Brain functional connectivity mirrors genetic pleiotropy in psychiatric conditions

Clara A. Moreau,[1,2,3] Kuldeep Kumar,[2] Annabelle Harvey,[2,3] Guillaume Huguet,[2] Sebastian Urchs,[3,4] Laura M. Schultz,[5] Hanad Sharmarke,[3] Khadije Jizi,[2] Charles-Olivier Martin,[2] Nadine Younis,[2] Petra Tamer,[2] Jean-Louis Martineau,[2] Pierre Orban,[6,7] Ana Isabel Silva,[8,9,10] Jeremy Hall,[8,9] Marianne B. M. van den Bree,[8,9] Michael J. Owen,[8,9] David E. J. Linden,[9,10] Sarah Lippé,[2] Carrie E. Bearden,[12] Laura Almasy,[5,13,14] David C. Glahn,[16,17] Paul M. Thompson,[17] Thomas Bourgeron,[1] Pierre Bellec[3,†] and Sebastien Jacquemont[2,†]

[†]**These authors contributed equally to this work.**

1 Human Genetics and Cognitive Functions, Institut Pasteur, UMR3571 CNRS, Université Paris Cité, Paris, France

2 Sainte Justine Research Center, University of Montréal, QC H3T 1C5, Montréal, Canada

3 Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, QC H3W 1W5, Montreal, Canada

4 Montreal Neurological Institute, McGill University, QC H3A 2B4, Montreal, Canada

5 Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, PA, USA

6 Centre de Recherche de l'Institut Universitaire en Santé Mentale de Montréal, QC H1N 3V2, Montréal, Canada

7 Département de Psychiatrie et d'Addictologie, Université de Montréal, Pavillon Roger-Gaudry, C.P. 6128, succursale Centre-ville, QC H3C 3J7, Montréal, Canada

8 Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK

9 MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

10 School for Mental Health and Neuroscience, Maastricht University, NL

11 Département des Sciences de la Décision, HEC, QC H3T 2A7, Montréal, Canada

12 Integrative Center for Neurogenetics, Semel Institute for Neuroscience and Human Behavior; Departments of Psychiatry and Biobehavioral Sciences and Psychology, University of California, Los Angeles, Los Angeles, CA 90095, USA

13 Department of Genetics, University of Pennsylvania, PA, USA

14 Lifespan Brain Institute, Children's Hospital of Philadelphia, PA, USA

15 Harvard Medical School, Department of Psychiatry, MA 02115, USA

16 Boston Children's Hospital, Tommy Fuss Center for Neuropsychiatric Disease Research, 300 Longwood Avenue, Boston, MA 02115, USA

17 Imaging Genetics Center, Stevens Institute for Neuroimaging and Informatics, Keck USC School of Medicine, Marina del Rey, CA, USA

Abstract

Pleiotropy occurs when a genetic variant influences more than one trait. This is a key property of the genomic architecture of psychiatric disorders and has been observed for rare and common genomic variants. It is reasonable to hypothesize that the microscale genetic overlap (pleiotropy) across psychiatric conditions and cognitive traits may lead to similar overlaps at the macroscale brain level such as large-scale brain functional networks.

We took advantage of brain connectivity, measured by resting-state functional MRI to measure the effects of pleiotropy on large-scale brain networks, a putative step from genes to behavior. We processed nine resting-state functional MRI datasets including 32,726 individuals and computed connectome-wide profiles of seven neuropsychiatric copy-number-variants, five polygenic scores, neuroticism, and fluid intelligence as well as four idiopathic psychiatric conditions.

Nine out of nineteen pairs of conditions and traits showed significant functional connectivity correlations ($r_{Functional\ connectivity}$), which could be explained by previously published levels of genomic ($r_{Genetic}$) and transcriptomic ($r_{Transcriptomic}$) correlations with moderate to high concordance: $r_{Genetic}$ - $r_{Functional\ connectivity}$= 0.71 [0.40-0.87] and $r_{Transcriptomic}$ - $r_{Functional\ connectivity}$= 0.83 [0.52; 0.94]. Extending this analysis to functional connectivity profiles associated with rare and common genetic risk showed that 30 out of 136 pairs of connectivity profiles were correlated above chance. These similarities between genetic risks and psychiatric disorders at the connectivity level were mainly driven by the overconnectivity of the thalamus and the somatomotor networks. Our findings suggest a substantial genetic component for shared connectivity profiles across conditions and traits, opening avenues to delineate general mechanisms - amenable to intervention - across psychiatric conditions and genetic risks.

Correspondence to: Clara A. Moreau
Sainte-Justine Hospital Pediatric Research Centre – Neuroscience
3175 Chemin de la Côte-Sainte-Catherine Montreal Quebec H3T 1C5
Canada
E-mail: clara.moreau@pasteur.fr

Correspondence may also be addressed to: Sebastien Jacquemont
E-mail: sebastien.jacquemont@umontreal.ca

Running title: Pleiotropic connectivity in psychiatry

Keywords: pleiotropy; psychiatry; functional connectivity; autism spectrum disorder; copy number variant

Abbreviations: ASD = autism spectrum disorder; ADHD = attention-deficit / hyperactivity disorders; BIP = bipolar disorder; CNV = copy number variant; CWAS = connectome-wide association studies; FC = functional connectivity; IBD = Inflammatory bowel disease; PGS = polygenic score; rs-fMRI = resting-state functional MRI; SNP = single nucleotide polymorphisms

Introduction

Genetic pleiotropy, a key feature of psychiatric conditions, refers to the situation in which a genetic variant or gene has effects on more than one phenotype [1]. Genetic correlation (r_G), a measure of the average effect of pleiotropy across genomic loci, has been computed using common variants (i.e., single nucleotide polymorphisms, SNPs) based on GWAS summary statistics [2]. SNP-based r_G are moderate to high between schizophrenia (SZ), bipolar disorder (BIP), and major depressive disorder (MDD) and lower between these three conditions and autism spectrum disorder (ASD) [3–5]. Moderate to mild genetic correlations are also observed between these psychiatric conditions and cognitive abilities or personality traits such as neuroticism and fluid intelligence [6,7]. Similar levels of correlations between pairs of these same psychiatric conditions have been shown at the brain transcriptomic level (r_T) [8].

Although r_G has only been computed for common variants, pleiotropy has also been reported for rare variants such as copy-number variants (CNVs) [9,10], which are often associated with a broad range of psychiatric diagnoses, and cognitive traits.

It is reasonable to assume that overlap at the microscopic scale (i.e., genetic and transcriptomic) between conditions and traits may lead to similar overlaps at the macroscopic scale, such as large-scale functional networks. The latter can be inferred using resting-state functional MRI (rs-fMRI). This imaging technique measures spontaneous, low-frequency temporal synchronization of the activity in different brain regions during rest [11,12]. An overlap between functional connectivity (FC) profiles of eight psychiatric disorders has been previously reported as driven by the default mode, salience, and frontoparietal networks [13]. A complementary dimensional reduction approach has identified a latent dimension mainly involving the somatosensory-subcortical networks spanning four psychiatric diagnoses [14].

FC similarity has also been investigated between two rare CNVs (ie 16p11.2 and 22q11.2 deletion) that both confer large risks for ASD, SZ, and cognitive deficits. Connectivity profiles of the thalamus, somatomotor, posterior insula and cingulate showed similarities between these 2 CNVs, as well as groups of individuals with either idiopathic ASD or SZ. Beyond these two genomic loci, nothing is known about the effects of rare high-risk variants on brain functional connectivity. Furthermore, little is known about the FC effects of common variants increasing risks for psychiatric conditions (i.e. polygenic scores, PGS) [15].

Knowledge gaps:

The relationship between the level of pleiotropy at the genetic (SNP-based) and large-scale functional brain connectivity network is unknown.

Pleiotropy observed for rare genomic variants associated with psychiatric disorder has not been investigated at the level of functional brain connectivity.

Our overarching aim was to investigate the relationship between pleiotropy at the genetic and functional connectivity levels.

Specifically, we aimed to 1) Investigate the concordance between previously established genetic correlations and FC correlations between conditions and traits; 2) Identify brain networks driving FC correlations observed between rare and common genetic risks, psychiatric conditions, and traits.

To this end, we used the same pipeline to analyze rs-fMRI data in n=32,726 individuals from 4 genetics-first clinical cohorts (e.g., recruited because they carry a high-risk genetic variant), 4 case-control idiopathic psychiatric datasets (ASD, SZ, attention-deficit / hyperactivity disorders (ADHD), BIP), and one unselected population. We performed 19 connectome-wide association studies (CWAS) for 7 CNVs, 5 PGS, 4 idiopathic psychiatric conditions, and 1 non-brain related disease (Inflammatory bowel disease: IBD), fluid intelligence, and neuroticism. We included 279 CNV carriers, 1022 individuals with either autism, schizophrenia, bipolar, or ADHD, and 31425 controls.

Materials and methods

Selecting CNVs, conditions and traits

We analyzed all of the available rs-fMRI data for neuropsychiatric CNVs with at least n=20 carriers to allow for the detection of large effect sizes (Cohen's $d > 0.8$) previously reported for CNVs. As a result, selected CNVs are those most frequently identified in the clinic: 22q11.2, 1q21.1, 15q11.2, 16p11.2. Fluid intelligence and neuroticism were selected because 1) CNVs that increase risk for ASD and/or SZ decrease cognitive ability [10,16] and 2) both traits show the highest genetic correlation, amongst commonly measured traits, with ASD [4] as well as with schizophrenia [6,7]. Inflammatory bowel disease (IBD) was selected as a non-psychiatric control condition with a sample size similar to those available for the psychiatric conditions included in

the study.

Cohorts

Our analysis included 32,726 individuals from nine datasets (**Table 1**). Each study of the corresponding dataset was approved by the research ethics review boards of the respective institutions. This project was approved by the research ethics review board at the Centre Hospitalier Universitaire Sainte Justine.

Clinical genetic datasets

We used 4 'genetics-first' CNV datasets, which were recruited based on the presence of a CNV associated with risk of neurodevelopmental and psychiatric disorders, regardless of symptomatology (detailed in eMethod in Supplement). These included the Simons Variation in Individuals Project (SVIP for 16p11.2 and 1q21.1 CNVs) [17], the University of California, Los Angeles 22q11.2 CNV project, the University of Cardiff, and the Montreal rare genomic disorder (MRG) datasets.

Unselected population

CNVs associated with neurodevelopmental and psychiatric disorders were also identified in the UK-Biobank dataset [18] (eMethods in the Supplement).

Idiopathic psychiatric conditions cohorts

We used the ABIDE1 [19], ABIDE2 [20], ADHD-200 [21], the Consortium for Neuropsychiatric Phenomics (CNP) [22], and an aggregate dataset of 10 SZ studies [23,24]; collectively these datasets include individuals with idiopathic ASD, ADHD, SZ, and BIP, as well as their respective controls (eMethods in the Supplement).

CNV calling and Polygenic scores (PGS) computation

CNVs were identified in the UK-Biobank using PennCNV[25] and QuantiSNP [26] following previously published methods [27] (eMethods in Supplement).

We computed 5 PGS for individuals of European ancestry in the UK-Biobank using PRS-CS, a polygenic prediction via Bayesian regression and continuous shrinkage priors [28] (**Table1**, eMethods, and **eTable1** in Supplement).

Resting-state functional MRI preprocessing

All datasets were preprocessed using the same parameters of Neuroimaging Analysis Kit (NIAK) [29]. Preprocessed data were visually controlled for quality of the coregistration, head motion, and related artifacts (eMethods in Supplement).

Computing connectomes

We segmented the brain into 64 functional regions defined by the multi-resolution MIST brain parcellation [30] to compute connectomes - defined by 2,080 connections between 64 regions, which are grouped into 12 functional networks [30]: https://simexp.github.io/multiscale_dashboard/index.html. MIST atlas was chosen as it has the advantage to include the cerebellum which appears to play a critical role in neurodevelopmental disorders and psychiatric conditions [31–34]. MIST parcellation is also performing on par or superior to other templates (such as AAL or Power) on a number of prediction benchmarks - in particular regarding ASD and SZ prediction [35–37].

Statistical analyses were performed using *scikit-learn* [38] and *stats* [39] libraries.

Connectome-wide association studies

We performed 19 connectome-wide association studies by either contrasting cases and their respective controls for:

- 7 CNVs associated with neurodevelopmental and psychiatric disorders (**Table1**), and 4 idiopathic psychiatric disorder cohorts (ASD, SZ, BIP, and ADHD). Controls refer to 1) individuals without a CNV, for analyses investigating the effect of CNVs or 2) individuals without a psychiatric diagnosis in analyses investigating the effects of psychiatric conditions.
- Or by investigating the linear effects of 5 continuous PGS: ASD, BIP, SZ, Cross-disorder, and MDD, as well as 2 continuous traits provided by UK-Biobank: Neuroticism, and Fluid intelligence.

FC was z-scored based on the variance of the pooled controls used for each connectome-wide association study. They were conducted by linear regression, in which z-scored FC values were the dependent variables and genetic or diagnostic status or traits were the explanatory variables. PGS and traits were normalized within the UKBB sample.

Models were adjusted for sex, scanning site, head motion, age, and global signal (defined as the mean of all 2,080 Fisher's Z values). FC profiles were defined as the 2,080 β values of 2,080 connections.

$$\textbf{Z-score}_{\text{Connection [i, … 2080]}} \sim \beta_0 + \beta_{\text{genetic status/conditions}} + \beta_{\text{age}} + \beta_{\text{motion}} + \beta_{\text{sex}} + \beta_{\text{site}} + \beta_{\text{global signal}} + \varepsilon$$

This linear regression was applied for each of the 2,080 functional connections. Since all raw connectomes were normalized on the variance of the controls, regression estimates (beta) can be interpreted as z-scores. We corrected for multiple testing using FDR ($q < 0.05$) as well as a permutation procedure. We corrected for the number of tests (2,080) using the Benjamini-Hochberg correction for FDR at a threshold of $q < 0.05$ [40,41]. We also computed an empirical p-value ('pval effect') by conducting a permutation test, shuffling the genetic or clinical status labels of the individuals included in each connectome-wide association study (5,000 permutations). We estimated the empirical p-value by calculating the frequency of obtaining an effect size equal to or greater than the original observation [42]. Effect-size of genetic risk, conditions, and traits on connectivity was defined as the top decile of the 2080 absolute β values.

Concordance between functional, genetic, and transcriptomic correlations

We computed correlations of whole-brain connectome profiles across pairs of conditions and traits (Pearson correlation) using the 2,080 beta values of each CWAS.

We obtained genetic correlation (r_G) values across pairs of conditions and traits (neuroticism [7], intelligence [6], cross-disorders (8 psychiatric conditions) [3,43]) from previously published GWAS. We also used previously published [8] correlation values of transcriptomic profiles between 6 pairs of conditions.

We performed concordance analyses between correlation at the genetic (r_G), and functional connectivity (r_{FC}) levels, as well as the transcriptomic (rT) and the FC (rFC), levels using DescTools R package to extract Lin's concordance correlation coefficient (CCC) [39,44]. The bias correction factor quantifies how far the best fit line deviates from 45 degrees.

Atlas of functional connectivity correlations across genetic risk, traits, and conditions.

We computed Pearson correlations between the 17 out of 19 whole-brain FC profiles with

significantly altered connections (FDR-corrected). For the significance of correlations between FC profiles, we generated a null distribution of 10,000 correlation values for each pair of conditions and traits. These 10,000 null correlations were computed using null FC profiles. The latter were obtained by conducting 5,000 CWAS after shuffling the clinical status or trait values. To obtain a *p*-value, the correlation value was compared to the null distribution. We corrected for the number of correlations (n=136) using the Benjamini-Hochberg correction for FDR at a threshold of $q < 0.05$ [41].

Principal Component Analysis

To identify the FC networks driving the correlations, we conducted a PCA on the 17 scaled FC-Profiles using the *prcomp* function from *stats R* package. Functional connections with 5% top loadings for principal components 1 and 2 (PC1, PC2) were represented on chord diagrams using the *circlize* R package (code available on Github). We also reported - per network - the average of absolute loadings of each connection, divided by the number of regions encompassed in each network (eFigure1).

Data and materials availability

Data from UK Biobank was downloaded under the application 40980, and can be accessed via their standard data access procedure (see http://www.ukbiobank.ac.uk/register-apply). UK Biobank CNVs were called using the pipeline developed in Jacquemont Lab, and described in https://github.com/labjacquemont/MIND-GENESPARALLELCNV. The final CNV calls are available from UK Biobank returned datasets (Return ID: 3104, https://biobank.ndph.ox.ac.uk/ukb/dset.cgi?id=3104). ABIDE1, COBRE, ADHD200, CNP, 16p11.2 SVIP data are publicly available: http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html , http://schizconnect.org/queries/new , http://fcon_1000.projects.nitrc.org/indi/adhd200/ , https://www.openfmri.org/dataset/ds000030/ , https://www.sfari.org/funded-project/simons-variation-in-individuals-project-simons-vip/. The 22q11.2 UCLA raw data are currently available by request from the PI. Raw imaging data for the Montreal rare genomic disorder family dataset is going to be available on the LORIS platform in 2023. The Cardiff raw data is not publicly available yet, contact the PI for further information.

All processed connectomes are available through a request to the corresponding authors.
Code for all analyses and visualizations, beta values, and p-values for the 19 FC profiles are available online through the GitHub platform with Jupyter notebook:
https://github.com/claramoreau9/NeuropsychiatricCNVs_Connectivity

Results

Pleiotropy: Similarities between genetic and functional connectivity correlations across psychiatric conditions and traits

To investigate overlap and pleiotropy at the connectivity level, we first computed seven brain-wide FC profiles across 4 psychiatric conditions, fluid intelligence, neuroticism, and one control non-brain related condition (IBD). Patients diagnosed with idiopathic SZ, BIP, and ASD, but not ADHD nor IBD, showed altered FC compared to controls (significance required both FDR and permutation test, **Table 2**).
To quantify FC overlap between conditions and traits, we performed correlations between FC profiles (r_{FC}) across 19 pairs of conditions and traits. Nine out of the 19 pairs showed correlation above chance (permutations and FDR) (**Figure 1. B**). The control trait (IBD) did not correlate with any of the psychiatric conditions or traits.
We then asked if the level of FC correlation (r_{FC}) could be explained by previously published levels of genetic or transcriptomic correlations (r_G and r_T) between the same pairs of conditions and traits (**Figure 1. A-B**).
We first observed a high concordance between r_T and r_{FC} across 6 pairs of conditions and traits (Lin's concordance correlation coefficient [45], CCC=0.83, 95%CI: [0.52; 0.94], without any bias correction factor = 0.85, **Figure 1. C**).
We also showed a significant concordance between r_G and r_{FC} across 19 pairs of conditions and traits (CCC=0.71, 95%CI: [0.40; 0.87] without any bias (bias correction factor = 0.99, **Figure 1D**). In other words, FC similarity between conditions and traits was neither systematically higher nor lower than r_G. All concordance remained significant even after removing the SZ-BIP pair, which showed the strongest correlations at the genetic and functional levels.

A landscape of functional connectivity correlation across genetic risk, psychiatric conditions, and traits

We asked if pleiotropy previously published for rare CNVs and PGS (i.e., a CNV confers risk for several psychiatric conditions) [3,34] was also observed at the level of brain functional connectivity. We, therefore, calculated the correlation for FC profiles associated with genomic risk, psychiatric conditions, and traits. We first computed brain-wide FC profiles associated with 7 CNVs and 5 PGS (**Table 2**). All 7 CNVs and PGS altered from 5 to 208 connections that survived false discovery rate (FDR $q<0.05$, and permutation analyses, **Table 2**). Of note, an alternative PGS-SZ computed using an older and smaller GWAS was associated with a much lower number of connections. Nevertheless, FC profiles of the old [46] and new GWAS [47]) were correlated ($r=0.89$).

We computed correlations between the FC profiles of CNVs, PGS, conditions, and traits. This analysis was limited to the 17 whole-brain FC profiles with significantly altered connections (**Table 2**) and showed that 30 out of 136 pairs of FC profiles have correlations above what is expected by chance (10,000 permutations and FDR, **Figure 2**). FC correlations (r_{FC}) between genetic risks, conditions, and traits ranged from weak to moderate, similar to those observed for r_G (Figure 1).

Thalamo-sensorimotor alterations are shared across CNVs, PGS, and idiopathic conditions.

We sought to investigate whether specific functional networks underlied the FC correlations observed above. We performed a principal component analysis (PCA) across the 17 FC profiles. The two first dimensions explained 24% and 10% of the variance, respectively, of the FC profiles. Dimension 1 was dominated by increased connectivity between the thalamus and the ventrolateral-, dorsolateral-, and medial-somatomotor, as well as the lateral default mode and auditory networks. Dimension 2 was characterized by decreased connectivity between the posterior cingulate, the precuneus, and the visual networks (**Figure 2C**). Beyond these dominant networks, both latent dimensions were distributed broadly across all 12 networks (**eFigure 1)**.

Neuroticism and psychiatric conditions showed higher loadings on dimension 1 than CNVs (**Figure 2D**). As a sensitivity analysis, we performed a second PCA on CNVs separately,

demonstrating that similar networks and connections were contributing to the main dimension (r=0.70 between PC1 of CNV + PGS + conditions + traits, and PC1 of CNVs only). The regional FC profiles of the thalamus (**Figure 2F** and **eFigure 2**) and dorsolateral motor network (**eFigure 3**) showed, as expected, much higher similarities among genetic risk, conditions, and traits (16 and 45 out of 136 correlations survived FDR respectively) compared to whole-brain correlations.

Discussion

Main findings

Our study provided the first systematic analysis of functional connectivity across genetic risk, psychiatric conditions, and traits. Results demonstrated a stable level of similarities between conditions and traits from genetics, to transcriptomics to brain connectomics. We posit that functional connectivity overlap measured by r_{FC} reflects pleiotropy at the level of functional networks. Functional connectivity profiles associated with rare psychiatric CNVs, psychiatric PGS, psychiatric conditions, and traits shared mild to moderate signatures. Although multivariate analyses showed that this shared functional connectivity dimension was dominated by overconnectivity of the thalamus and somatomotor networks as well as the underconnectivity of the visual network, similarities were distributed across all networks.

Shared functional connectivity profiles across conditions and traits parallel genetic and transcriptomic overlap.

Stable concordance of pleiotropy from genes to connectivity suggests that a major component of FC-profile correlations (r_{FC}) reflects genetically-based biological processes, consistent with the previously reported SNP-based heritability of the inter-individual differences in brain functional networks [48,49]. Previous studies have shown that similarity in cortical thickness or surface between psychiatric conditions were associated with SNP-based genetic similarity (r_G) between the same conditions albeit with lower levels of concordance[50,51].

This suggests that genetic pleiotropy is reflected across multiple MRI modalities with

seemingly similar levels of concordance. All of the well-studied rare variants (i.e. CNVs) have been associated with more than one condition (i.e. ASD, SZ, and ADHD) but genetic correlations used in this study were only based on SNPs. It is unknown if r_G may be higher or lower once rare variants are included [2].

Genetic risks converge on the thalamus and somatomotor network.

Overlap between genetic risk, psychiatric conditions, and neuroticism was driven by shared overconnectivity of the thalamus/basal ganglia and the somatomotor networks. The implication of the somatomotor and basal ganglia/thalamus network across genetic risk and psychiatric conditions is in line with previous transdiagnostic and single-condition neuroimaging studies [14,52]. These functional hubs may be highly sensitive to a broad range of genetic risks for neuropsychiatric conditions. This is consistent with the fact that i) most if not all rare CNVs - and rare deleterious variants in general- increasing risk for psychiatric conditions are also associated with delayed gross motor milestones [10,53] and development coordination disorders [54] ii) delay in motor milestones has been demonstrated in individuals with schizophrenia [55], and ASD [56]. Of note, functional and structural measures of the thalamus, basal ganglia [57], and unimodal regions (i.e. somatomotor) show less interindividual variability and higher heritability compared to heteromodal regions [49]. Fluid intelligence showed the opposite thalamic pattern. This is in line with i) negative genetic correlation between cognitive ability and most psychiatric conditions; ii) prior functional MRI studies demonstrating that thalamocortical pathways are engaged in memory, attention, and mental representations [58,59].

Clinical translation

Sensory-motor alterations are important dimensions that may underlie some of the pleiotropic effects of genomic risk for psychiatric conditions (Figure 3). This is in line with the fact that gross and fine motor skills are widely impaired in patients referred to autism and neurodevelopmental disorder clinics [56]. Furthermore, motor impairments are greater in ASD patients with rare genetic mutations [53]. As well, studies demonstrate that soft motor neurological signs in schizophrenia are present in neuroleptic naive patients, and are associated with the severity and persistence of psychopathological symptoms and with poor social functioning [60,61]. However, motor abnormalities of severe mental disorders have been neglected

both in clinical practice and research. These results represent additional evidence in favor of including motor symptoms in the dimensional assessments of psychiatric conditions.

While psychiatric disorders continue to be defined by their symptoms, course, age of onset, it is reasonable to expect that future efforts to build nosological classifications will be influenced by the increasingly refined characterization of overlaps between conditions at the genetic, transcriptomic and large scale brain network levels [1].

Limitations

FC correlations performed at the whole-brain level are dependent on the sample size used to determine the FC profiles for each genetic risk, condition, and trait. Larger samples will likely improve our correlation estimates. This is especially true for conditions such as ADHD, which have been associated with very small effect sizes and will likely require larger samples to identify robust rs-fMRI differences. The same issue applies to genetic correlations which are dependent on the sample size used in the genome-wide association study. As an example, 2 FC profiles associated with 2 PGS-SZ computed on the basis of 2 GWAS of different sample sizes were correlated (r=0.89) but the number of significant connections was lower for the profile associated with the older SZ-GWAS (computed with 23,585 subjects with SZ) compare to the new one (computed with 69,369 subjects with SZ). However, our sensitivity analysis showed that the levels of rFC were not confounded by sample size.

This multisite study including clinically and non-clinically ascertained cohorts may have introduced biases. Confounding factors include sex bias, age differences, and medication status, which may have influenced some of the results. However, carefully conducted sensitivity analyses, matching case and control groups for sex, site, age, motion, and excluding individuals with medications (in idiopathic psychiatric cohorts) provided similar results (see in the supplementary results).

Finally, and because our dataset spans a broad age range, and some CNVs impact total brain volume, we showed in sensitivity analyses that covarying for brain volume did not influence some of the results (Supplemental result, eFigure4).

Conclusion

The level of brain architecture similarities across genetic risks, conditions, and traits is consistent with the level of genetic pleiotropy measured across the same conditions and traits. We, therefore, posit that research on psychiatric conditions will benefit from a neuroimaging genomic multiscale approach. Results highlight the critical contribution of the thalamus and the somatomotor networks across genetic risks and psychiatric conditions suggesting that more attention should be directed towards motor symptoms and mechanisms in psychiatric conditions. Such strategies open promising avenues to help reshape psychiatric nosology as well delineate general mechanisms - amenable to intervention - across conditions and genetic risks.

Competing interests

P.M.T. received partial research grant support from Biogen, Inc., for research unrelated to this study. Other authors did not have a conflict of interest.
M.J.O., J.H., and M.V.B. have a research grant from Takeda Pharmaceuticals outside the scope of the present work.
J.H. is a founding director of the company Meomics (unrelated to this work).

Funding

This research was supported by Compute Canada (ID 3037 and gsf-624), the Brain Canada Multi investigator research initiative (MIRI), Canada First Research Excellence Fund, Institute of Data Valorization, Healthy Brain Healthy Lives (Dr. Jacquemont). Dr. Jacquemont is a recipient of a Canada Research Chair in neurodevelopmental disorders, and a chair from the Jeanne et Jean Louis Levesque Foundation. This work was supported by a grant from the Brain Canada Multi-Investigator initiative (Dr. Jacquemont) and a grant from The Canadian Institutes of Health Research (CIHR 400528, Dr. Jacquemont). 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 (code 100202/Z/12/Z). The CHUV cohort was supported by the SNF (Maillard Anne, Project, PMPDP3 171331). Data from the UCLA cohort provided by Dr. Bearden (participants with 22q11.2 deletions or duplications and

controls) was supported through grants from the NIH (U54EB020403), NIMH (R01MH085953, R01MH100900, 1U01MH119736, R21MH116473), and the Simons Foundation (SFARI Explorer Award). Finally, data from another study were obtained through the OpenFMRI project (http://openfmri.org) from the Consortium for Neuropsychiatric Phenomics (CNP), which was supported by NIH Roadmap for Medical Research grants UL1-DE019580, RL1MH083268, RL1MH083269, RL1DA024853, RL1MH083270, RL1LM009833, PL1MH083271, and PL1NS062410. Dr P. Bellec is a fellow ("Chercheur boursier Junior 2") of the "Fonds de recherche du Québec - Santé", Data preprocessing and analyses were supported in part by the Courtois foundation (Dr Bellec). This work was supported by Simons Foundation Grant Nos. SFARI219193 and SFARI274424. We thank all of the families at the participating Simons Variation in Individuals Project (VIP) sites, as well as the Simons VIP Consortium. We appreciate obtaining access to imaging and phenotypic data on SFARI Base. Approved researchers can obtain the Simons VIP population dataset described in this study by applying at https://base.sfari.org. We are grateful to all families who participated in the 16p11.2 European Consortium. Dr. P. Thompson was funded in part by the U.S. NIH grants R01MH116147, P41EB015922, R01MH111671, and U01 AG068057. Ms. Petra Tamer received the Canadian Institute of Health Research (CIHR) Scholarship.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Lee PH, Feng YCA, Smoller JW. Pleiotropy and Cross-Disorder Genetics Among Psychiatric Disorders. *Biol Psychiatry*. Published online October 10, 2020. doi:10.1016/j.biopsych.2020.09.026

2. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47(11):1236-1241. doi:10.1038/ng.3406

3. Lee PH, Anttila V, Won H, et al. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*. 2019;179(7):1469-1482.e11. doi:10.1016/j.cell.2019.11.020

4. Grove J, Ripke S, Als TD, et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat Genet*. 2019;51(3):431-444. doi:10.1038/s41588-019-0344-8

5. Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet*. 2018;50(3):381-389. doi:10.1038/s41588-018-0059-2

6. Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet*. 2018;50(7):912-919. doi:10.1038/s41588-018-0152-6

7. Nagel M, Jansen PR, Stringer S, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat Genet*. 2018;50(7):920-927. doi:10.1038/s41588-018-0151-7

8. Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 2018;359(6376):693-697. doi:10.1126/science.aad6469

9. Chawner SJRA, Owen MJ, Holmans P, et al. Genotype-phenotype associations in children with copy number variants associated with high neuropsychiatric risk in the UK (IMAGINE-ID): a case-control cohort study. *Lancet Psychiatry*. 2019;6(6):493-505. doi:10.1016/S2215-0366(19)30123-3

10. Douard E, Zeribi A, Schramm C, et al. Effect Sizes of Deletions and Duplications on Autism Risk Across the Genome. *Am J Psychiatry*. 2021;178(1):87-98. doi:10.1176/appi.ajp.2020.19080834

11. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34(4):537-541. https://www.ncbi.nlm.nih.gov/pubmed/8524021

12. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol*. 2010;20(8):519-534. doi:10.1016/j.euroneuro.2010.03.008

13. Sha Z, Wager TD, Mechelli A, He Y. Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders. *Biol Psychiatry*. Published online March 1, 2019. doi:10.1016/j.biopsych.2018.11.011

14. Kebets V, Holmes AJ, Orban C, et al. Somatosensory-Motor Dysconnectivity Spans Multiple Transdiagnostic Dimensions of Psychopathology. *Biol Psychiatry*. Published online June 25, 2019. doi:10.1016/j.biopsych.2019.06.013

15. Cao H, Zhou H, Cannon TD. Functional connectome-wide associations of schizophrenia polygenic risk. *Mol Psychiatry*. Published online March 3, 2020. doi:10.1038/s41380-020-0699-3

16. Stefansson H, Meyer-Lindenberg A, Steinberg S, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature*. 2014;505(7483):361-366. doi:10.1038/nature12818

17. Simons Vip Consortium. Simons Variation in Individuals Project (Simons VIP): a genetics-first approach to studying autism spectrum and related neurodevelopmental disorders. *Neuron*. 2012;73(6):1063-1067. doi:10.1016/j.neuron.2012.02.014

18. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

19. Di Martino A, Yan CG, Li Q, et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry*. 2014;19(6):659-667. doi:10.1038/mp.2013.78

20. Di Martino A, O'Connor D, Chen B, et al. Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Sci Data*. 2017;4:170010. doi:10.1038/sdata.2017.10

21. ADHD-200 Consortium. The ADHD-200 Consortium: A Model to Advance the Translational

Potential of Neuroimaging in Clinical Neuroscience. *Front Syst Neurosci*. 2012;6:62. doi:10.3389/fnsys.2012.00062

22. Poldrack RA, Congdon E, Triplett W, et al. A phenome-wide examination of neural and cognitive function. *Sci Data*. 2016;3:160110. doi:10.1038/sdata.2016.110

23. Orban P, Desseilles M, Mendrek A, Bourque J, Bellec P, Stip E. Altered brain connectivity in patients with schizophrenia is consistent across cognitive contexts. *J Psychiatry Neurosci*. 2017;42(1):17-26. doi:10.1503/jpn.150247

24. Moreau CA, Urchs SGW, Kuldeep K, et al. Mutations associated with neuropsychiatric conditions delineate functional brain connectivity dimensions contributing to autism and schizophrenia. *Nat Commun*. 2020;11(1):1-12. doi:10.1038/s41467-020-18997-2

25. Wang K, Li M, Hadley D, et al. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. *Genome Res*. 2007;17(11):1665-1674. doi:10.1101/gr.6861907

26. Colella S, Yau C, Taylor JM, et al. QuantiSNP: an Objective Bayes Hidden-Markov Model to detect and accurately map copy number variation using SNP genotyping data. *Nucleic Acids Res*. 2007;35(6):2013-2025. doi:10.1093/nar/gkm076

27. Huguet G, Schramm C, Douard E, et al. Measuring and Estimating the Effect Sizes of Copy Number Variants on General Intelligence in Community-Based Samples. *JAMA Psychiatry*. Published online March 21, 2018. doi:10.1001/jamapsychiatry.2018.0039

28. Ge T, Chen CY, Ni Y, Feng YCA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun*. 2019;10(1):1776. doi:10.1038/s41467-019-09718-5

29. Bellec P, Carbonell FM, Perlbarg V, et al. A neuroimaging analysis kit for Matlab and Octave. In: *Proceedings of the 17th International Conference on Functional Mapping of the Human Brain*. ; 2011:2735-2746.

30. Urchs S, Armoza J, Benhajali Y, St-Aubin J, Orban P, Bellec P. MIST: A multi-resolution parcellation of functional brain networks. *MNI Open Res*. 2017;1:3. doi:10.12688/mniopenres.12767.1

31. Fu Z, Sui J, Turner JA, et al. Dynamic functional network reconfiguration underlying the pathophysiology of schizophrenia and autism spectrum disorder. *Hum Brain Mapp*. 2021;42(1):80-94.

doi:10.1002/hbm.25205

32. Laidi C, Boisgontier J, Chakravarty MM, et al. Cerebellar anatomical alterations and attention to eyes in autism. *Sci Rep*. 2017;7(1):12008. doi:10.1038/s41598-017-11883-w

33. Guell X, Anteraper SA, Ghosh SS, Gabrieli JDE, Schmahmann JD. Neurodevelopmental and Psychiatric Symptoms in Patients with a Cyst Compressing the Cerebellum: an Ongoing Enigma. *Cerebellum*. 2020;19(1):16-29. doi:10.1007/s12311-019-01050-4

34. Moreau CA, Raznahan A, Bellec P, Chakravarty M, Thompson PM, Jacquemont S. Dissecting autism and schizophrenia through neuroimaging genomics. *Brain*. Published online March 11, 2021. doi:10.1093/brain/awab096

35. Dadi K, Rahim M, Abraham A, et al. Benchmarking functional connectome-based predictive models for resting-state fMRI. *Neuroimage*. 2019;192:115-134. doi:10.1016/j.neuroimage.2019.02.062

36. Dadi K, Varoquaux G, Machlouzarides-Shalit A, et al. Fine-grain atlases of functional modes for fMRI analysis. *Neuroimage*. 2020;221:117126. doi:10.1016/j.neuroimage.2020.117126

37. Mellema CJ, Nguyen KP, Treacher A, Montillo A. Reproducible neuroimaging features for diagnosis of autism spectrum disorder with machine learning. *Sci Rep*. 2022;12(1):3057. doi:10.1038/s41598-022-06459-2

38. Pedregosa F, Varoquaux G, Gramfort A. Scikit-learn: Machine learning in Python. *J Mach Learn Res*. Published online 2011. http://www.jmlr.org/papers/v12/pedregosa11a

39. Team RC. R: A Language and Environment for Statistical Computing (Version 3.5. 2, R Foundation for Statistical Computing, Vienna, Austria, 2018). *There is no corresponding record for this reference*. Published online 2019. https://scholar.google.ca/scholar?cluster=7867649181275189008,12785896441631966750,17433060647574105173&hl=en&as_sdt=0,5&sciodt=0,5

40. Bellec P, Benhajali Y, Carbonell F, et al. Impact of the resolution of brain parcels on connectome-wide association studies in fMRI. *Neuroimage*. Published online August 1, 2015. doi:10.1016/j.neuroimage.2015.07.071

41. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Series B Stat Methodol*. 1995;57(1):289-300.

http://www.jstor.org/stable/2346101

42. Phipson B, Smyth GK. Permutation P-values should never be zero: calculating exact P-values when permutations are randomly drawn. *Stat Appl Genet Mol Biol*. 2010;9:Article39. doi:10.2202/1544-6115.1585

43. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-994. doi:10.1038/ng.2711

44. Signorell A. Tools for Descriptive Statistics [R package DescTools version 0.99.44]. Published online November 23, 2021. Accessed April 1, 2022. https://CRAN.R-project.org/package=DescTools

45. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989;45(1):255-268. https://www.ncbi.nlm.nih.gov/pubmed/2720055

46. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address: douglas.ruderfer@vanderbilt.edu, Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. *Cell*. 2018;173(7):1705-1715.e16. doi:10.1016/j.cell.2018.05.046

47. The Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke S, Walters JTR, O'Donovan MC. Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia. *medRxiv*. Published online September 13, 2020:2020.09.12.20192922. doi:10.1101/2020.09.12.20192922

48. Elliott LT, Sharp K, Alfaro-Almagro F, et al. Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature*. 2018;562(7726):210-216. doi:10.1038/s41586-018-0571-7

49. Anderson KM, Ge T, Kong R, et al. Heritability of individualized cortical network topography. *Proc Natl Acad Sci U S A*. 2021;118(9). doi:10.1073/pnas.2016271118

50. Writing Committee for the Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Bipolar Disorder, et al. Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders. *JAMA Psychiatry*. Published online August 26, 2020. doi:10.1001/jamapsychiatry.2020.2694

51. Radonjić NV, Hess JL, Rovira P, et al. Structural brain imaging studies offer clues about the effects of the shared genetic etiology among neuropsychiatric disorders. *Mol Psychiatry*. Published online January 17, 2021. doi:10.1038/s41380-020-01002-z

52. Van Dam NT, O'Connor D, Marcelle ET, et al. Data-Driven Phenotypic Categorization for Neurobiological Analyses: Beyond DSM-5 Labels. *Biol Psychiatry*. 2017;81(6):484-494. doi:10.1016/j.biopsych.2016.06.027

53. Bishop SL, Farmer C, Bal V, et al. Identification of Developmental and Behavioral Markers Associated With Genetic Abnormalities in Autism Spectrum Disorder. *Am J Psychiatry*. 2017;174(6):576-585. doi:10.1176/appi.ajp.2017.16101115

54. Cunningham AC, Fung W, Massey TH, et al. Movement Disorder Phenotypes in Children With 22q11.2 Deletion Syndrome. *Mov Disord*. 2020;35(7):1272-1274. doi:10.1002/mds.28078

55. Sørensen HJ, Mortensen EL, Schiffman J, Reinisch JM, Maeda J, Mednick SA. Early developmental milestones and risk of schizophrenia: a 45-year follow-up of the Copenhagen Perinatal Cohort. *Schizophr Res*. 2010;118(1-3):41-47. doi:10.1016/j.schres.2010.01.029

56. Bishop SL, Thurm A, Farmer C, Lord C. Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking. *Pediatrics*. 2016;137(3):e20152959. doi:10.1542/peds.2015-2959

57. Roshchupkin GV, Gutman BA, Vernooij MW, et al. Heritability of the shape of subcortical brain structures in the general population. *Nat Commun*. 2016;7:13738. doi:10.1038/ncomms13738

58. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The Human Thalamus Is an Integrative Hub for Functional Brain Networks. *J Neurosci*. 2017;37(23):5594-5607. doi:10.1523/JNEUROSCI.0067-17.2017

59. Wolff M, Vann SD. The Cognitive Thalamus as a Gateway to Mental Representations. *J Neurosci*. 2019;39(1):3-14. doi:10.1523/JNEUROSCI.0479-18.2018

60. Jahn T, Hubmann W, Karr M, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Res*. 2006;142(2-3):191-199. doi:10.1016/j.psychres.2002.12.003

61. Peralta V, Cuesta MJ. Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders. *Schizophr Bull*. 2017;43(5):956-971.

doi:10.1093/schbul/sbx089

62. Huguet G, Schramm C, Douard E, et al. Genome-wide analysis of gene dosage in 24,092 individuals estimates that 10,000 genes modulate cognitive ability. *Mol Psychiatry*. Published online January 7, 2021. doi:10.1038/s41380-020-00985-z

63. Davies RW, Fiksinski AM, Breetvelt EJ, et al. Using common genetic variation to examine phenotypic expression and risk prediction in 22q11.2 deletion syndrome. *Nat Med*. 2020;26(12):1912-1918. doi:10.1038/s41591-020-1103-1

64. Kendall KM, Rees E, Escott-Price V, et al. Cognitive Performance Among Carriers of Pathogenic Copy Number Variants: Analysis of 152,000 UK Biobank Subjects. *Biol Psychiatry*. 2017;82(2):103-110. doi:10.1016/j.biopsych.2016.08.014

65. Kirov G, Rees E, Walters JTR, et al. The penetrance of copy number variations for schizophrenia and developmental delay. *Biol Psychiatry*. 2014;75(5):378-385. doi:10.1016/j.biopsych.2013.07.022

66. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell*. 2012;148(6):1223-1241. doi:10.1016/j.cell.2012.02.039

67. Marshall CR, Howrigan DP, Merico D, et al. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet*. 2017;49(1):27-35. doi:10.1038/ng.3725

68. Rees E, Kirov G, Sanders A, et al. Evidence that duplications of 22q11.2 protect against schizophrenia. *Mol Psychiatry*. 2014;19(1):37-40. doi:10.1038/mp.2013.156

69. Sanders SJ, He X, Willsey AJ, et al. Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. *Neuron*. 2015;87(6):1215-1233. doi:10.1016/j.neuron.2015.09.016

70. Bernier R, Steinman KJ, Reilly B, et al. Clinical phenotype of the recurrent 1q21.1 copy-number variant. *Genet Med*. 2016;18(4):341-349. doi:10.1038/gim.2015.78

71. D'Angelo D, Lebon S, Chen Q, et al. Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities. *JAMA Psychiatry*. 2016;73(1):20-30. doi:10.1001/jamapsychiatry.2015.2123

Figure legends

Figure 1 Concordance across genetic, transcriptomic, and connectomic correlations. A) Previously published genetic correlations between pairs of conditions and traits. [3,6,7,43]. B) Functional connectivity correlations between pairs of conditions and traits. Correlations values are available in eTable 4. Stars represent significant correlations (* p<0.05, ** p<0.005, *** q FDR). C) Concordance between functional connectivity correlation across pairs of conditions and previously published transcriptomic correlation [8]. D) Concordance between functional connectivity correlations across pairs of conditions and traits (cognitive ability and neuroticism) and previously published genetic correlation. X and Y axis: r values of correlations. The brain FC correlations (r_{FC}) represent the correlation between the FC profiles of a pair of conditions-traits. The diagonal represents a perfect concordance. Colors indicate papers that computed r_G: green [3], brown [43], purple [7], pink [6], black [8]. Abbreviations: CCC: Lin's concordance correlation coefficient, CI: confidence interval, ASD: autism spectrum disorder, SZ: schizophrenia, BIP: bipolar disorder, MDD: major depressive disorder, NT: neuroticism, Del: deletion, Dup: duplication, Fluid intel: fluid intelligence, IQ: intelligence quotient, ADHD: Attention-Deficit / Hyperactivity-Disorder, IBD: Inflammatory bowel disease.

Figure 2 Atlas of functional connectivity relationships across psychiatric conditions, genetic risks, and traits. A. Pearson correlation between 17 FC-profiles (2080 beta values from CWAS). Stars represent significant correlations (* p<0.05, ** p<0.005, *** q FDR). B-D. PCA conducted on the 17 FC profiles: B-C Loadings of functional connections on PC1 (B) and PC2 (C) (overconnectivity in red, underconnectivity in blue). Each chord diagram shows the top 5% of connections' loadings. All 64 seed regions are represented in the black inner circle. Seed regions are grouped into functional networks. The width of the seed region in the black inner circle corresponds to the contribution of regions to the PC. Dimension 1 was dominated by overconnectivity of the thalamus, basal ganglia, and the somatomotor network. Dimension 2 was dominated by altered connectivity between the visual network and the posterior-medial default mode network. D. Loadings of conditions and traits on PC1 (blue) and PC2 (orange) explaining respectively 24 and 10% of the connectome-wide variance across FC-profiles. E. Density plots show examples of null distributions of correlations used to determine significance. FC profiles of ASD and PGS ASD have the lowest correlation that survives FDR.

F. Brain maps represent thalamic FC profiles (64 beta values for each connection between the thalamus and all other functional regions). Red = overconnectivity; blue underconnectivity. color scale represents the beta value (z-score). Abbreviations: ASD: autism spectrum disorder, SZ: schizophrenia, BIP: bipolar disorder, MDD: major depressive disorder, CD: Cross-disorder, NT: Neuroticism, Fluid intel: fluid intelligence, PRS: Polygenic score (=PGS), Del: deletion, Dup: duplication, Fluid intel: fluid intelligence, DMN pm: posteromedial default mode network.

Figure 3 Schematic diagram summarizing some of the main results and their interpretations. They are integrated into a broader bottom-up perspective representing mechanistic convergence from genes to diagnoses. Rare genetic variants (bottom level) converge on a limited set of transcriptomic modules. The latter may converge on brain alterations (e.g. thalamo-somatomotor overconnectivity, middle-level). Brain alterations may underly differences in cognitive and clinical dimensions altered across several diagnoses (eg. ASD and SZ, top-level). We showed convergence on sensory-motor FC networks and a pleiotropic effect of sensory-motor dimensions across psychiatric diagnoses.

Table 1 Data demographics

Genetic variants Conditions Traits	Status	n tot / n clin	Age	Sex (F/M)	Cohorts	IQ loss	OR ASD	OR SZ
						Previously published		
1q21.1 1: 146.53-147.39 7 genes (*CHD1L*)	DEL	25/15	44.4 (19)	12/13	UKBB-MRG-Cardiff-SFARI	15	3.2	6.4
	DUP	19/6	50.9 (19)	13/6		25	5.3	2.9
22q11.2 22: 19.04-21.47 49 genes (*TBX1*)	DEL	43/43	16.9 (7)	19/24	UCLA	28.8	32.3	23
	DUP	22/12	39.4 (23)	12/10	UCLA-UKBB Cardiff-MRG	8.3	2	0.2
16p11.2 16: 29.65-30.20 27 genes (*KCTD13*)	DEL	32/28	21.7 (20)	13/19	SFARI - MRG -UKBB	26	14.3	1.1
	DUP	35/29	34.1 (19)	14/21		11	10.5	11.7
15q11.2 15: 22.81-23.09 4 genes (*CYFIP1*)	DEL	103/0	64.3 (7)	55/48	UKBB	3	1.3	1.9
Idiopathic psychiatric conditions	SZ	283	33.9 (9.2)	73/210	Montreal-SZ, CNP	-	-	-
	BIP	44	35 (9)	20/24	CNP	-	-	-
	ASD	472	14.9 (6)	0/472	ABIDE1, ABIDE2	-	-	-
	ADHD	223	14.8 (9.5)	66/157	ADHD-200 CNP	-	-	-
Non-psychiatric condition	IBD	287	64.7(7.5)	144/143	UKBB			
Polygenic scores	ASD	29460	64.2 (7.5)	15840/ 13620	UKBB	-	2.7	-
	SZ					-	-	3.5
	BIP					-	-	-
	MDD							
	Cross-D					-	-	-
Traits	FI	27522	64 (7.5)	14777/ 12745		-	-	-
	NT	24025	64 (7.5)	12723/ 11302		-	-	-
Controls	UKBB	30185	64.1 (7.5)	16260/13925	UKBB	-	-	-
	SFARI	84	26.7 (15)	35/49	SFARI	-	-	-
	MRG	39	34 (16)	25/14	MRG	-	-	-
	Cardiff	8	39.8 (4)	4/4	Cardiff			
	UCLA	43	13 (4.6)	22/21	UCLA	-	-	-
	Psychiatric cohorts	1066	20 [11)	244/822	-	-	-	-

CNV carriers, individuals with idiopathic psychiatric conditions, and controls after MRI quality control. Chr: chromosome number, and coordinates are presented in Megabases (Mb, Hg19). The number of genes encompassed in each CNV is detailed below the genomic coordinates, followed by a well known gene to help identify the CNV. n = tot /Clin: total number of participants /number of participants clinically ascertained. Age (in years, mean ± standard deviation); M: male; All sites scanned controls and sensitivity analyses were performed to investigate the potential bias introduced by differences in scanning site, age, and sex. IQ loss: mean decrease in IQ points associated with each CNV [27,62]. Odd-ratios (OR) for the enrichment of CNVs in ASD and schizophrenia were previously published [63–71]. ORs for the enrichment of CNVs in ADHD were not available. Detailed information relative to diagnosis, IQ, and motion, are available in Supplementary information (eTable2). Abbreviations: DEL: deletion; DUP: duplication; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit / Hyperactivity-Disorder, BIP: Bipolar disorder, MDD: Major Depression Disorder, CrossD: Cross-disorder, IBD: Inflammatory Bowel Disease, CNP: Consortium for Neuropsychiatric Phenomics, MRG: Montreal rare genomic disorder; IQ: intelligence quotient.

Table 2 CWAS summary

Genetic variants / Conditions / Traits	Status	Connections		Beta values		Top-decile β values	p-value effect
		pos	neg	min	max		
1q21.1	DEL	1	11	−1.07	0.62	0.44	0.002
	DUP	4	0	−0.62	0.84	0.48	0.002
22q11.2	DEL	4	13	−1.48	1	0.65	$<2 \times 10^{-4}$
	DUP	0	2	−0.78	0.69	0.43	0.04
16p11.2	DEL	124	149	−0.98	1.67	0.57	$<2 \times 10^{-4}$
	DUP	4	3	−1.04	0.55	0.38	0.002
15q11.2	DEL	1	0	−0.29	0.36	0.2	0.01
Idiopathic psychiatric conditions	SZ	221	258	−0.41	0.51	0.30	$<2 \times 10^{-4}$
	BIP	33	24	−0.66	0.65	0.43	$<2 \times 10^{-4}$
	ASD	51	55	−0.26	0.36	0.16	$<2 \times 10^{-4}$
	ADHD	0	0	−0.22	0.22	0.15	$<2 \times 10^{-4}$
Non-psychiatric condition	IBD	0	0	−0.16	0.16	0.11	ns
Polygenic scores	Autism	3	1	−0.02	0.02	0.01	0.04
	Schizophrenia	93	115	−0.02	0.04	0.02	$<2 \times 10^{-4}$
	Bipolar	16	2	−0.02	0.03	0.01	0.002
	MDD	6	21	−0.02	0.03	0.01	0.003
	Cross-Disorder	23	22	−0.02	0.03	0.01	$<2 \times 10^{-4}$
Traits	Fluid intelligence	311	281	−0.04	0.04	0.02	$<2 \times 10^{-4}$
	Neuroticism	208	208	−0.03	0.04	0.02	$<2 \times 10^{-4}$

The number of significantly altered connections (FDR corrected) for each connectome-wide association study (n=19). min-max: minimum-maximum of z-scored beta values; top decile: top decile of beta values; Connection pos: number of positive connections surviving FDR; Connection neg: number of negative connections surviving. Abbreviations: DEL: deletion; DUP: duplication; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit / Hyperactivity-Disorder, BIP: Bipolar disorder, MDD: Major Depression Disorder, Cross Dis: Cross-disorder, IBD: Inflammatory Bowel Disease.

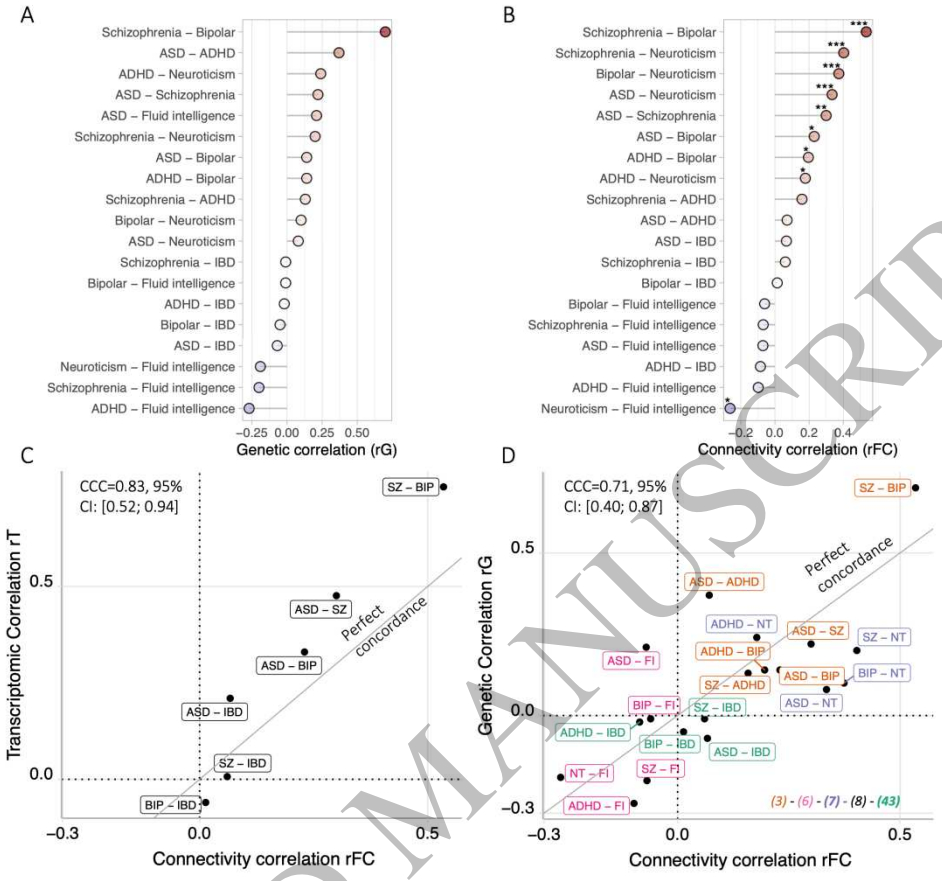

Figure 1
559x432 mm (x DPI)

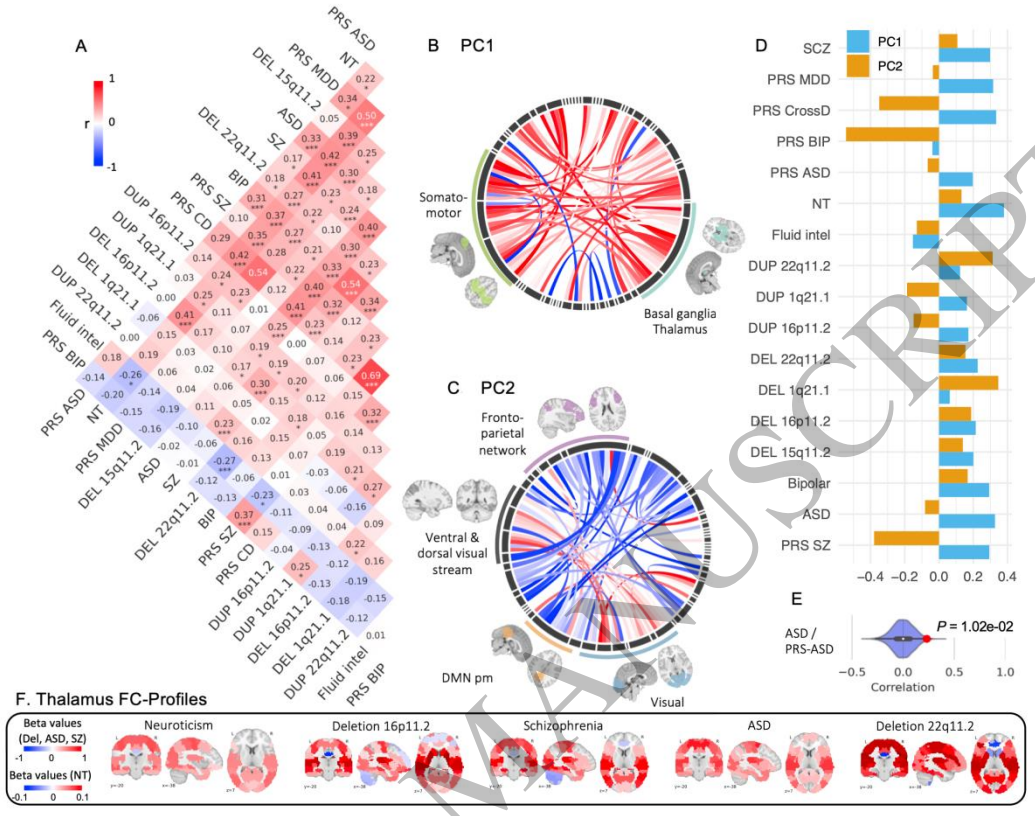

Figure 2
559x432 mm (x DPI)

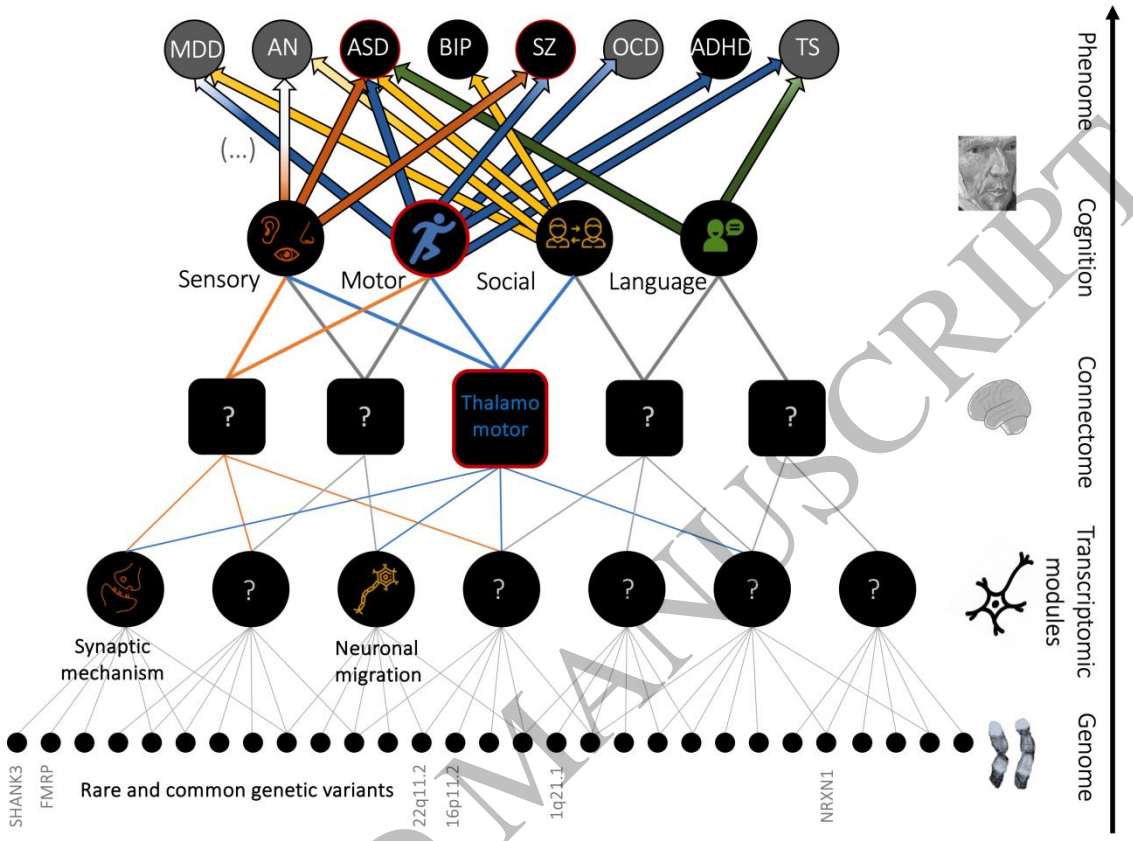

Figure 3
559x432 mm (x DPI)