Supplementary Materials, Methods, and Results

Title: Brain functional connectivity mirrors genetic pleiotropy in psychiatric conditions

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Supplementary Materials and Methods

Cohorts

SFARI SimonsVIP-dataset

Copy number variants (CNV) carriers were clinically ascertained. Imaging data of 16p11.2 CNV carriers and typically developing controls were acquired by the Simons variation in individuals project (VIP) consortium [1] across 2 sites. We excluded 50 individuals from the analysis due to the insufficient quality of the imaging data. The final 16p11.2 sample includes 146 individuals: 16p11.2 deletion (n=25) and duplication (n=26) carriers, 1q21.1 deletion (n=7) and duplication (n=4) carriers, and extrafamilial controls (n=84). Over 90% of the deletion carriers and 69% of the duplication carriers met the criteria for at least one clinical psychiatric diagnosis. Control subjects were recruited from the general population (extra-familial subjects) and had no major DSM-V diagnosis. The 16p11.2 duplication group includes 2 individuals with a triplication.

UCLA 22q11.2-dataset

CNV carriers were clinically ascertained. Imaging data of 22q11.2 CNV carriers and typically developing (TD) controls were acquired at the University of California, Los Angeles (UCLA). Patients were ascertained from the UCLA or Children's Hospital, Los Angeles Pediatric Genetics, Allergy/Immunology and/or Craniofacial Clinics. Demographically comparable TD comparison subjects were recruited from the same communities as patients via web-based advertisements and by posting flyers and brochures at local schools, pediatric clinics, and other community sites. Exclusion criteria for all study participants included significant neurological or medical conditions (unrelated to 22q11.2 mutation) that might affect brain structure, history of head injury with loss of consciousness, insufficient fluency in English, and/or substance or alcohol abuse or dependence within the past 6 months. The UCLA Institutional Review Board approved all study procedures and informed consent documents. Scanning was conducted on an identical 3 T Siemens Trio MRI scanner with a 12-channel

head coil at the University of California at Los Angeles Brain Mapping Center or at the Center for Cognitive Neuroscience [2]. We excluded 25 individuals from the analysis due to the insufficient quality of the imaging data. The final 22q11.2 sample includes 22q11.2 BPA-BPD deletion (n=43) and BPA-BPD duplication (n=10) carriers and extrafamilial controls (n=43).

Montreal rare genomic disorder family dataset (MRG)

Cognitive and behavioral measures were collected in families with at least one child who carries a CNVs classified as pathogenic or VUS (variation of uncertain significance). CNV carriers and their first-degree relatives were ascertained neurodevelopmental disorder clinic at the Sainte Justine Montreal hospital, Quebec-Canada (MP-21-2016-946, 4165). The characteristics of this cohort reflect the criteria for Chromosomal microarray testing in the neurodevelopmental disorder clinic which include: intellectual disabilities, learning disabilities, autism spectrum disorder (ASD) as well as children with several comorbidities including attention deficit hyperactivity disorder (ADHD), speech and language disorders and developmental coordination disorders. The same assessments performed on first-degree relatives (carriers and non-carriers) allow adjusting for the effect of the additional genetic and environmental background. All the MRI scans have been performed at the Montreal Neurological Institute using the same scanner (Prisma 3T). The acquisition time for the resting-state sequence was 7 minutes. The neuroimaging protocol was designed by John D. Lewis and is available online: http://www.bic.mni.mcgill.ca/users/jlewis/BrainCanada/MCIN/

Data from this cohort include 16p11.2 deletion (n=7) and duplication (n=3) carriers, 1q21.1 deletion (n=5) and duplication (n=1) carriers, 15q11.2 (n=1) duplication carrier, 22q11.2 (n=1) duplication carrier, and intrafamilial controls (n=47) after exclusion of 16 individuals due to quality control criteria.

Cardiff DEFINE-dataset

The Cardiff CNV cohort was supported by the Wellcome Trust Strategic Award "DEFINE" and the National Centre for Mental Health with funds from Health and Care Research Wales. CNV carriers were clinically ascertained. MRI data were acquired on a 3 Tesla General Electric HDx MRI system (GE Medical Systems, Milwaukee, WI) using an eight-channel receive-only head RF coil (as described

in [3]). The acquisition time for functional resting-state data was 7 minutes. Following parameters have been used: Repetition Time = 2000 ms, Echo time = 35 ms, Slice Thickness = 3.4 mm (eyes open, fixation cross). The full protocol has been developed for the 100 brains project. 16p11.2 deletion (n=1) carrier, 1q21.1 deletion (n=3) and duplication (n=1) carriers, 15q11.2 (n=1) deletion carrier, 22q11.2 (n=1) duplication carrier, and extrafamilial controls (n=8) were included after the exclusion of 4 individuals due to quality control criteria.

Idiopathic ASD dataset - ABIDE

The ABIDE dataset [4,5] is an aggregate sample of different studies including imaging and behavioral data for individuals with an ASD diagnosis and typically developing peers matched for age. Due to the small number of females in the ABIDE dataset, we excluded female individuals. To better account for biases in connectivity estimation due to differences in recording sites, subject age, and scanner motion, we created age and motion-matched subsamples for each recording site in ABIDE of individuals that passed our quality control criteria. We then excluded recording sites with fewer than 20 individuals (10 ASD, 10 controls). Our final ABIDE sample thus includes 943 male individuals, 472 individuals with ASD, and 471 healthy controls, from 28 recording sites.

Idiopathic schizophrenia dataset

We used fMRI data retrospectively aggregated from 10 distinct sites and studies. Brain imaging multi-state data were obtained through either the SchizConnect and OpenfMRI data sharing platforms (http://schizconnect.org [6]; https://openfmri.org [7]) or local scanning at the University of Montréal. All patients were diagnosed with schizophrenia (SZ) according to DSM-IV or DSM-V criteria, as a function of the time of the study. Sites samples were obtained after subjects were selected in order to ensure even proportions of SZ patients and controls within each site (from N = 9 to N = 42 per group) and to reduce between-group differences with regards to gender ratio (74% vs. 75% males in patients and controls, respectively), age distribution (34 vs. 32 years old on average) and motion levels (averaged frame displacement: 0.16 vs. 0.14 mm). Such matching of SZ and control subjects was achieved based on propensity scores. In total, we retained 242 SZ patients and 242 healthy controls in statistical analyses.

Depending on the study, positive and negative symptoms were assessed with either the Positive and negative syndrome scale (PANSS,[8]) or the Scales for the assessment of positive/negative symptoms (SAPS/SANS,[9]). In order to allow for group analyses, SAPS/SANS scores were converted into PANSS scores using published regression-based equations[10].

Idiopathic ADHD dataset - ADHD200

We used data provided by the ADHD-200 consortium and the neuro bureau ADHD-200 Preprocessed repository (8 cohorts http://fcon_1000.projects.nitrc.org/indi/adhd200/ [11]). Data from seven sites were retained after the exclusion of 447 individuals. We included in our study a total of 518 subjects, 187 patients diagnosed with ADHD and 331 healthy controls.

UCLA Consortium for Neuropsychiatric Phenomics - CNP

We downloaded T1-weighted Anatomical MPRAGE and resting-state fMRI BOLD data on the OpenfMRI platform (ds000030, https://www.openfmri.org/dataset/ds000030/) [12]. Subjects were scanned across 2 sites (UCLA) - with a similar 3T Siemens Trio machine. We excluded 13 individuals after visual quality control. Data included in our study (n=237) encompassed healthy individuals (n=113) and individuals diagnosed with SZ (n=41), BIP (n=44), or ADHD (n=39). These diagnoses followed the Structured Clinical Interview for DSM-IV.

UK-BioBANK dataset

The UK biobank genomics data [13] were available for 31,225 individuals with MRI. After standard quality control procedure, we were able to add to our sample: 16p11.2 deletion (n=4) and duplication (n=6) carriers, 1q21.1 deletion (n=10) and duplication (n=13) carriers, 15q11.2 deletion (n=103) carriers and non-carriers (n=30,185) from UK-Biobank.

CNVs calling procedure in UK-BioBANK

The individual DNA (blood samples) were genotyped using the Affymetrix Axiom Array and UK BiLEVE Axiom array with common 733,256 markers mapped on the human genome version hg19. The

UK Biobank provided normalized signal data of Log R Ratio and B Allele Frequency for each marker, which was formatted into standard input data suitable for the most common CNV calling software. We developed a CNV calling workflow with the ability to compute per individual CNV calling in parallel. The pipeline is compatible with Unix architectures and optimized for low-resource computers. We implemented CNV calling procedures for PennCNV[14] and QuantiSNP [15]. Our protocol was executed on Compute Canada servers. The pipeline is available through GitHub (https://github.com/labjacquemont/MIND-GENESPARALLELCNV) and a QuantiSNP docker image version were also made available [16]. We used default parameters for both algorithms to harmonize the CNV calling procedure (SNP coverage ≥ 3, likelihood score ≥ 15, and CNV length ≥1000 nt). Results were merged using CNVision script (n_{cnv}= 97,252) [17]. We annotated CNV within the 4 loci (1q21.1, 15q11.2, 16p11.2, 22q11.2). Each detected CNV was visually checked with SnipPeep (http://snippeep.sourceforge.net/). We pooled these data with previous observations reported by Kendall et al 2017[18].

SNP Sample Size Determination for polygenic scores

Polygenic prediction via Bayesian regression and continuous shrinkage priors (PRS-CS) [19] requires a single SNP sample size as an input. Given that most of our discovery GWAS were actually meta-GWAS that were comprised of individual studies that varied in terms of their sample size and the SNPs they included, the sample size often varied considerably between SNPs. To account for this reality, we examined the distribution of SNP sample sizes in R and excluded SNPs that had sample sizes that were less than half of the maximum SNP sample size. Of the remaining SNPs, the median SNP sample size was used as the PRS-CS sample size input.

To ensure convergence of the underlying Gibbs sampler algorithm, we ran 25,000 Markov chain Monte Carlo iterations and designated the first 10,000 MCMC iterations as burn-in. The PRS-CS global shrinkage parameter was set to 0.01 when the discovery GWAS had a sample size that was less than 200,000; otherwise, it was learned from the data using a fully Bayesian approach. Default settings were used for all other PRS-CS parameters. The EUR posterior effects were fed into PLINK 1.9 [20] to produce

raw PGS separately for the EUR and white British UKBB cohorts, and R [21] was used to standardize the PGS for each cohort to mean = 0 and SD = 1.

Standardized PGS were then adjusted by regressing out the first ten within-ancestry PCs.

eTable 1. Discovery GWAS used to compute polygenic scores with PRS-CS

Discovery GWAS used to compute polygenic scores with PRS-CS

Trait	Discovery GWAS	SNP Sample Size[a] (for PRS-CS)	SNP Count[b] (for PRS-CS)
BIP	Stahl et al. (2019)[22]	51,710	1,105,066
SZ	Ripke et al (2020) [23]	87,491	1,079,332
ASD	Grove et al. (2019)[24]	46,350	1,094,054
MDD	Howard et al. (2019)[25]	500,199	1,086,563
Cross-D	Lee, P.H. et al. (2019)[26]	438,997	1,028,452

SZ, schizophrenia; ASD, autism spectrum disorder; BIP, Bipolar disorder, Cross-D: Cross-disorder.
[a]PRS-CS requires a single SNP sample size.
[b]The "SNP count" is the number of SNPs in common between the discovery GWAS, the PRS-CS LD panel, and the genomic dataset; only these SNPs were used to calculate posterior effects.

Legend: PGS were computed using discovery GWAS for 4 psychiatric conditions (BIP, SZ, ASD, MDD), cross-disorder. We used the most recent GWAS to compute all PGS. There were instances we intentionally used an older GWAS to avoid using a GWAS that included UKBB.

Resting-state fMRI Preprocessing

All datasets were preprocessed using the same parameters with the same Neuroimaging Analysis Kit (NIAK) version 0.12.4, an Octave-based open-source processing and analysis pipeline [27]. The first four volumes of each rs-fMRI time series were discarded to allow for magnetization to reach a steady state. Each data set was corrected for differences in slice acquisition time. Head motion parameters were estimated by spatially re-aligning individual timepoints with the median volume in the time series. This reference median volume was then aligned with the individual anatomical T1 image, which in turn was co-registered onto the MNI152 template space using an initial affine transformation, followed by a

nonlinear transformation. Finally, each individual time point was mapped to the MNI space [28] using the combined spatial transformations. Slow frequency drifts were modeled on the entire time series as discrete cosine basis functions with a 0.01 Hz high-pass cut-off. Timepoints with excessive in-scanner motion (greater than 0.5 mm framewise displacement) were then censored from the time series by removing the affected timepoint as well as the preceding and following two-time points [29]. Nuisance covariates were regressed from the remaining time series: the previously estimated slow time drifts, the average signals in conservative masks of the white matter and lateral ventricles, and the first principal components (95% energy) of the estimated six rigid-body motion parameters and their squares. Data were then spatially smoothed with a 3D Gaussian kernel (FWHM = 6mm).

Quality Control - preprocessed rs-fMRI data

Preprocessed data were visually controlled for the quality of co-registration, head motion, and related artifacts by three raters. Not all datasets were examined by the same raters, yet all raters followed the same standardized quality-control procedure [30]. Individuals were excluded from the analysis if co-registration errors could not be fixed. Individuals were also excluded from the analysis if the average framewise displacement after motion censoring exceeded 0.5 mm or if fewer than 40-time frames remained.

eTable2: Additional information on motion and scanning sites

CNV (hg19)		**Status**	**Motion**	Frames	**Sites**	Cohorts
15q11.2 15: 22.81-23.09		DEL	0.19 (0.06)	389 (118)	3	UKBB
1q21.1 1: 146.53-147.39		DEL	0.18 (0.07)	271 (172)	6	UKBB-MRG-Cardiff-SFARI
		DUP	0.21 (0.08)	276 (188))	7	
22q11.2 22: 19.04-21.47		DEL	0.18 (0.07)	120 (36)	1	UCLA
		DUP	0.19 (0.09)	225 (163)	5	UCLA-UKBB Cardiff-MRG
16p11.2 16: 29.65-30.20		DEL	0.22 (0.09)	108 (99)	5	SFARI - MRG -UKBB
		DUP	0.21 (0.09)	148 (140)	4	
Idiopathic Psychiatric Conditions		**SZ**	0.17 (0.06)	147 (50)	12	Montreal-SZ CNP
		BIP	0.17(0.07)	127 (25)	2	CNP
		ASD	0.16 (0.05)	157 (118)	28	ABIDE1 ABIDE2
		ADHD	0.15 (0.04)	135 (23)	8	ADHD-200 CNP
Non psychiatric condition		IBD	0.19 (0.06)	371 (123)	3	UKBB
Polygenic scores	Cross-Disorder		0.18 (0.05)	388 (116)	3	UKBB
	BIP					
	ASD					
	SZ					
	IQ					
Controls	UKBB		0.19 (0.05)	387 (116)	3	UKBB
	SFARI		0.18 (0.07)	81.4 (19)	2	SFARI
	MRG		0.21 (0.07)	381 (177)	1	MRG
	Cardiff		0.12 (0.06)	151.4 (35)	1	Cardiff
	UCLA		0.14 (0.04)	130 (24)	1	UCLA
	Psychiatric cohorts		0.15 (0.05)	163 (100)	44	-

Legend: CNV carriers, individuals with idiopathic psychiatric conditions, and controls after MRI quality control. Chr: chromosome number, coordinates are presented in Megabases (Mb, Hg19). Motion: framewise displacement (in mm). Quantitative variables are expressed as the mean ± standard deviation. All site scanned controls and sensitivity analyses were performed to investigate the potential bias introduced by differences in scanning site, age, and sex.

Computing connectomes

We segmented the brain into 64 functional seed-based regions defined by the multi-resolution MIST brain parcellation [31]. FC was computed as the temporal pairwise Pearson's correlation between the average time series of the 64 seed-based regions, and then Fisher-z transformed. The connectome of each individual encompassed 2,080 connectivity values: (63x64)/2 = 2016 region-to-region connectivity + 64 within seed-based region connectivity. We chose the 64 parcel atlas of the multi-resolution MIST parcellation as it falls within the range of network resolution previously identified to be maximally sensitive to FC alterations in neurodevelopmental disorders such as ASD[32]. We corrected for multiple comparisons using a false discovery rate strategy [33].

We performed 19 connectome-wide association studies (CWAS, **Table 2**):

1) 7 CNVs associated with neurodevelopmental psychiatric disorders CNVs identified in 1,003 carriers from 4 clinical cohorts and the UK Biobank ;

2) 30,185 and 174 non-CNV carriers from the UK Biobank and clinical cohorts respectively,

3) 1022 individuals with idiopathic ASD, SZ, BIP or ADHD from 4 datasets and their respective 1066 controls (**Table 1**).

eTable 3. Psychiatric diagnoses and FSIQ

CNV	Status	n clin	FSIQ	ASD	ADHD	SZ	BIP
1q21.1	DEL	15	97 (17)	2	2	0	0
	DUP	6	88 (29)	2	2	0	0
22q11.2	DEL	43	77 (14)	23	19	3	0
	DUP	12	96 (20)	4	5	0	0
16p11.2	DEL	28	87 (15)	7	7	0	0
	DUP	29	90 (21)	3	3	0	0
Idiopathic Psychiatric Conditions	**SZ**	283	-	-	-	242	-
	BIP	44	-	-	-	-	44
	ASD	472	104 (17)	472	-	-	-
	ADHD	223	107 (14)	-	223	-	-

Legend: Diagnoses information and full-scale intelligence quotient (FSIQ, mean (standard deviation)) for the clinically ascertained CNV carriers, and psychiatric conditions. n clin: number of participants clinically ascertained; DEL: deletion; DUP: duplication; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity-Disorder, BIP: Bipolar disorder.

eTable 4. Psychiatric diagnoses in UK-Biobank

CNV	Status	F17.1 Harmful use	F20-F29 SZ	F30.0 Hypomania	F32 Depressive episode	F41.9 Anxiety disorder	F42 OCD	F03 Dementia	F84.5 Asperger's syndrome	F90.0 ADHD	F99 Mental disorder unspecified
15q11.2	DEL	2	0	0	2	0	0	0	0	0	0
	DUP	0	0	0	2	3	0	1	0	0	0
1q21.1	DEL	0	0	0	0	0	0	0	0	0	0
	DUP	0	0	0	1	0	0	0	0	1	1
	DUP-TAR	0	0	0	1	1	0	0	0	0	0
22q11.2	DUP	0	0	0	1	0	0	0	0	0	0
16p11.2	DEL	0	0	0	1	0	0	0	0	0	0
	DUP	0	0	0	0	0	0	0	0	0	0
IBD		1	0	1	8	1	0	0	0	0	0
Controls		69	6	1	97	44	2	0	1	0	0

Legend: Diagnosis information for the CNV carriers identified in the UK Biobank and in patients with inflammatory bowel disease (IBD). More information about diagnostic codes is available on UK Biobank website.

Supplementary Results

eTable 4. Genetic, transcriptomic, and functional correlation values

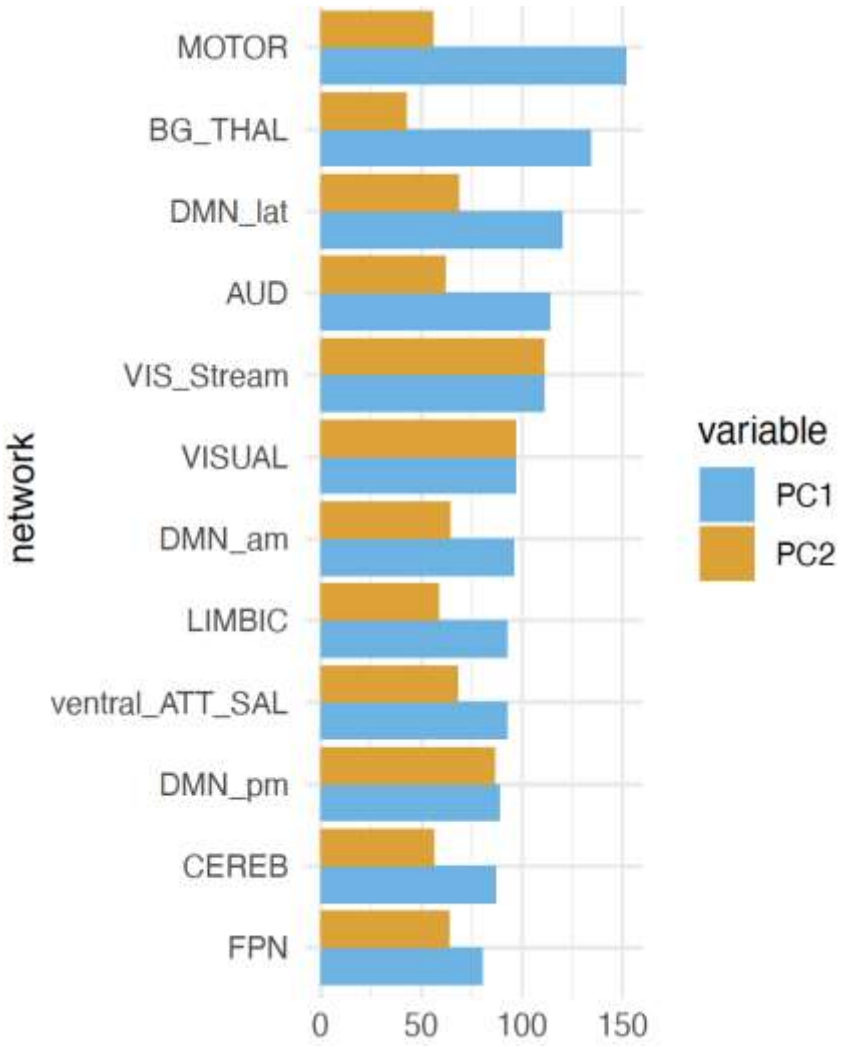
Pairs of conditions/traits	r_G	r_{FC}	r_T	*p-value* r_{FC}	References r_G	References r_T
SZ BIP	0.7	0.53	0.76	0.0001	Lee et al., 2019	Gandal et al., 2018
SZ ASD	0.22	0.3	0.48	0.001	Lee et al., 2019	Gandal et al., 2018
SZ ADHD	0.13	0.16		0.06	Lee et al., 2019	
ASD BIP	0.14	0.23	0.34	0.01	Lee et al., 2019	Gandal et al., 2018
ASD ADHD	0.37	0.07		0.24	Lee et al., 2019	
BIP ADHD	0.14	0.20		0.02	Lee et al., 2019	
IQ ADHD	-0.27	-0.09		0.18	Savage et al., 2018	
IQ SZ	-0.2	-0.07		0.25	Savage et al., 2018	
IQ NT	-0.19	-0.26		0.02	Savage et al., 2018	
IQ BIP	-0.01	-0.06		0.28	Savage et al., 2018	
IQ ASD	0.21	-0.07		0.24	Savage et al., 2018	
NT ADHD	0.24	0.18		0.04	Nagel et al., 2018	
NT SZ	0.2	0.4		0.0004	Nagel et al., 2018	
NT ASD	0.08	0.33		0.0006	Nagel et al., 2018	
NT BIP	0.1	0.37		0.0004	Nagel et al., 2018	
IBD ASD	-0.07	0.07	0.21	0.24	Lee et al., 2013	Gandal et al., 2018
IBD SZ	-0.01	0.06	0.007	0.29	Lee et al., 2013	Gandal et al., 2018
IBD BIP	-0.05	0.02	-0.06	0.42	Lee et al., 2013	Gandal et al., 2018
IBD ADHD	-0.02	-0.08		0.21	Lee et al., 2013	

Papers that computed r_G and r_T [26,34–37] Abbreviations: ASD: autism spectrum disorder, SZ: schizophrenia, BIP: bipolar disorder, NT: Neuroticism, IQ: intelligence quotient.

Cases / Controls matching

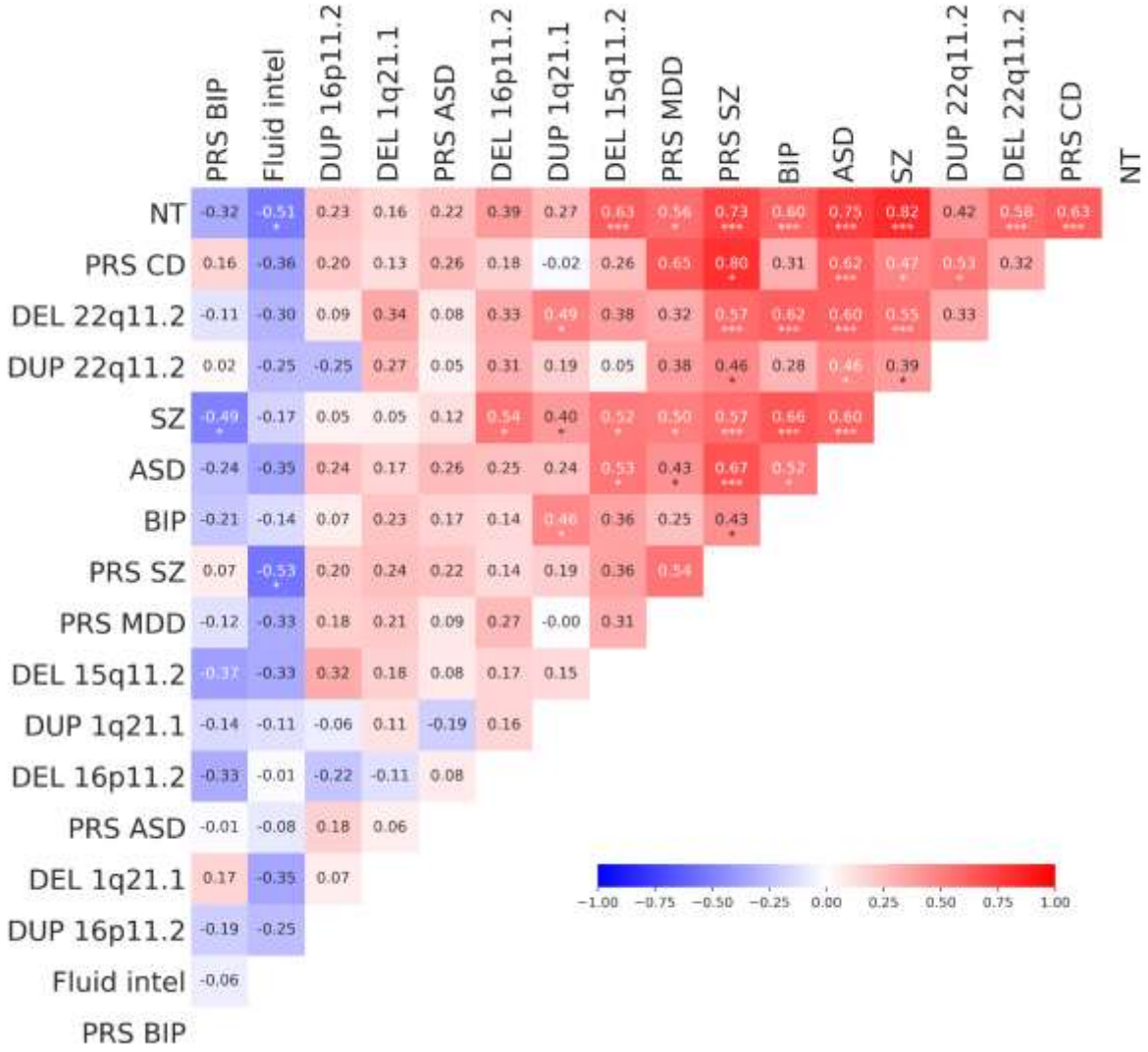
To test if careful matching of cases and controls influences the results, we performed a sensitivity analysis on the 22q11.2 duplication matching 1 CNV to 10 controls (22 CNV carriers and 220 controls) for scanning site, age, sex, and motion using the "matchControls" function in the {e1071} R package. FC-profiles before and after matching were strongly correlated (r=0.96, CI=[0.95;0.97]).

eFigure 1. PCA loadings per network



Legend: Average of absolute connections' loadings per network, divided by the number of regions encompassed in each network.

eFigure 2. Thalamus

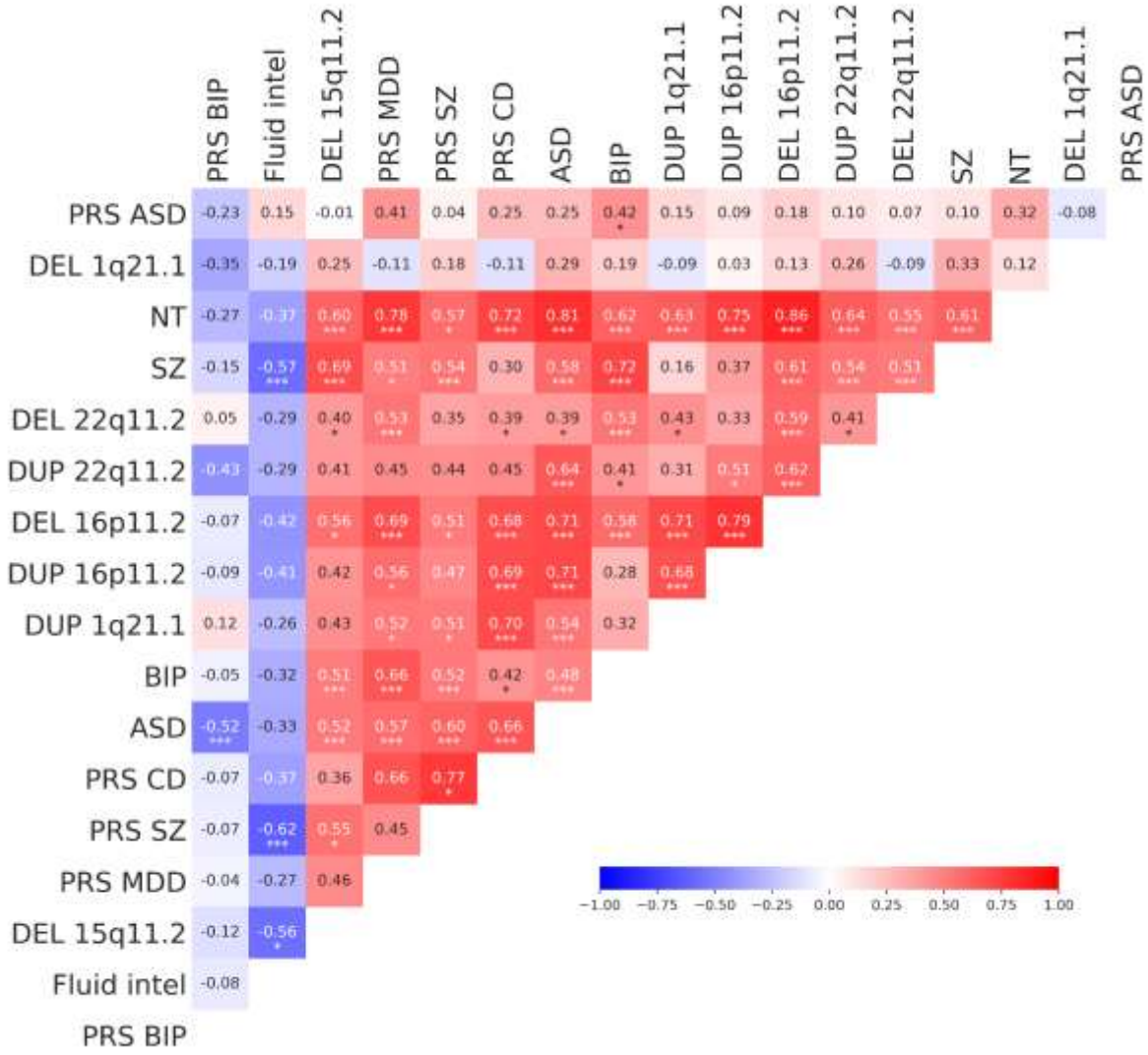


Legend. Pearson correlation between FC-profiles of the thalamus (64 beta values from 17 CWAS). Stars represent significant correlations (p<0.05, ** p<0.005, *** q FDR).*

16 out of 136 pairs of FC profiles showed correlations above what is expected by chance and survived FDR (10,000 null correlations).

Abbreviations: ASD: autism spectrum disorder, SZ: schizophrenia, BIP: bipolar disorder, MDD: major depressive disorder, NT: Neuroticism, PRS: Polygenic score (=PGS), Del: deletion, Dup: duplication, Fluid intel: fluid intelligence, CD: Cross-disorder.

eFigure 3. Dorsolateral Motor network



Legend. Pearson correlation between FC-profiles of the dorsolateral motor network (64 beta values from 17 CWAS). Stars represent significant correlations (p<0.05, ** p<0.005, *** q FDR).*

45 out of 136 pairs of FC profiles showed correlations above what is expected by chance and survived FDR (10,000 null correlations).

Abbreviations: ASD: autism spectrum disorder, SZ: schizophrenia, BIP: bipolar disorder, MDD: major depressive disorder, NT: Neuroticism, PRS: Polygenic score (=PGS), DEL: deletion, DUP: duplication, Fluid intel: fluid intelligence, CD: Cross-disorder.

Sensitivity analyses of brain volume effect on FC

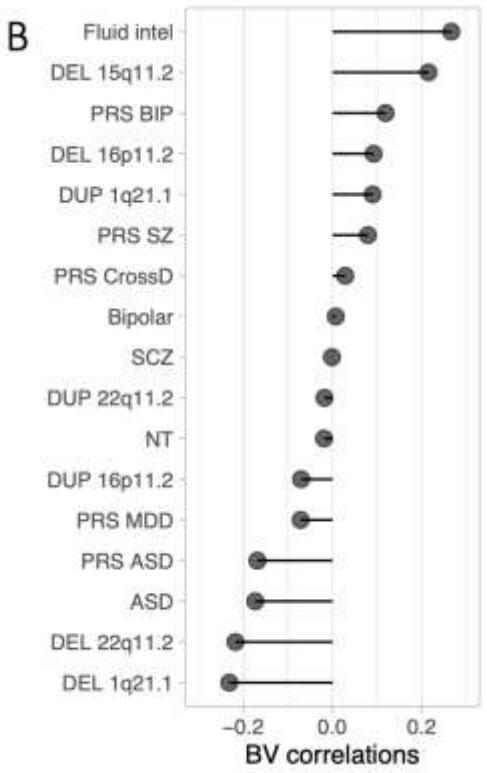
We performed sensitivity analyses by adding brain volume (BV) as a confounding variable in 4 CWAS (PRS-ASD, PRS-SZ, as well as 2 CNVs known to have the largest effects on brain volume: 16p11.2 and 1q21.1 deletions). The number of surviving connections was slightly decreased for each CWAS (see eFigure 4 in supplementary results). All four brain volume-adjusted FC profiles were highly correlated with the initial corresponding unadjusted FC profiles reported in the manuscript (ranging from r=0.96 to 0.99). We also tested for the reviewer the main effect of BV on FC in a linear model using total BV measured across all clinical and unselected population. We show that total BV has a pervasive effect on FC (1452 significant connections with an effect size of 0.07). We then tested the resemblance of the BV FC profile to 17 profiles used in Figure 2. We observed mild correlations ranging from -0.23 (1q21.1 deletion) to 0.26 (fluid intelligence) (see eFigure 4B).

eFigure 4. Effect of brain volume on FC

A

	CNV/PRS	Connections		Beta values	
		pos	*neg*	*min*	*max*
Not BV adjusted	1q21.1 DEL	1	11	-1.07	0.62
	16p11.2 DEL	124	149	-0.98	1.67
	PRS ASD	3	1	-.02	.02
	PRS SZ	93	115	-.02	.04
BV adjusted	1q21.1 DEL	1	9	-0.91	0.62
	16p11.2 DEL	122	138	-1.01	1.62
	PRS ASD	3	1	-.02	.02
	PRS SZ	90	115	-.02	0.03

B



Legend: A. Table of comparison between CWAS performed with and without brain volume as a confounding variable. B. Correlation between the FC-Profile of brain volume ('BV') and the 17 FC profiles included in Figure 2.

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