by the CNV literature is whether they lead to similar behavioral and cognitive phenotypes via numerous or a limited number of brain mechanisms. A cross-CNV study in unaffected CNV carriers suggested that SCZ-associated CNVs at seven genomic loci were associated

with subcortical and cortical alterations resembling those previously associated with idiopathic SCZ (67,82). However, there was substantial heterogeneity across the effects of CNVs, suggesting different neurobiological gateways into SCZ. A recent study of six CNVs and aneuploidies also suggested a relatively specific association between neuroimaging alterations and spatial patterns of gene expression in the brain (83).

A recent multivariate analysis of eight CNVs (deletions and duplications at the 22q11.2, 16p11.2 proximal, 1q21.1 distal, and 15q11.2 loci) in 484 carriers and 1296 control subjects identified the cingulate gyrus, insula, supplementary motor cortex, and cerebellum as top regions contributing to shared alterations across the 8 CNVs (29). However, mechanisms underlying the relationship between genomic variants and global or regional MRI alteration are largely unknown. A recent study suggested that the spatial patterning of altered brain anatomy in CNVs and aneuploidies is organized according to the spatial distribution of gene expression in the adult brain. Brain developmental trajectories of gene expression may also provide important clues. As such, heritability partitioning showed that prenatally expressed genes preferentially impact cortical surface, while thickness is mostly influenced by postnatally expressed genes (76). To date, the limited number of CNVs with MRI data limits the feasibility of such analyses associating gene function and large-scale network alterations.

Ascertainment and Methodology Bias

Neuroimaging phenotypes have typically only been investigated in the most frequent recurrent CNVs, which represents a minuscule fraction of the diverse landscape of deleterious CNVs diagnosed in individuals referred for neurodevelopmental disorders.

Ascertainment biases and reverse causality are concerns regularly raised in CNV studies. Specifically, in clinically referred CNV carriers, neuroimaging features thought to be associated with CNVs may in fact be associated with other factors related to ASD and SCZ. For specific CNVs, this question was addressed by showing that neuroimaging findings 1) are similar in clinically and nonclinically ascertained individuals (29), 2) are mainly unchanged after excluding CNV carriers with diagnoses (28,48), 3) are present in individuals before the onset of symptomatology (50), and 4) have much larger effect sizes than those observed in psychiatric conditions. Importantly, data collection is not possible in carriers with the most severe behavioral symptoms owing to the requirement of staying still during scanning protocols.

Other biases are related to the history of method development. As an example, many DS studies were conducted during a period when voxel-based methods were more frequently used, while surface-based methods were mainly used in more recent CNV investigations.

Studies selected in this review have adopted disparate processing, analytical methods, and statistical models. A meta-analysis on global measures was possible, but sufficient data for a meta-analysis on regional neuroanatomical measures were not available. The field needs to adopt standard algorithms, systematic adjustments for covariates, and guidelines for reporting effect sizes. Moreover, the characterization of the potentially complex effects of CNVs on CT maturation will require the integration of large normative datasets as well as large control groups (50).

Neurobiological Interpretation of Morphometry Results

T1-weighted imaging is a potential major source of variability among morphometric studies. Independent from the methods used for feature extraction and statistical analysis, e.g., surface or voxel based, the contrast is reliant on the underlying brain tissue properties that T1-weighted MRI protocols do not capture. Advances in quantitative MRI sensitive to myelin, iron, and tissue free water content provide a window of opportunity to assess in vivo specific tissue properties in the healthy and in the diseased brain (84,85). Recent evidence about the occasional misinterpretation of the nature and directionality of morphometric changes is given in the context of brain maturation (86) and aging (85,87). Multivariate analyses of multimodal protocols should improve our understanding of the underlying tissue properties and microstructural alterations of neuroimaging findings summarized in this review.

PERSPECTIVE AND FUTURE DIRECTIONS

Neuroimaging for rare genomics variants is still in its infancy. Although greatly improved, sample sizes, and thus power, are still a major issue, preventing stratification, testing for interactions, and conducting genome-wide analyses. Although neuroimaging findings have been well replicated in the most frequently studied CNVs (e.g., 22q11.2, 16p11.2 proximal), robustness needs to be demonstrated for the more recently studied variants. Sources of combined neuroimaging and CNV data are scarce and are obtained either through studies scanning individuals with rare variants or from cohorts with neuroimaging and genotyping data allowing CNV detection. Large-scale initiatives such as ENIGMA-CNV (Enhancing NeuroImaging Genetics through Meta-Analysis CNV) will certainly help increase power by collation of smaller datasets but often lack phenotypic depth/information. Likewise, access to large cohorts such as the UK Biobank (88) and Adolescent Brain Cognitive Development Study (89) will lead to exciting developments, but individuals with significant psychopathology and carrying large-effect variants are significantly underrepresented in these datasets (18). The most viable strategy remains, in parallel, to recruit individuals selected on the basis of a broad spectrum of 1) cognitive and behavioral symptoms and 2) deleterious genomic variants from the genetic clinic. Such developmental psychiatric/genetic-first datasets would provide a 20- to 100-fold enrichment in deleterious variants in comparison with unselected populations (17,18).

With the availability of exome and whole-genome data, the rare genomic variant neuroimaging field needs a roadmap to transition from candidate genes to whole-genome discovery studies. Although sample sizes will not allow gene-based association studies in the near future, function-based genome-wide association studies could be conducted by partitioning and scoring rare variants based on gene functions and pathways. Such analytical strategies have been used successfully for the investigation of CNV effects on cognition (90,91) and risk for ASD (17), but they imply some level of functional

convergence (i.e., CNVs encompass genes with similar functional annotation that also show similar alterations at the neuroimaging level). Such an approach would provide insight into mechanisms linking microscale variation to macroscale brain network alterations.

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