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Mapping Genome-wide Neuropsychiatric Mutation Effects On Functional Brain Connectivity

Copy Number Variants Delineate Dimensions Contributing To Autism And Schizophrenia

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Résumé

Les recherches menées pour comprendre les troubles du spectre autistique (TSA) et la schizophrénie (SZ) ont communément utilisé une approche dite descendante, partant du diagnostic clinique pour investiguer des phénotypes intermédiaires cérébraux ainsi que des variations génétiques associées. Des études transdiagnostiques récentes ont remis en question ces frontières nosologiques, et suggèrent des mécanismes étiologiques imbriqués. L'approche montante propose de composer des groupes de porteurs d'un même variant génétique afin d'investiguer leur contribution aux conditions neuropsychiatriques (NPs) associées. Les variations du nombre de copies (CNV, perte ou gain d'un fragment d'ADN) figurent parmi les facteurs biologiques les plus associés aux NPs, et sont dès lors des candidats particulièrement appropriés.

Les CNVs induisant un risque pour des conditions similaires, nous posons l'hypothèse que des classes entières de CNVs convergent sur des dimensions d'altérations cérébrales qui contribuent aux NPs.

L'imagerie fonctionnelle au repos (rs-fMRI) s'est révélée un outil prometteur en psychiatrie, mais presqu'aucune étude n'a été menée pour comprendre l'impact des CNVs sur la connectivité fonctionnelle cérébrale (FC).

Nos objectifs étaient de: 1) Caractériser l'effet des CNVs sur la FC; 2) Rechercher la présence des motifs conférés par ces signatures biologiques dans des conditions idiopathiques; 3) Tester si la suppression de gènes intolérants à l'haploinsuffisance réorganise la FC de manière indépendante à leur localisation dans le génome.

Nous avons agrégé des données de rs-fMRI chez: 502 porteurs de 8 CNVs associées aux NPs (CNVs-NP), de 4 CNVs sans association établie, ainsi que de porteurs de CNVs-NPs éparses; 756 sujets ayant un diagnostic de TSA, de SZ, ou de trouble déficitaire de l'attention/hyperactivité (TDAH), et 5377 contrôles. Les analyses du connectome entier ont montré un effet de dosage génique positif pour les CNVs 22q11.2 et 1q21.1, et négatif pour le 16p11.2. La taille de l'effet des CNVs sur la FC était corrélée au niveau de risque psychiatrique conféré par le CNV. En accord avec leurs effets sur la cognition, l'effet des délétions sur la FC était plus élevé que celui des duplications. Nous avons identifié des similarités entre les motifs cérébraux conférés par les CNVs-NP, et l'architecture fonctionnelle des individus avec NPs. Le niveau de similarité était associé à la sévérité du CNV, et était plus fort avec la SZ et les TSA qu'avec les TDAH. La comparaison des motifs conférés par les délétions les plus sévères (16p11.2, 22q11.2) à l'échelle fonctionnelle, et d'expression génique, nous a confirmé l'existence présumée de relation entre les mutations elles-mêmes. À l'aide d'une mesure d'intolérance aux mutations (pLI), nous avons pu inclure tous les porteurs de CNVs disponibles, et ainsi identifier un profil d'haploinsuffisance impliquant le thalamus, le cortex antérieur

cingulaire, et le réseau somato-moteur, associé à une diminution de mesure d'intelligence générale. Enfin, une analyse d'exploration factorielle nous a permis de confirmer la contribution de ces régions cérébrales à 3 composantes latentes partagées entre les CNVs et les NPs. Nos résultats ouvrent de nouvelles perspectives dans la compréhension des mécanismes polygéniques à l'œuvre dans les maladies mentales, ainsi que des effets pléiotropiques des CNVs.

Mots clés

Troubles du spectre autistique, Schizophrénie, Variation du nombre de copies, Connectivité, IRM fonctionnelle au repos, Pléiotropie, Thalamus, Neuropsychiatrie

Summary

Research on Autism Spectrum Disorder (ASD) and schizophrenia (SZ) has mainly adopted a 'top-down' approach, starting from psychiatric diagnosis, and moving to intermediate brain phenotypes and underlying genetic factors. Recent cross-disorder studies have raised questions about diagnostic boundaries and pleiotropic mechanisms. By contrast, the recruitment of groups based on the presence of a genetic risk factor allows for the investigation of molecular pathways related to a particular risk for neuropsychiatric conditions (NPs). Copy number variants (CNVs, loss or gain of a DNA segment), which confer high risk for NPs are natural candidates to conduct such bottom-up approaches.

Because CNVs have a similar range of adverse effects on NPs, we hypothesized that entire classes of CNVs may converge upon shared connectivity dimensions contributing to mental illness.

Resting-state functional MRI (rs-fMRI) studies have provided critical insight into the architecture of brain networks involved in NPs, but so far only a few studies have investigated networks modulated by CNVs.

We aimed at 1) Delineating the effects of neuropsychiatric variants on functional connectivity (FC), 2) Investigating whether the alterations associated with CNVs are also found among idiopathic psychiatric populations, 3) Testing whether deletions reorganize FC along general dimensions, irrespective of their localization in the genome.

We gathered rsfMRI data on 502 carriers of eight NP-CNVs (high-risk), four CNVs without prior association to NPs as well as carriers of eight scarcer NP-CNVs. We also analyzed 756 subjects with idiopathic ASD, SZ, and attention deficit hyperactivity disorder (ADHD), and 5,377 controls. Connectome-wide analyses showed a positive gene dosage effect for the 22q11.2 and 1q21.1 CNVs, and a negative association for the 16p11.2 CNV. The effect size of CNVs on relative FC (mean-connectivity adjusted) was correlated with the known level of NP-risk conferred by CNVs. Consistent with results on cognition, we also reported that deletions had a larger effect size on FC than duplications. We identified similarities between high-risk CNV profiles and the connectivity architecture of individuals with NPs. The level of similarity was associated with mutation severity and was strongest in SZ, followed by ASD, and ADHD. The similarity was driven by the thalamus, and the posterior cingulate cortex, previously identified as hubs in transdiagnostic psychiatric studies. These results raised questions about shared mechanisms across CNVs. By comparing deletions at the 16p11.2 and 22q11.2 loci, we identified similarities at the connectivity, and at the gene expression level. We extended this work by pooling all deletions available for analysis. We asked if connectivity alterations were associated with the severity of deletions scored using pLI, a measure of intolerance to haploinsufficiency. The haploinsufficiency profile

involved the thalamus, anterior cingulate cortex, and somatomotor network and was correlated with lower general intelligence and higher autism severity scores in 3 unselected and disease cohorts. An exploratory factor analysis confirmed the contribution of these regions to three latent components shared across CNVs and NPs.

Our results open new avenues for understanding polygenicity in psychiatric conditions, and the pleiotropic effect of CNVs on cognition and on risk for neuropsychiatric disorders.

Keywords

Autism spectrum disorder, Schizophrenia, Copy number variant, Connectome-wide association study, Resting-state functional MRI, Pleiotropy, Thalamus, Bottom-up approach, Neuropsychiatric conditions

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List of abbreviations

ABIDE: Autism Brain Imaging Data Exchange
ACC: Anterior cingulate cortex
ADHD: Attention Deficit Hyperactivity Disorder
ADI-R: Autism Diagnostic Interview-Revised
ADOS: Autism Diagnostic Observation Schedule
ASD: Autism Spectrum Disorder
BIP: Bipolar disorder
BOLD: Blood oxygen level-dependent
BP: Breakpoints
CNV: Copy number variants
COS: Childhood-onset schizophrenia
CPRS-LV: Conner's Parent Rating Scale-Revised, Long Version
CSF: Cerebrospinal fluid
CT: Cortical Thickness
CWAS: Connectome-wide analysis studies
DEL: Deletion
DMN: Default mode network
DSM: Diagnostic and Statistical Manual of Mental Disorders
DUP: Duplication
DWI: Diffusion-weighted imaging
EFA: Exploratory factor analysis
ENIGMA: Enhancing Neuro Imaging Genetics through Meta-Analysis
FC: Functional Connectivity
fMRI: Functional MRI
FSIQ: Full-scale intelligence quotient
GWAS: Genome-wide association studies
HG: Human genome
ICV: Intracranial volume
ID: Intellectual Disability
IPC: Idiopathic psychiatric conditions
IQ: Intelligence quotient
kb: Kilobase
MAF: Minor Allele Frequency
Mb: Megabases
MIST: Multiresolution intrinsic segmentation template
MRI: Magnetic resonance imaging
MRSPP: Multidimensional Scale for Rating Psychiatric Patients
NPs: Neuropsychiatric disorders
OCD: Obsessive-compulsive disorder
PDD-NOS: Pervasive developmental disorder–not otherwise specified
PGC: Psychiatric Genomics Consortium
pLI: Probability of being loss-of-function intolerant score
PRS: Polygenic Risk Score
RDoC: Research Domain Criteria Initiative
RMET: Reading Mind in the Eyes Test
Rs-fMRI: Resting-state functional MRI method
SA: Surface Area
SD: Standard deviation
SNP: Single nucleotide polymorphisms
SNV: Single nucleotide variants
SRS: Social Responsiveness Scale
SZ: Schizophrenia

À mes parents

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I. Introduction

Recent technical and methodological advances in imaging, genomics and imaging genetics, have offered new insights into the architecture of biological underpinnings of psychiatric conditions. Autism spectrum disorder (ASD) and schizophrenia (SZ) occur in more than 2% of live births; they are severe developmental conditions encompassing a wide range of clinical manifestations throughout the lifespan. Attempts to shed light on mechanisms of both conditions have mainly adopted a 'top-down' approach, starting with a diagnosis, and moving to intermediate brain phenotypes and underlying genetic factors (1). With ever-larger sample sizes in ASD and SZ research, the top-down framework has identified reproducible multi-scale biomarkers (2). This has revealed genetic and imaging commonalities underlying biology across conditions, raising questions about diagnostic boundaries, pleiotropic mechanisms, and heterogeneity of categorical diagnoses. Predictive and multivariate data-driven methods have identified latent components shared across ASD and SZ, that are also present as continuous dimensions in the general population. The 'bottom-up' approach offers an alternative strategy to study mechanisms related to biological risk irrespective of the clinical manifestations. It relies on the study of individuals who carry genetic risk factors for ASD or SZ (such as copy number variants, or CNVs). By contrast to the top-down approach, this genetics-first strategy can build proxies from a lower level in the hierarchy (e.g., functional imaging traits) to investigate how low-level models may explain observations higher up in the hierarchy (1,3). Such studies can identify intermediate brain phenotypes and biological shifts that accompany behavioural alterations and psychiatric risk, while they remain hidden in heterogeneous groups of mental illnesses (4,5). The reported effect-size of rare variants on neuroimaging traits are concordant with effects measured on cognitive and behavioural traits. This is in striking contrast with neuroimaging studies of behaviorally defined groups of patients (top-down) that have required very large samples to yield reproducible results. This promising strategy can only be applied to a few recurrent pathogenic variants that are frequent enough to establish a case-control study design. How can we close the gap between the ever-growing landscape of rare genetic variants identified in psychiatry and the knowledge of their effects on intermediate brain phenotypes? Recent approaches suggest that entire classes of genetic mutations exert their effects along shared dimensions, perhaps due to mechanistic molecular commonalities across conditions, reflecting emerging properties of the genome (6). This introduction will first consider results from the classical top-down approach in ASD and SZ and discuss key challenges in the quest for diagnostic biomarkers: clinical complexity, heterogeneous neuroimaging findings, and a mismatch between traditional clinical study designs and the architecture of genetic risk in psychiatric disorders. After reviewing each obstacle, we will explain potential solutions offered by a bottom-up framework, in conjunction with multivariate predictive modelling. The two complementary frameworks

offer insights into ASD and SZ mechanisms and open new avenues to understand polygenicity in mental illnesses and pleiotropic effects of genetic variants on risk for psychiatric disorders.

Evolution of classification and technology

Categorical diagnoses in psychiatry: The definition of boundaries

Psychiatric diagnoses were built on the principle that mental disorders fall into separate categories with distinct etiologies and clinical presentations. An international manual to cluster co-occurring cognitive and clinical impairments was developed after World War II (Figure 1) to group mental disorders into clinically homogeneous subgroups, and with the objective of facilitating patient care (7,8). However, many patients do not fit neatly within the boundaries of any one diagnostic category. Comorbidity (the coexistence of two or more disorders) is common: half of those meeting diagnostic criteria for one disorder will also meet criteria for at least one other condition (9). Shared etiological mechanisms might go beyond any of the nosographic boundaries commonly used. Despite a strong push for dimensional approaches in psychiatric illnesses such as the Research Domain Criteria Initiative (RDoC) (10), identifying and validating domain criteria has been difficult, and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, 2013) remains centred on categorical diagnoses.

Technological insights into imaging and genetic biomarkers

Recent technological and methodological advances in imaging, genomics and imaging genetics, have helped identify biomarkers involved in neuropsychiatric conditions (NPs). A biomarker may be defined as a ‘‘characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention’’ (11). Therefore, biomarkers can be useful for diagnostic purposes, and by extension for classification, identification of a disease stage, or prediction of the illness trajectory and treatment response.

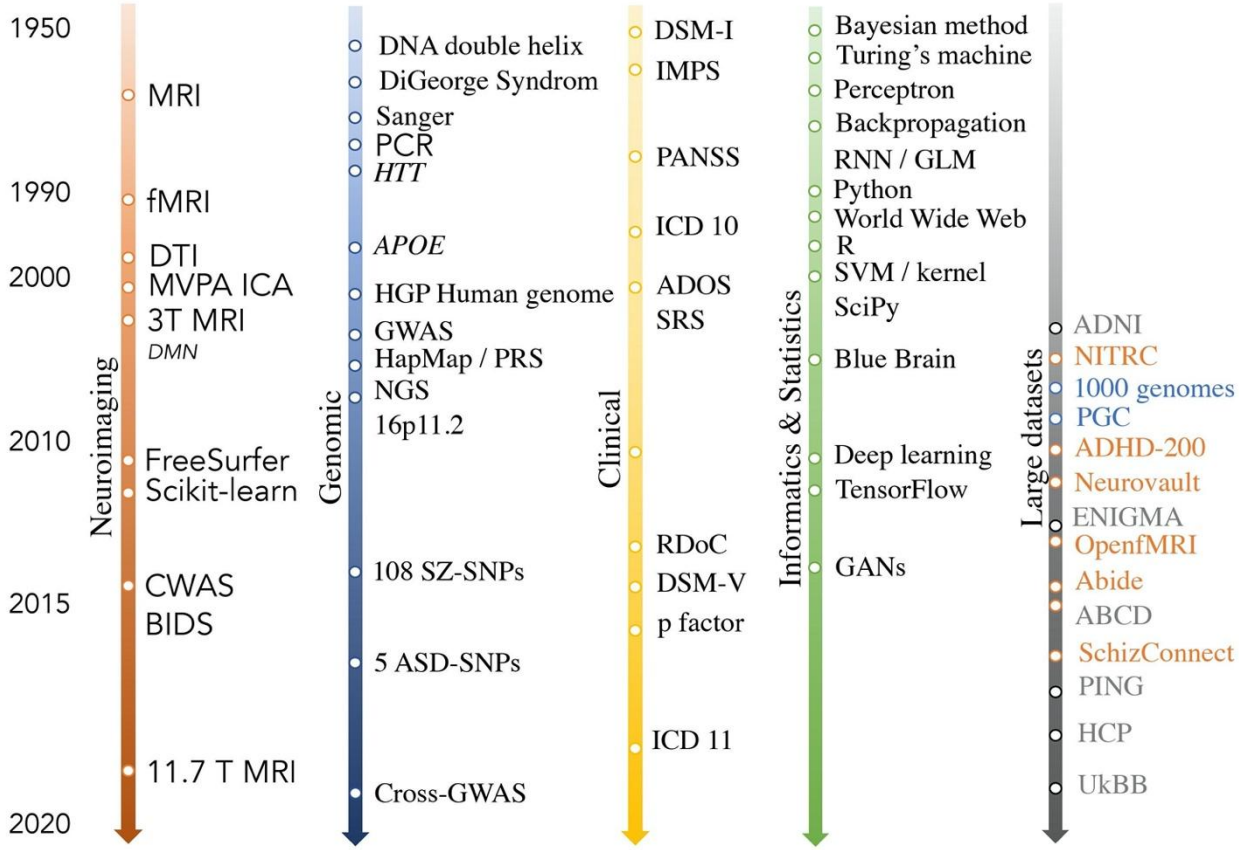

Figure I-1 Recent advances in acquiring brain imaging and high-throughput genomics data

Legend: Many advances in brain imaging genomics have been made by large-scale initiatives and cohort studies, such as the Autism Brain Imaging Data Exchange (ABIDE)(12), the Psychiatric Genomics Consortium (PGC) (13), the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium (14) and the UK Biobank (15). These initiatives (non-exhaustive list of examples) facilitate advances in psychiatry by providing large brain imaging and genomics datasets to the research community worldwide (16).

From the first human brain scan to connectome-wide association studies

Measures of brain architecture provided by neuroimaging tools are among the most extensively studied endophenotypes.

Anatomical MRI: static cartography of the brain

Principles of magnetic resonance imaging (MRI) were introduced by Paul Lauterbur in 1973 (Figures 1-2) (17) and provide rich quantification of in vivo human brain structural organization (18). Among the many methods used to investigate such data, one of the most widely-used is voxel-based morphometry (19). This method is using a regional smoothing kernel to quantify and compare between subjects the concentration of grey matter across voxels in the brain. A voxel is a cubic element of brain volume with a typical size of 1 mm^3.

The thickness of the cortex is a complementary metric that quantifies the distance between the white matter surface and the grey cerebrospinal fluid (CSF) intersection (20,21). Contrary to voxel-based morphometry, the cortical thickness metric (CT) provides a direct index of cortical morphology, and analyses are performed at nodes of a polygonal mesh rather than on a voxel grid (21).

Additional anatomical sequences such as diffusion-weighted imaging (DWI) were introduced (22,23) and are commonly used to map the three-dimensional motion of water in order to capture the microstructural properties of the white matter (24).

Functional MRI: studying the brain as a network

Functional MRI (fMRI) techniques have also been extensively used to measure blood oxygen level-dependent (BOLD) contrast, providing information on cerebral blood flow which is indirectly coupled to neuronal activity (25). Low-frequency oscillations (0.01-0.1 Hertz) are mainly driven by the observed spontaneous BOLD signals. By measuring changes in the BOLD signal during a task, regional brain activity has been associated with specific cognitive processes (task-fMRI).

In contrast, resting-state fMRI methods (rs-fMRI, figures 1-2) measure the temporal covariance of spontaneous BOLD fluctuations across areas when no explicit task is performed (26,27). Rs-fMRI is particularly appropriate to study the young population because it enables data acquisition without patient participation (contrary to task-fMRI), and limits excessive motion during scanning. This is even more critical in studies investigating individuals with neurodevelopmental conditions.

Recent advances in acquisition and analysis techniques have also catalysed the investigation of functional connectivity (FC), thereby revealing the brain's intrinsic functional architecture. The brain's activity is distributed across multiple topographical levels, from distributed networks to the localized areas they are derived from (28). Brain cartography based on connectivity-based parcellation has highlighted a set of regions for which activity is suppressed during tasks and specifically active during a resting condition (29). This network is often called the default mode network (DMN (30)). Using a cluster analysis on rs-fMRI data of 1000 subjects, Yeo and colleagues delineated a parcellation of the human cerebral cortex activity falling into seven networks: the DMN, the limbic, the dorsal attentional, the ventral attentional, the frontoparietal, the somatomotor and the visual networks (31). This functional brain map is one of the most commonly used in the field, but different parcellations have been developed to investigate other levels of observation. Urchs and colleagues introduced the multiresolution intrinsic segmentation template (MIST) that provides the field with a hierarchical decomposition of networks across nine resolutions (7 to 444 functional parcels) (28). Analysing FC at a higher resolution (e.g. at the voxel level) has been tested but is neither practical nor appropriate due to a number of statistical issues (e.g. collinearity and multiple comparisons) in the vast majority of applications (32). FC is therefore mostly studied at a regional or network level. A computationally efficient, data-driven technique (independent of a priori hypotheses) for connectome-wide association studies (CWAS, Figure 1) has recently been introduced and provides a comprehensive region-wise and network-wide survey of activity synchronisation across the connectome (32,33).

These complementary anatomical and functional metrics are of great interest in a wide range of NPs and have been used extensively to identify brain biomarkers of ASD and SZ (34–38).

From the first candidate gene to genome-wide association studies

Several waves of genomic technology contributed to genetic discoveries across disciplines. Huntington's disease was identified in 1983 (Figure 1) through linkage analysis using a small number of markers, and the association between Alzheimer's disease and common variation in the *APOE* gene was discovered in 1993 in a candidate gene study of 30 cases (39). Likewise, exome sequencing identified the genetic cause of the Miller syndrome analyzing only 3 families without any a priori knowledge (40). With these successes in mind, many early studies in psychiatric genetics were performed assuming a simple genetic architecture. A first wave of underpowered linkage and candidate gene studies led to many claims of risk gene discovery that were not subsequently replicated (41).

Rare variants: Linkage studies to whole-genome sequencing

Our understanding of rare, large effect-size mutations in psychiatric conditions has emerged from the field of intellectual disability (ID) (5). *FMR1* was among the first gene to be linked to ID in 1991. Around the turn of the century, a series of ID-genes were discovered on the X chromosome. The large-scale implementation of chromosomal microarray (aCGH) in clinical research was a game changer in the field, as it enabled the genome-wide identification of copy-number variants (CNV, Figure 2), genomic deletions or duplications of more than 1000 base pairs. A complex landscape of large rare and ultra-rare CNVs has since been discovered, some of them disrupting or encompassing entire genes, and conferring greatly increased risk for NPs (42). Together, these CNVs are present in 1 to 3% of the general population (6,42).

Whole-genome sequencing is now increasingly used clinically to identify rare variants conferring large risk for NPs. This technique can identify all types of genetic variation across the genome. Whole-exome sequencing is an alternative technique that is limited to the coding part of the genome (~3%). It provides a less expensive but focused way to identify gene-disrupting variants in exons (43).

Common variants: From candidate gene studies to GWAS

Common variants are genetic polymorphisms with an allele frequency of at least 1% in the general population. They are identified using genotyping arrays that typically cover between 600,000 to a million single nucleotide polymorphisms (SNPs, Figure 2). Genome-wide association studies (GWAS, Figures 1-2) are mass univariate approaches to test associations of each SNP with a psychiatric condition or quantitative trait (43–45).

The multiple testing issues associated with GWAS required a large amount of data, and have led to the development of consortia almost exclusively focused on the study of common genetic variants. The largest such consortium in psychiatric genetics is the Psychiatric Genomics Consortium (PGC, Figure 1) (13), that was initiated in 2007 and has led to many major genetic advances in the field. As most SNPs contributing to NPs are not in protein-coding regions, understanding the link between variants and potentially disrupted genes remains challenging. This requires the annotation of non-coding regions, a key goal of consortia such as ENCODE (46), Roadmap (47), and GTEx (48). The latter has produced genome-wide regulatory maps and transcriptional profiles across a wide spectrum of cells and tissues.

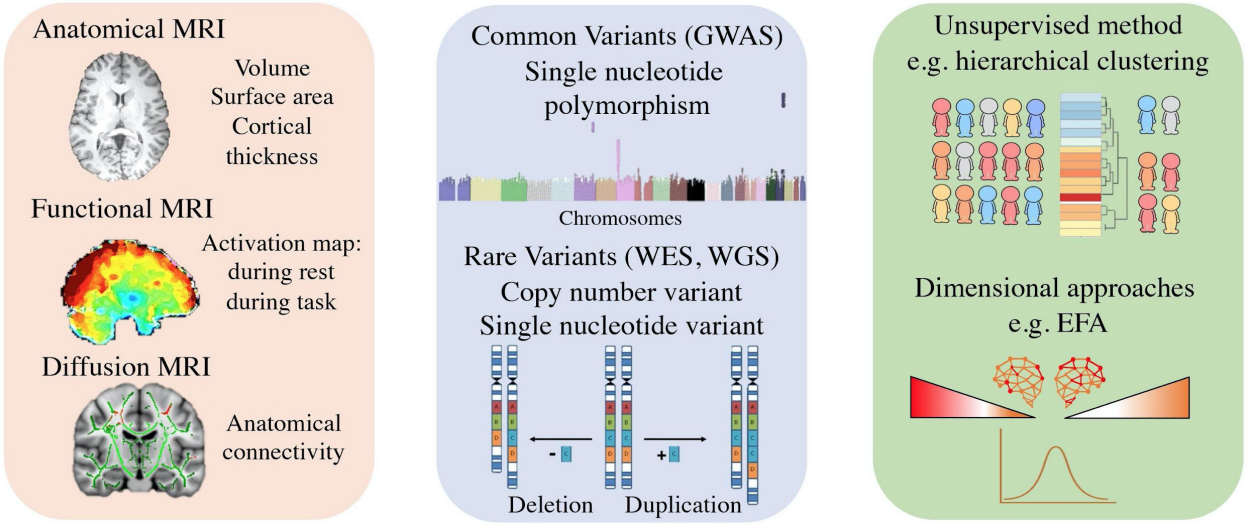

Figure I-2 Unprecedented access to neuroimaging and genetic biomarkers

Legend: Recent technological and methodological advances in imaging and genomics have permitted the identification of biomarkers involved in neuropsychiatric conditions (NPs). Genome-wide association studies (GWAS), Whole-genome sequencing (WGS), Whole-exome sequencing (WES), Magnetic resonance imaging (MRI).

Schizophrenia and autism spectrum disorders as evolving concepts

NPs have mainly been studied using a top-down approach starting from the diagnosis and moving down to cognitive dimensions, brain phenotypes, and genetic factors. In other words, "symptom-first" approaches have attempted to characterize biomarkers of each psychiatric condition independently by comparing groups with a diagnosis of interest to typically developing controls. However, although diagnostic definitions are core to classical approaches, these definitions have undergone significant revisions over time.

The early nosology of Autism and Schizophrenia

The autism classification has evolved over time, merging and splitting clinical features, and genetic syndromes. Autism was introduced as a term in 1911 as one of 4 'types of impairment in SZ: Autism, Affectivity, Association, and Ambivalence' (51). Autism was later described by Kanner (1943) and (1944), to refer to a dimension of schizoid disorders (49,50). By the 1970s, researchers had clearly defined autism and childhood SZ as separate conditions (52). To help distinguish autism from SZ, a "trumping rule" accompanied autism in the DSM-III (in the 1980's). This rule stated that this condition should not be diagnosed in the presence of delusions, hallucinations, and incoherence.

Autism heterogeneity and comorbidity are challenges for disease modelling

Spectrum terminology unifies three previously separate (DSM-IV) but highly related diagnoses: autistic disorder, Asperger's disorder, and pervasive developmental disorder–not otherwise specified. Shifting diagnostic borders have led to a notable increase of ASD prevalence reported in the last decades, reaching estimates of up to 1 in 59 (53).

Comorbid clinical features have been shown to be the rule rather than the exception, adding to the complexity of proper diagnostic boundaries delineation. Over a third of ASD patients meet criteria for other conditions such as obsessive-compulsive disorder (OCD), anxiety, mood disorders, ID, Attention Deficit Hyperactivity Disorder (ADHD), or epilepsy (54,55). Although 15 to 25% of youth with ADHD meet the criteria for ASD, and 50 to 70% of those with ASD present comorbid ADHD (56), diagnostic criteria for ADHD and ASD did not allow their simultaneous diagnosis until the last revision of the DSM-V (57). Hyper and hypo-sensitivity were previously listed as frequent comorbidities. They were recently added within the repetitive and restrictive domain into the core diagnosis. ID is observed in ~35% of ASD and can confound diagnostic instruments (58,59). This condition is classified as an ASD specifier in the DSM-V.

These comorbidities present challenges in disease modelling and have direct consequences on genetic and neuroimaging studies because findings may be related to either core features of the disease or comorbidities.

Schizophrenia, an association of positive and negative symptoms

The terminology schizophrenia is derived from *schizein* "split" and *phren* "mind, volition" (Greek). Eugen Bleuler used "group of schizophrenia(s)" to point out that there is a clinical diversification of SZ. Positive (productive, psychotic) and negative (deficit) symptoms were used in the 80s' to delineate subgroups of SZ patients. At the same time and with the emergence of neuroleptic drugs, a focus on brain chemistry diminished "the mind".

The population prevalence of SZ is approximately 1% and has remained stable during the last decades (60). This condition is now defined as a severe mental illness involving disordered thought and perception, with a characteristic onset in late adolescence/early adulthood (61). DSM-V and International Classification of Diseases (ICD-10) criteria for SZ request the presence of at least 2 of the following group of symptoms: delusions, hallucinations (positive symptoms), disorganized speech, catatonic behaviour, and negative symptoms.

Psychometric instruments to delineate diagnostic boundaries

Standardized instruments designed to measure symptoms of ASD and SZ have been developed during the past decades and had a major influence for clinical and research purposes worldwide, changing the way that assessments were conducted (62).

The most widely-used instruments for diagnosing ASD are the Autism Diagnostic Interview-Revised (ADI-R; (63)) and the Autism Diagnostic Observation Schedule (ADOS; (64,65)). The first one is a structured interview conducted with the subject's parent or caregiver. ADI-R consists of 93 items covering the subject's full developmental history. This score alone is usually sufficient for ASD diagnosis. The second one is an observation instrument based on a series of structured and semi-structured tasks involving social interaction between the examiner and the subject. The examiner will score observations in categories (social reciprocity, restricted and repetitive behaviours, communication, and behavioural difficulties not specific to ASD) (66). The combination of ADI and ADOS instruments is considered the gold standard for diagnosing (67).

As opposed to diagnostic instruments, other scales attempt to record dimensional measures of autistic traits. The Social Responsiveness Scale (SRS; (68)), which is completed by parents and teachers, is the most broadly used. This score has been reported as a tool capable of quantifying subtle differences in the degree of cognitive impairment (69).

In the 1950s, Lorr began a series of studies to provide a more efficient framework for delineating the symptomatology of psychoses, conducting a therapeutic evaluation and studying patient evolution (70,71). Though Kraepelin's system was still in use during the early post-World War II era, he rejected this typological approach and proposed an alternative method using factor analysis (72). Lorr and colleagues introduced the Multidimensional Scale for Rating Psychiatric Patients (MSRPP) to quantify symptom severity and changes in patients with psychoses who had been lobotomized. The early 1980s saw the development of a 2-dimensional model for SZ by the British psychiatrist T. Crow, who introduced the concept of positive and negative symptoms (72,73). To date, the Positive and Negative Syndrome Scale (PANSS) is considered the gold standard for assessing psychotic symptoms through a semi-structured interview (74).

Beyond discrete clinical entities

"Most psychiatric disorders do not represent single disease entities, and single disease processes cut across psychiatric boundaries" Beauchaine and Constantino, 2017 (75)

Neurodevelopmental continuum in autism and schizophrenia

Models based on clinical data suggest that autism and schizophrenia may represent extreme values on diverse continuous dimensions that extend into the normal range (10,76). This hypothesis introduced by Crespi and colleagues in 2010 has become widely accepted but the nature of such dimensions remains unclear and controversial (52,76–78). Childhood-onset schizophrenia (COS) is a recognized subtype of SZ, defined by an onset before the age of 13 years. Studies have suggested clinical and genetic commonalities across both COS and ASD (79,80) and 30% of children and adolescents with COS have comorbid ASD (81). Negative symptoms present in SZ (such as social avoidance and emotional flatness) may be also related to impairments in communication and motivation found in autism (Figure 3, (82)). Measures of autistic-like traits have been developed (e.g. SRS) to examine subthreshold autistic features in other conditions and in the general population (83). Finally, patients with either ASD or SZ present high difficulties in interpreting social cues associated with eye gaze, as well as deficits on the theory of mind tasks, which is considered a major dimension contributing to autism (84).

General psychopathology factor and RDoC initiative

Large-scale studies identified general psychopathology dimensions that cut through diagnostic boundaries (85). The psychopathology-factor (p-factor), analogous to the concept of general intelligence (g-factor), represents the tendency of an individual who scores highly on certain symptoms of psychopathology to also score highly on others. This metric has been developed to account for lifespan functional impairment and prospective pathology going beyond current symptom-based predictions (86,87). A recent study used this metric to link the dimension of psychopathology to intermediate brain imaging phenotypes and reported for example that fear symptoms were associated with a brain-wide reduction in CT and grey matter volumes (88). Such approaches open avenues for understanding how abnormalities of brain development may be associated with dimensions of psychopathology. This is in line with dimensional models such as the National Institute of Mental Health's Research Domain Criteria Project (RDoC, Figure 3) (10). The introduction of the RDoC initiative, in conjunction with the revised diagnostic classification of a broad ASD

category, emphasized the need for novel ways of conceptualizing NPs. Clusters of features may, therefore, be helpful to better understand the etiology of various phenotypic presentations and comorbidities of NPs.

In search of lost markers: lessons learned from neuroimaging studies

Neuroanatomical signatures of psychiatric conditions

Larger brain volume as the only reproducible finding in ASD

The most consistent structural MRI finding reported to date is a higher total brain volume. This is mainly the case before 24 months (89–92) but is also observed in older individuals with autism (+0.25 Cohen's d) (34). Other consistent changes have been identified by a review of 123 MRI studies. They reported reduced cerebellum and corpus callosum volumes, and increased CSF in ASD compared to controls (91,93). Results across studies were mostly inconsistent for the hippocampus, amygdala, thalamus and basal ganglia (91). Non-replicable findings and small effect sizes raised the necessity for conducting meta-analytical studies.

The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium aggregated 49 scanning sites (n=1,571 ASD and 1,651 controls) to study brain morphometry in autism. They identified smaller subcortical volumes of the pallidum, putamen, amygdala, and nucleus accumbens (effect-sizes, 0.13 to -0.13), as well as higher CT in the frontal cortex and smaller CT in the temporal cortex (effect-sizes, -0.21 to 0.20) (34). Subsequent large multi-site studies (n=1,327 ASD and controls) examined cortical morphometry in ASD (94), demonstrating higher CT in the superior temporal gyrus and the inferior frontal sulcus, which negatively correlated with age and full-scale intelligence quotient (FSIQ). Asymmetry in ASD has also been under scrutiny. A study across 54 datasets (n=1,774 ASD and 1,809 controls) reported CT asymmetries involving medial frontal, orbitofrontal, inferior temporal, and cingulate regions, decreasing in ASD compared to controls (95).

Among strategies used to tackle ASD heterogeneity (1,96,97), stratifying large samples of patients using data-driven methods has been one of the most promising avenues (Figure 4) (98). Using hierarchical clustering method on neuroanatomical data, Hong and colleagues reported that individuals with ASD were distributed into three distinct morphometric subtypes (ASD-I: cortical thickening, increased surface area (SA), tissue blurring; ASD-II: cortical thinning, decreased geodesic distance; ASD-III: increased geodesic distance) (99). These subtypes were also associated with gradual symptom severities. The existence of such subgroups illustrates the clinical heterogeneity and may help to reconcile previous inconsistent results in autism.

Grey matter deficits in prefrontal areas and hippocampus in SZ

Schizophrenia condition has been extensively studied during the last decades, and results have been less conflicting than ASD, suggesting a lower level of clinical heterogeneity compared to autism. Remaining heterogeneity may be due to medication exposure, stage of the disease, and the existence of genetic sub-groups of SZ.

A large-scale neuroimaging initiative pooled data over 15 sites (n=2,028 SZ and n=2,540 controls) and reported smaller hippocampus (Cohen's d=-0.46), amygdala (d=-0.31), thalamus (d=-0.31), nucleus accumbens (d=-0.25), and intracranial volumes (ICV, d=-0.12), and larger pallidum (d=0.21) and lateral ventricle volumes (d=0.37) (100). A meta-analysis of thirty-seven studies reported consistent grey matter deficits in frontal, limbic, and subcortical areas (101).

CT and SA differences have also been as well under scrutiny. Aggregating data from 39 sites (n=4,474 SZ and n=5,098 controls), a mega-analysis found a smaller SA (d= -0.254) in frontal and temporal lobe regions) and widespread thinner CT (d=-0.516). CT differences were larger in individuals with antipsychotic medication and were correlated with illness duration (2).

Thus, taken together, these studies suggest that there are only a few candidate MRI markers for reliable differential diagnosis of ASD and SZ.

Neuroanatomical commonalities among DSM categories

Altered regions shared across ASD and SZ also extended to other diagnoses (figure 4). This observation led researchers to speculate on shared mechanisms across multiple psychiatric diagnoses.

A first meta-analysis performed by Goodkind and colleagues in 2015, reported that grey matter loss observation in the dorsal anterior cingulate cortex (ACC) and the insula was present across SZ, bipolar (BIP), depression, addiction, OCD, and anxiety (102). Surprisingly, only a few diagnosis-specific effects have been identified, suggesting common neural substrates across disorders (102).

Neuroimaging commonalities have been explored by another meta-analysis of Cauda and colleagues in 2017 across ASD, SZ, ADHD, and OCD. Psychiatric conditions were distributed in two neuroanatomical alteration clusters: SZ was mainly included in the first one, which was driven by the anterior insula, the ACC, the ventromedial PFC, and frontopolar areas. OCD was located in the second cluster, associated with sensorimotor, premotor, visual, and lingual areas. ASD was uniformly distributed between both clusters

(103). Using structural covariance, the same group extended their study in 2018 and confirmed co-atrophy networks across conditions involving specific pathoconnectivity hubs such as the anterior insula, prefrontal cortices, the thalamus, superior temporal and precentral gyri (104).

Another suggested approach is to use severity metrics in individuals with a range of NP conditions. For example, Baribeau and colleagues found a negative correlation between social communication deficits, and right insula CT and ventral striatum grey matter volume in individuals with ASD, ADHD and OCD. Specifically, they reported that smaller subcortical volumes were associated with severe social deficits in ASD and ADHD and with mild social deficits in OCD. Larger amygdala and hippocampus volumes were associated with RMET (Reading the Mind in the Eyes Test) score (105).

Relationship between anatomical alterations and functional architecture may be used to investigate shared underlying biological factors. One hypothesis is that anatomical deficit commonality across NPs is distributed into functional resting-state networks rather than clustered spatially (106). Using this hypothesis, Park and colleagues reported in 2018 that ASD and SZ alterations of CT profiles were preferentially encompassed within the frontoparietal and limbic networks, while ASD and ADHD profiles were similarly enriched in the DMN. Finally, ADHD and SZ profiles spanned across the ventral attentional network (106).

Collectively, the extensive literature reported to date is going toward common underlying biology across NP conditions and raises questions about diagnostic boundaries and typical top-down approaches.

Attempt to delineate functional connectivity fingerprints of psychiatric conditions

Lack of consensus and reproducibility in ASD

Numerous studies have attempted to characterize rs-fMRI networks as ASD biomarkers but findings reported across studies were mostly inconsistent (107,108). Phenotypic heterogeneity, small samples, and different analytical methods used across studies may have contributed to these inconsistencies (108,109). Non-aggregated autism rs-fMRI datasets are way below 1000 individuals, which is a limiting factor to investigate the heterogeneity of this condition, and calls for meta and mega analyses.

A meta-analysis conducted by Lau and colleagues in 2019 across eight rs-fMRI studies was however able to report consistent under-connectivity in the dorsal posterior cingulate cortex and right medial paracentral lobule in ASD (109). Furthermore, the largest rs-fMRI study led by Holiga and colleagues in 2019, which aggregated four datasets (ABIDE1, ABIDE2, EU-AIMS LEAP and InFoRX), identified reproducible patterns of alterations across datasets (110). These patterns included under-connectivity within sensory-motor networks and over-connectivity within the prefrontal and parietal networks. These findings are encouraging but they required really large multi-site datasets of subjects to compensate for uncontrolled heterogeneity and small effect-size issues (37). Other studies still report conflicting findings in ASD (108,111).

In this context, data-driven methods attempted to identify homogeneous functional subgroups within the ASD cohort. For example, Easson and colleagues used clustering approaches to identify two separate functional patterns that distinguished ASD patients from controls (107). The first one was characterized by over-connectivity within networks and under-connectivity across networks. The second one involved DMN, cingulo-opercular, sensorimotor, and occipital networks. They did not report an interaction between subtypes and diagnostic groups. These findings showed that distinct clusters may be shared and co-exist across ASD subjects and controls (107). Other approaches have been proposed such as predictive modelling. Using patterns of connectivity from individuals with ASD and controls, Abraham and colleagues were able to obtain 67% prediction accuracy for the ASD diagnosis (37), and showed that prediction power was improved by the number of subjects included. The most informative networks to predict autism were the DMN, the parieto-insular, and the language networks (specific under-connectivity between temporo-parietal junction, insula and parietal lobes). This set of findings supports the need of a data-driven and predictive method, combined with large sample size, as essential to tackle heterogeneity in ASD.

Overall underconnectivity in SZ

Rs-fMRI studies in SZ suggested a reduction of activity in the DMN, with increased activity in the lingual gyrus (38,101,112). The latest review performed on 52 studies reported that SZ was characterized by under-connectivity within the default mode, thalamus, affective, ventral attention, frontoparietal, and somatosensory networks. The only reported overconnectivity was between the affective and the ventral attention networks (38).

The DMN connectivity profile has been more largely examined across psychosis diagnosis (113,114), showing a decrease of connectivity in the medial prefrontal cortex, anterior and posterior cingulate cortex, and precuneus across the psychosis spectrum. SZ and BD studies reported the medial prefrontal cortex as a major hub altered in psychosis (115).

The thalamus dysconnectivity is also a well-established biomarker of SZ (116–118). This structure has been reported as over-connected with middle temporal gyrus (correlated with positive symptoms) and under-connected with cerebellar regions (correlated with delusions and bizarre behaviour) (119).

Overall, results provided by fMRI in SZ suggest general underconnectivity of large-scale brain networks, mainly driven by the DMN, the thalamus and frontoparietal networks. These results are more consistent than in ASD. However, since no large (n>200) public MRI and/or fMRI dataset is yet available in SZ, these results should be interpreted with caution.

Functional findings across diagnostic boundaries

ACC and anterior insula were among the first set of regions to demonstrate shared dysconnectivity across psychiatric illnesses (120). Transdiagnostic functional disruptions were reported by further research in the prefrontal cortex, the intraparietal sulcus, and the mid-cingulate/pre-supplementary motor area (121). Functional signatures of patients with major depression, BIP, SZ, and schizoaffective disorders were overlapping within the frontoparietal network (122). In other words, psychotic illnesses were all associated with alterations in frontoparietal network connectivity.

The largest meta-analysis performed by Sha and colleagues in 2019 across eight psychiatric disorders (n=8298 patients and n=8165 controls) identified commonalities predominantly in the ventral salience, the frontoparietal and the DMN (123). An under-connectivity pattern was more specifically identified between the DMN and the ventral salience network and between the frontoparietal and the salience networks. An

over-connectivity pattern was then observed between the DMN and frontoparietal network and between the DMN and dorsal salience network. These functional findings raise questions about these alterations being the cause or the consequence to have a NP disorder. This also reinforces a hypothesis of shared mechanisms across NP that may be related to the generalized cognitive deficits observed in psychiatric disorders (p-factor / RdoC approaches).

Overall, NPs appear to be distributed along a gradient of connectivity alterations based on vulnerable hubs including the ACC, the frontoparietal (especially prefrontal), and the insular networks. This may be due to the role of these regions in complex functions such as social cognition (120). The frontoparietal network seems more specifically disrupted in SZ and ADHD, whereas the salience and the limbic networks appear to be more particularly affected in ASD.

Missing heritability and pleiotropic effect

Genomic architecture of ASD and SZ

Half a century of twin studies has established the genetic contribution to ASD and SZ between 70 and 91% (124–126). Genetic heterogeneity and pleiotropy mechanism may be related to the lack of reliable established macroscopic or microscopic pathognomonic features in ASD and SZ.

Contribution of common variants to ASD and SZ

Heritability estimates using SNP data demonstrate that commonly inherited genetic variants (Minor Allele Frequency (MAF) > 1% in the general population) explain a large proportion of the variance in susceptibility to ASD (45). However, the most extensive GWAS study to date, performed in a Danish population-based sample (n=18,381 individuals with ASD, n= 27,969 controls) identified only five genome-wide-significant loci and an SNP heritability of 0.118 (45)). Much larger sample size will be required to identify common variation implicated in the disorder.

Twin studies estimate the heritability of SZ around 79% (126). The "common-allele" model posits that SZ results from the cumulative effect of multiple common alleles with small effects. In 2014, a GWAS study conducted by the PGC (n= 36,000 individuals of SZ and over 100,000 controls), reported 108 SNPs associated with this condition (127). A follow-up study performed by Pardinas and colleagues extended this PGC result on the UK CLOZUK sample (128). They identifying 50 novel loci associated with SZ (145 in total). These heritability's estimates are based on an over simplistic model (phenotype = G(genetic) + E(environment)) and have to be interpreted with caution. They do not take into account the contribution of the interaction between G and E. These estimates values might, therefore, arise from indirect mechanisms such as assortative matting or dynastic effect (see (129)) and are likely inflated.

Contribution of rare variants to ASD and SZ

Rare variants with large effects explain less than 5% of the overall liability to autism. However, they were identified in 20% of individuals with ASD (130,131) and have important implications for carriers. Studies estimated that rare variants in close to 1000 genes may confer large risk for ASD. Among these rare variants, CNVs are routinely screened in the clinic using chromosomal microarray methods. De novo or transmitted

CNVs, such as the 16p11.2 deletion are identified in 7–14% of patients with ASD (59,132). Whole-exome and whole-genome sequencing techniques are also able to detect single nucleotide variants (SNVs). Studies have estimated that rare deleterious SNVs are identified in 13 to 15% of individuals with ASD (133). Satterstrom and colleagues performed the most extensive exome sequencing study of ASD to date (n=35,584 individuals). They identified 102 genes conferring risk for ASD and neurodevelopmental conditions. These genes were enriched in GWAS results of SZ and educational attainment (134), again raising questions about etiological overlap in ASD and SZ.

Early linkage and candidate gene studies in SZ identified loci (e.g., *COMT*, *DISC1*, *DTNBP1*, and *NRG1* for SZ) but were not subsequently replicated (41). In 2008, the first large scale study showed that rare CNVs can greatly increase the risk for SZ (odds ratios ranging from 2 to 30) (61,135). The latest study conducted by the PGC associated eight CNVs with SZ (including 1q21.1, 2p16.3 (NRXN1), 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2 and 22q11.2) (136,137). Burden analysis showing that rare CNVs overall are enriched in SZ suggest that many more CNVs increase the risk for SZ. WES studies have also reported that there is an excess of *de novo* loss of function variants in SZ (138).

Overall, ASD and SZ conditions are highly polygenic, involving hundreds of common and rare risk variants (Figure 3).

Pleiotropy and shared genetic factors across psychiatric conditions.

Genetic overlap among psychiatric conditions was demonstrated by family and twin studies, well before the era of genomic research. Large-scale collaborations (Figure 1) now provide the opportunity to study genetic relationships across NP conditions and related traits (139).

Evidence for pleiotropic effects in NPs was established in studies of common and rare variants (140,141). Pleiotropy is defined as "a single mutation causing more than one observable phenotypic effect or change in characteristic." (*Encyclopedia of Genetics, Brenner et al.*). A pleiotropic effect would likely manifest at the micro- and macroscopic level, resulting in genetic correlation between psychiatric conditions and heterogeneity within individual diagnostic categories.

Common variants

In 2013, the PGC's Cross-Disorder Group identified loci with pleiotropic effects across ASD, ADHD, SZ, BIP, and major depression (33,332 cases and 27,888 controls, (142)). They recently extended their approach

to GWAS of eight NP conditions (232,964 cases and 494,162 controls) to model genome-wide joint architecture (143,144). Over the 146 genome-wide significant SNPs reported in at least one condition, 109 loci (75%) showed association with two or more NP conditions and 23 loci with four or more NP conditions. These 23 SNPs were located within genes expressed in the brain from the second trimester, which are known to play prominent roles in neurodevelopmental processes. Such findings support the clear existence of pleiotropy mechanisms underlying NPs etiology. Further exploratory factor analysis identified three groups of inter-related disorders, explaining together 51% of the genetic variation across NPs. The first factor was linked to anorexia nervosa, OCD, and Tourette syndrome. The second factor was associated with mood disorder, major depression, BIP, and SZ. The last one encompassed early-onset NPs (ASD, ADHD, Tourette syndrome) and again major depression. These results do illustrate a substantial pleiotropy at the common variants level, associated with NPs (144).

Other convincing results were provided by the Brainstorm consortium. Authors used GWAS data from 265,218 patients and 784,643 control, as well as 17 phenotypes. They quantified the degree of overlap for genetic risk factors of 25 common brain disorders (145) and reported that SNPs for NP conditions were positively correlated, especially among ADHD, SZ, BIP, and major depression. ASD was positively correlated to SZ and epilepsy but not with any other conditions. This study also showed that neurological conditions were distinct from psychiatric disorders.

Together, and even though there are evident specificities in clinical, imaging, and genetic phenotypes for each NP condition, these findings converged on shared etiological mechanisms across NPs.

Rare variants converge on biological pathways that contribute to mental illnesses

Among the earliest evidence of shared factors across psychiatric conditions were also observations from rare CNVs associated with ASD, ADHD, SZ, epilepsy and ID (42). Kushima and colleagues investigated 1108 ASD, 2458 SZ, and 2095 controls (146) and identified pathogenic CNVs (29 loci common to both conditions) in about 8% of individuals with ASD and SZ, showing an association between pathogenic CNVs and IQ. Further gene set analyses underlined a substantial overlap of biological pathways involved in both disorders. Identified mechanisms included synapse/neuron projection, cell adhesion/junction, MAPK signalling, transcription/gene expression regulation, and the actin cytoskeleton. Such findings support the hypothesis of shared biological mechanisms in ASD and SZ.

Using a dataset of 4,297 patients with NPs, Andrews and colleagues (147)) identified 197 carriers of pathogenic CNVs and reported functional molecular relations amongst the genes disrupted in half of the CNVs carriers. Phenotypic commonalities were observed amongst carriers of CNVs contributing to the same molecular pathway. Their findings attest to the general idea that patients with mutations in distinct rare genetic variants could be etiologically grouped using molecular pathways analyses. The authors suggest that these data-driven identified pathways could be used to subgroup patients and may help in the future to devise personalized interventions (Network Based Stratification).

Other work investigated the same hypothesis with RNA sequencing data. Gandal and colleagues aggregated gene-expression microarray data from cerebral cortex samples across five NPs (148). Comparison of differential gene expression signatures revealed shared gene-expression profiles between ASD and SZ, and BD and SZ (148). More specifically, there was a gradient of synaptic gene down-regulation, where ASD was superior to SZ, and SZ was equal to bipolar disorder. ASD showed a distinct up-regulated microglial signature. As reported by Kushima and colleagues, and Andrews and colleagues (see above), this new set of results at the gene expression level reinforces the hypothesis that an important amount of shared genetic factors might underly a proportion of overlaps at the clinical and imaging level, observed in psychiatric conditions.

Overall, the results provided by these multi-scale studies do converge on the existence of shared mechanisms across psychiatric conditions. This suggests that genetically informed analyses may support a restructuring of psychiatric nosology, which likely will require the incorporation of many levels of information.

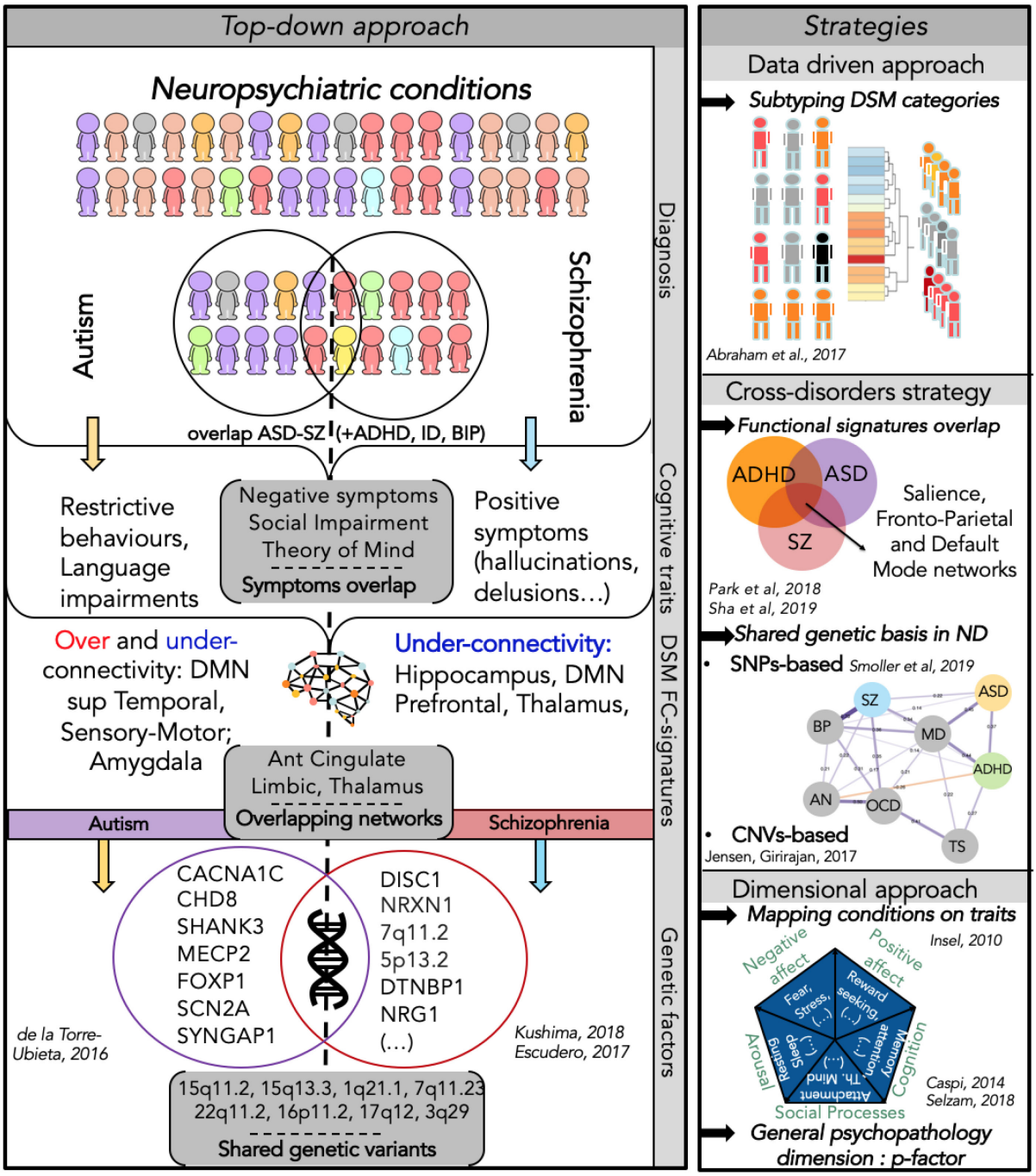

Figure I-3 Top-down approach to identify autism and schizophrenia biomarkers, and strategies used to tackle heterogeneity and comorbidity issues

Legend: Attempts to shed light on mechanisms of neuropsychiatric disorders have mainly adopted a top-down approach, starting with a psychiatric diagnosis, and moving to brain endophenotypes and further down to genes.

Bottom-up approach: from genetic variants to imaging and cognitive phenotypes

"As many have noted, our genes don't seem to have read the DSM." (Smoller, 2018 (139))

The second part of the introduction will put forward genetic-first approaches as an alternative way to disentangle the complexity of psychiatric conditions. As seen in the first part, attempts to shed light on mechanisms of NPs have mainly adopted a top-down approach, starting with a psychiatric diagnosis, and moving to brain endophenotypes and further down to genes. By contrast, the recruitment of groups based on the presence of a genetic risk factor for NPs (see Figure 4) allows for the investigation of pathways related to a particular biological risk for psychiatry. This approach may help to boost the effect size for signals of interest (3).

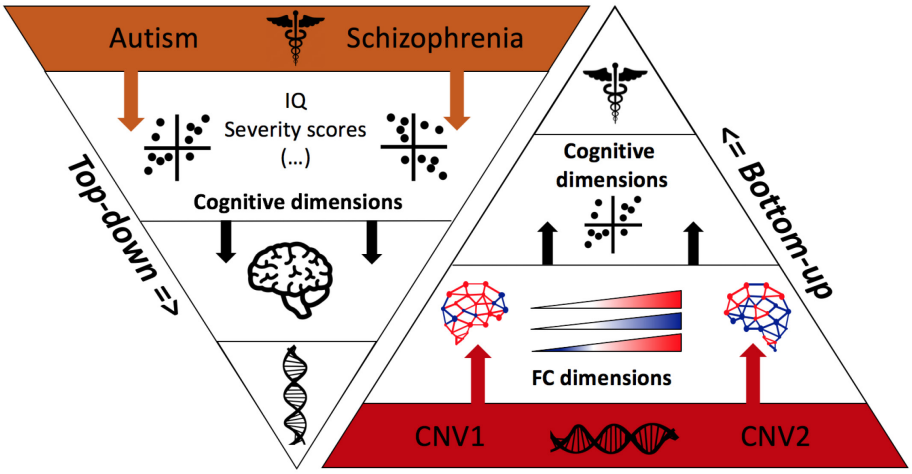

Figure I-4 Overview of the Top-down versus the Bottom-up approaches

Legend: Illustration of both approaches to dissect the complexity of neuropsychiatric conditions.

Copy Number Variation as a magnifying glass to study general mechanisms of psychiatry

With modern genetic mass-screening technologies, we can detect thousands of variants across genomes. The increased resolution of analyses informed us that CNV type of events are both highly prevalent in human genomes and highly relevant to the pathogenesis of both rare and complex traits (42,149–152). CNVs typically range in size from a kilobase (kb) to several megabases (Mb, 153) and affect several genes simultaneously. Clinical routine investigation using whole-genome chromosomal microarrays revealed that CNVs are present in 10 to 15% of children with neurodevelopmental conditions (154).

The statistical power required to conduct bottom-up studies limits this approach to genetic variants with a large enough effect size and a large enough population frequency. Some CNVs are relevant candidates for this approach. They have large effect sizes (around 1 standard deviation (sd)) and are frequently identified in the neurodevelopmental disorder clinic (3,154). A CNV-first, bottom-up approach can, therefore, build models/signatures from a lower level in the hierarchy (e.g. imaging trait), and then will ask questions about how such low-level models can explain observations higher up in the hierarchy ((1), Figure 4).

High-risk neuropsychiatric CNVs and mirror gene-dosage effects

16p11.2 CNVs

Prevalence and association with neuropsychiatric conditions

Recurrent deletions and duplications between breakpoints (BP) 4 and 5 on chromosome 16p11.2 (chr16:29,65–30,20 Mb, human genome (hg) 19, Figure 5) were first identified and linked to ASD in 2008 (Figure 1, (155)). 16p11.2 CNVs are also high-risk genomic variants associated with a wide range of neurodevelopmental conditions (156,157). Deletions and duplications are occurring de novo in 57% and 23% of individuals with neurodevelopmental conditions, respectively (Decipher platform).

Niarchou and colleagues compared the frequency of neurodevelopmental conditions in 331 children with 16p11.2 deletions (n=217) and duplications (n=114) (157). Deletion carriers exhibited higher risk of ADHD (odd-ratio= 4.0), ID (odd-ratio=58.7), and of ASD (odd-ratio= 39.9) than controls. Duplication carriers exhibited higher risk of ADHD (odd-ratio= 7.0), and ID (odd-ratio=56.7) than controls. Further work reported similar OR for ASD in deletions and duplications (odd-ratio=14 (5,136)). This translates into a risk of 15% to develop ASD for a 16p11.2 CNV carrier (155,158), and among individuals with ASD, 16p11.2 CNVs will typically occur in 0.3 to 1%. Carriers of the reciprocal duplication have a higher risk of

developing SZ (odd-ratio=9.4, (5,136)). Finally, both 16p11.2 deletions and duplications have been enriched in a broad spectrum of epilepsy (21% of carriers), from benign focal to severe epileptic syndromes (159).

Effect-sizes of -1.5 sd on IQ, and -1.4 sd on phonological memory have been reported in 16p11.2 deletion carriers (158,160). A smaller decrease in IQ has been identified in duplication carriers. Deletion carriers exhibited more severe impairments of phonology and of inhibition skills beyond what is expected for their IQ level (158,161). Finally, both CNVs affect social responsiveness behaviour (-3 SD) and gross and fine motor skills (4,161).

Partially mirroring gene-dosage anthropometric phenotype has also been reported in 16p11.2: the deletion is mainly associated with diabetes-independent obesity (body mass index > 40 in adults) and macrocephaly. Interestingly, obesity is also a well-known comorbidity of ADHD (162). Conversely, the reciprocal duplication is associated with underweight/anorexia (body mass index <18.5 in adult), and microcephaly (156,163). Jacquemont and colleagues have therefore proposed that head circumference and neuronal circuitry abnormalities could be linked to cognitive function and energy balance impairments in 16p11.2 CNV carriers. The abnormal food intake may be a direct result of a particular neurodevelopmental conditions. The effects on body mass index and head circumferences were large (approximately -1 z-scores for duplication carriers, and +1 z-scores for deletion carriers) (158,160).

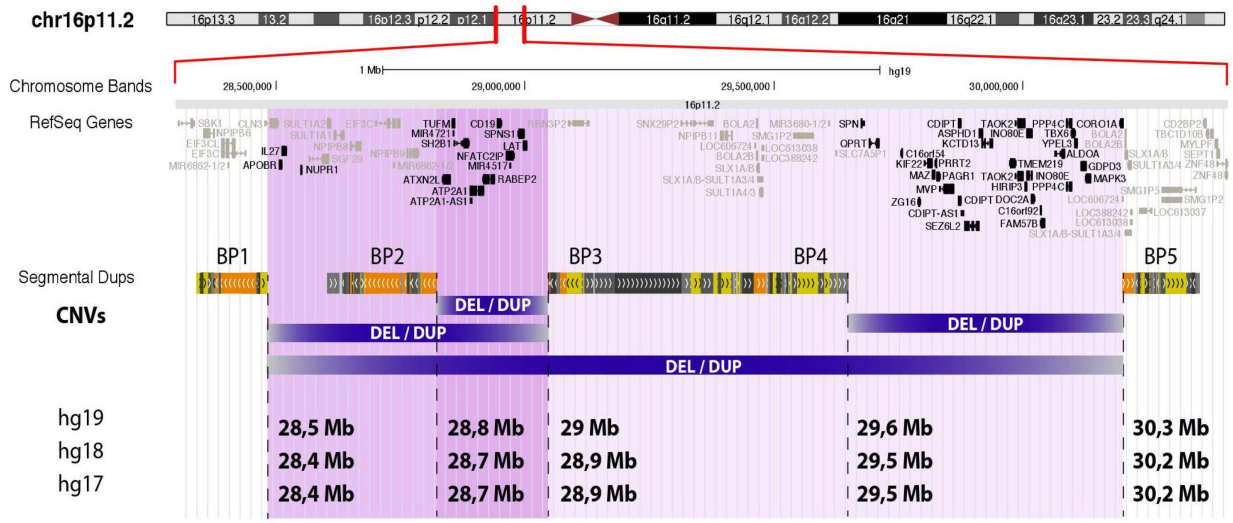

Figure I-5 16p11.2 CNV overview

The proximal 16p11.2 chromosomal region contains approximately 29 genes encompassed between breakpoints (BP) 4 and 5 on chromosome 16p11.2 (chr16:29,65–30,20 Mb, human genome (hg) 19). The distal segment contains nine genes (including SH2B1) between BP2 and BP3.

Anatomical MRI findings

Neuroimaging analyses also reported a global negative gene-dosage effect on total, Intracranial volume, total grey matter and white matter (164). The largest brain morphometry study on 16p11.2 was conducted in 2018 with a voxel-based morphometry method by Martin-Brevet and colleagues on 78 deletion carriers, 71 duplication carriers and 212 controls (4). Once effects on global volumes are taken into account, regional mirror negative gene dosage effect was associated with the insula volume (deletion>control>duplication). They identified specific effects of deletion on volumes of the transverse temporal gyrus, the calcarine cortex (deletion > control, Cohen's d > 1), and on volumes of the superior and the middle temporal gyrus (deletion < control, Cohen's d < -1). They also showed regional effects of duplication on volumes of the caudate, and the hippocampus (control> duplication, -0.5 > Cohen's d > -1) (4). Interestingly, these large effect-sizes reported on brain morphometry were consistent with effect-sizes on cognitive traits.

Functional MRI findings

To date, only one study investigated the impact of the 16p11.2 deletion on functional connectivity in childhood. This study showed that 16p11.2 deletion carriers (n=19) exhibit impaired PFC connectivity compared to controls (n=28), resulting in weaker long-range functional coupling with temporo-parietal regions (165). The reciprocal duplication effect on connectivity has not yet been investigated.

Mouse models and deletion effect-size

Knock-out (KO) mouse models using syntenic regions showed a more severe consequence of the deletion than duplication on multiple phenotypes (166). Notably, half of the deletion mice did not survive until adulthood. Regarding behaviour, 16p11.2-deletion mice showed hyperactivity, difficulty adapting to change, sleeping abnormalities, and repetitive or restricted behaviours, while 16p11.2-duplication animals showed a mirror hypoactivity phenotype (166). Horev and colleagues recapitulated human MRI findings by showing a gene dosage on brain volume size.

22q11.2 CNVs

Prevalence and association with NPs

The deletion syndrome is identified on aCGH results reporting haploinsufficiency on chromosome 22 from 1.5 to 3 Mb (~60 genes) at the band q11.2 (167). Also known as the DiGeorge syndrome, the deletion at the 22q11.2 locus was the first CNV implicated in SZ (odd-ratio=68, (136)) and is now considered as one of the strongest known genetic risk factors for psychotic illness, accounting for up to 1–2% of sporadic cases of SZ (168,169). The associated phenotype includes congenital malformations (cleft palate), hypocalcaemia, cardiac defects, immune problems and other NPs (170). Children with 22q11.2 deletion have a high risk of developing ASD (odd-ratio = 32, (5)), ADHD, anxiety disorders and psychotic features, and up to 30% of adolescents and adults with 22q11.2 deletion will develop SZ or psychosis traits (171,172). Children have a significant decline in FSIQ, dropping to [70-84] (173), then remain stable in adulthood (174).

The reciprocal 3 Mb duplication is inherited in 70% of the cases (compared to the deletion which is *de novo* in 85% of the cases) and has been associated with a wide range of phenotypes, including ASD, psychomotor development, speech delay and cognitive deficits (175). Studies suggested a protective effect for SZ (175) (odd-ratio = 0.15, (136)).

Overall, 22q11.2 deletion carriers have a substantially elevated risk of developing SZ, with onset typically occurring after mid to late adolescence. The reciprocal 22q11.2 duplication is possibly protective for SZ (136) and is associated with ASD (5).

Anatomical MRI findings

The ENIGMA 22q11.2 Working Group represents the largest dataset (10 centres including 474 subjects with 22q11.2 carriers). Using this dataset, Sun and colleagues reported that compared to controls, deletion carriers showed thicker cortical grey matter (Cohen's d= -0.6), particularly in temporal and cingulate cortices, a result that was consistent across sites (176). This overall result was extended to surface area (reduction in deletion compared to controls, Cohen's d = -1.0). Using neuroanatomical patterns, the authors managed to classify carriers with 93.8% accuracy. Interestingly, and for the first time, psychotic illness in deletion carriers was correlated to anatomical abnormalities present in idiopathic SZ. A follow-up work was recently published by Ching and colleagues on aggregated data from 533 carriers of the deletion and 330 matched controls, where volume and subcortical shape morphometry data were now closely scrutinised. Results showed lower intracranial, thalamus, putamen, hippocampus, and amygdala volumes (Cohen's d=

-0.9), as well as a greater lateral ventricle volume. Interestingly, deletion carriers with psychosis, and carriers of the largest deletion (A-D), exhibited a higher effect on volumetric data compared to carriers without psychosis and carriers with the smaller deletion (A-B). Additional shape analyses highlighted lower CT and SA in the same subcortical structures (177).

The contrast between effect sizes of neuroimaging studies of CNVs and idiopathic psychiatric conditions highlight the mechanistic homogeneity provided by a bottom-up approach.

The 22q11.2 duplication has been far less investigated. Lin and colleagues (178) studied 66 deletion versus 22 duplication carriers and reported a negative gene dosage effect on CT and a positive gene dosage effect on ICV (deletion<control<duplication). Mirror patterns were extended into subcortical regions volumes for the hippocampus.

Functional MRI findings

Only few studies have investigated brain organization using functional connectivity during rest in 22q11.2 deletion, and none have enquired into the reciprocal duplication or their relation.

Mattiaccio and colleagues used independent component analysis to determine the association of functional network connectivity, with severity metric of psychosis and CNV status (179). They investigated 55 young adult deletion carriers compared to 29 age-matched non-carrier individuals. Underconnectivity was reported in visual, frontoparietal, and default mode networks in deletion, compared to control. Decreased connectivity in the posterior cingulate was associated with higher thought disturbance score. Overconnectivity was reported in the precuneus and superior parietal lobule and positively associated with the same severity metric (179).

Using the known penetrance of 22q11.2 deletion CNV in schizophrenia and recurrent SZ findings pointing to the hippocampus and the thalamus, Schleifer and colleagues performed hypothesis-driven whole-brain seed-based functional analysis. They restricted their investigation to these two regions of interest. The thalamus displayed overconnectivity with somatomotor regions and underconnectivity with frontoparietal networks in 22q11.2 deletion compared to controls. The opposite pattern was reported for the hippocampus. No functional MRI study has been conducted on the reciprocal duplication.

1q21.1 CNVs

Prevalence and association with NPs

The recurrent 1q21.1 BP4-BP5 CNVs (146.6-147.5 Mb, hg19) span 1.35 million base pairs, and are among the most frequently identified CNVs in ASD and neurodevelopmental conditions (180). They were reported for the first time in 2008 and are associated with a highly variable phenotype (181). Deletions are over-represented in individuals with SZ (odd-ratio del=4 and OR-dup=4), ASD (odd-ratio del=3, odd-ratio dup=5), and neurodevelopmental conditions (odd-ratio del=11, odd-ratio dup=5) (5,136,182). 1q21.1 CNVs encompass 10 genes (Figure 6) and have an estimated population frequency of 1/3500 for deletion and 1/2300 for duplication (180). Both deletions and duplications are inherited in over 70% of cases, which can be interpreted as a mild effect on neurodevelopment. This is discordant however with effect sizes reported for cognitive (IQ: -1.5 sd for deletion and -1.3 sd for duplication) and clinical phenotypes (head circumference: -1.5 sd for deletion and +1sd for duplication) (181,182). These CNVs also impact fine motor skills (-2.3 sd for deletion and -1.8 sd for duplication) and language (measures of phonology: -2 sd for both) (182).

No MRI or fMRI study has been performed yet on this population.

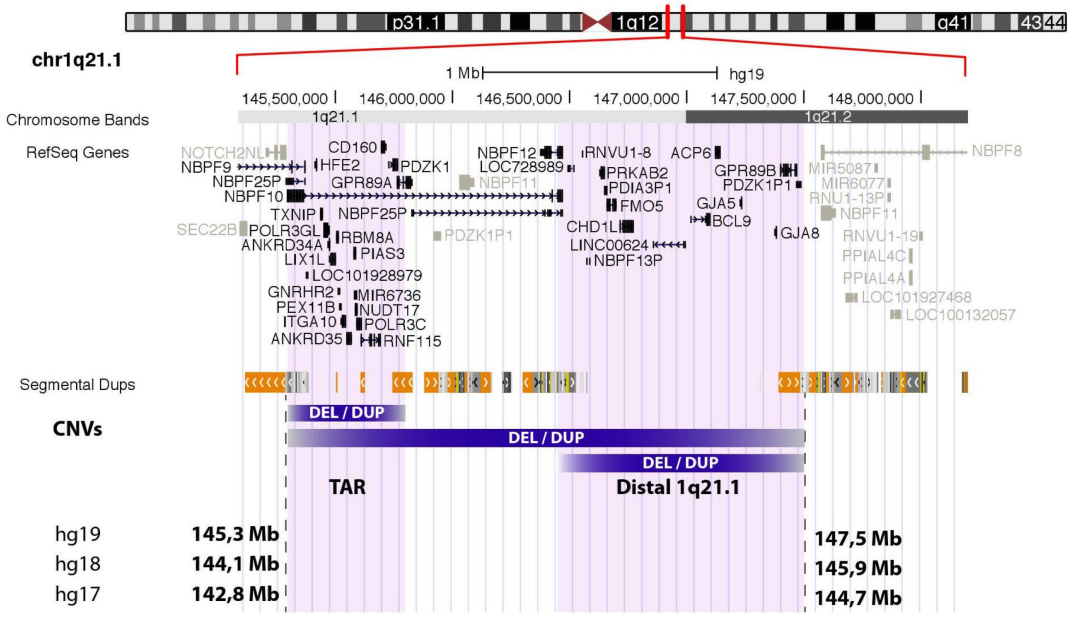

Figure I-6 1q21.1 CNV overview

Legend: The 1q21.1 chromosomal region contains approximately 10 genes. The TAR region (Thrombocytopenia with absent radii) involves approximately 10 genes

15q11.2 CNVs

Prevalence and association with NPs

15q11.2 deletions and duplication (BP1-BP2, encompassing 4 genes) are examples of variants with intermediate frequency and effect size. They are both being relatively frequent with a prevalence of approximately 0.36% in the general population (180). The deletion odds ratio for ASD (odd-ratio = 1.3), intellectual disabilities (odd-ratio = 1.7), epilepsy (odd-ratio = 3.1) dyslexia and dyscalculia (odd-ratio = 4.4 (183)) and SZ (odd-ratio = 2, (136)) classified this CNV as a 'pathogenic of mild effect size' (184). The deletion is associated with a small decrease in IQ (-4.3 points of IQ, -0.28 z-scores) (150,184). Jønch and colleagues showed no significant difference in symptom frequency between deletions and reciprocal duplications. Epilepsy types distribution was also similar between deletion and duplication (generalized seizures were observed in 6.4%–5.7%) (184).

Anatomical MRI findings

In 2014, a first neuroanatomical study restricted to few brain regions associated with SZ reported smaller grey matter volume in the perigenual ACC and left insula, and a larger corpus callosum volume in 15q11.2 deletion (n=15) (150). Reciprocal changes were found in duplication carriers for the same regions (n=55, positive gene dosage effect). The ENIGMA consortium investigated 203 deletion carriers and 306 duplication carriers (185). Compared to non-carriers, the deletion was associated with a lower total SA (Cohen's d=-0.41), higher mean CT (Cohen's d=0.36), and a smaller nucleus accumbens volume. A negative gene dose effect on mean CT was also identified. Strongest mirror gene dosage effects were localized in the frontal, and anterior cingulate cortices, and in the precentral and postcentral gyri. Duplication carriers exhibited larger SA and lower CT than non-carriers with effect sizes about half of those observed in deletion carriers. No association was reported between the number of copy and intracranial volume. Finally, there were more severe cognitive impairments in deletion compared to duplication for 5 over 7 tasks (185).

What have bottom-up approaches taught us so far?

Several lessons have been learned so far from genetic-first approaches.

The effect sizes of rare variants on neuroimaging traits are concordant with effects measured on cognitive and behavioural traits. This is in striking contrast with neuroimaging studies of behaviorally defined groups of patients (top-down) that have required very large samples to reach significant results. On average, the effect sizes observed in SZ, ASD and ADHD range from 0.4 to 0.15 and lower which is discordant with the severity of those conditions that lie well beyond 2 sd with respect to behavioural and adaptive traits. Diagnostic-first group encompassed subjects that are carrying a large diverse combination of common and rare variants. Small effect size is, therefore, an expected finding because these typical patients vs. controls study mixed apples and oranges at the genetic level. Comparison of effect sizes obtained by genetic-first and diagnostic-first approaches is useful to validate the power of the genetic-first approach.

We also learned that deletions have a larger effect size than duplications on several phenotypes.

Genetic first studies can readily identify brain endophenotypes and biological change that accompany behavioural alterations and psychiatric risk, while these remain hidden in heterogeneous groups of psychiatric conditions.

Finally, CNV studies showed that mirror gene-dosage effects are observed for multiple traits at several levels of observation.

How common and how specific are CNV effect on intermediate brain phenotypes?

Genetic variants may serve as important causal anchors to understand mechanisms leading to complex psychiatric disorders. Gene-first approaches can however only be applied to a few recurrent pathogenic CNVs frequent enough to establish a case-control study design. Thus, the effect of the vast majority of rare deleterious CNVs will remain undocumented. Because a highly diverse landscape of rare variants is conferring elevated risk to a spectrum of NPs, studies focusing on individual mutations will furthermore not be able to properly disentangle the relationship between mutations, molecular mechanisms and psychiatric disorders.

A cross-CNVs study compared and clustered neuroanatomical alterations across twenty-six different mouse genetic models of autism (such as 16p11.2 deletion and duplication, *MECP2*, *NRXN1*, and *FMR1*). Ellegood and colleagues first reported effect sizes difference in total brain volume and their findings illustrated the well-known heterogeneity in ASD (186). Out of the 26 ASD mice models, 8 were smaller (effect-size<-0.5) and 5 were larger (effect-size>0.5). Regional relative differences (adjusted for total brain volume) were heterogeneous and the most affected regions across models were the parieto-temporal lobe, the cerebellar cortex, the frontal lobe, the hypothalamus, and the striatum. To tackle this heterogeneity, authors clustered anatomical alteration (data-driven) and identified three distinct subgroups. The first one was driven by the limbic system, while the second one included white matter structure such as corpus callosum, and basal ganglia circuit (with the thalamus). The last one consisted of cerebellar regions.

KO mice models used in this study might recapitulate the heterogeneity seen with the imaging findings in autism patients. Overall, results reported in this study illustrated once again that there is not a single neuroanatomical pattern defining autism but clustered patterns driven by separate but convergent molecular mechanisms related to ASD. However, we cannot really know how ASD or SZ would present in mice. First, because it is extremely difficult to generalize cognitive impairment from mice to humans, second because there is no genetic model of ASD or SZ (as illustrated in the above study for autism).

Only a few studies simultaneously investigated several rare genomic variants in humans. Warland and colleagues investigated the impact of twelve CNVs associated with SZ in the general population (n=49 unaffected SZ-CNVs carriers, including 16p11.2, 22q11.2, *NRXN1*, 15q11.2, and 1q21.1 CNVs) (187). The thalamus, the hippocampus, and the nucleus accumbens were smaller in SZ-CNVs. The authors reported that thalamic and hippocampal alterations mediated IQ. These regions have been repeatedly associated with SZ in neuro-anatomical and functional studies (see paragraph on SZ).

This set of results suggest that rare genetic variants associated with NPs may converge on shared patterns of alterations. Whether common patterns extend to any NP-CNVs across the genome remains unknown.

Genome-wide effects of CNVs

Results reported by cross-CNVs studies suggest a linear effect of NPs-CNVs. A large study investigated linear effects of CNVs associated with NPs on cognitive performance and measures of occupational and social outcomes in general population (n>400,000) (151). Kendall and colleagues reported a correlation between the penetrance of CNVs for neurodevelopmental conditions and the average effect size on seven

cognitive tests (r=0.74). They showed that 24 out of 33 NP-CNVs were associated with diminished performance on at least one cognitive test (worst performances were reported in 16p11.2 and 22q11.2 CNVs carriers). This suggests a general deleterious effect of NP-CNVs on cognitive traits.

Huguet, Schramm and colleagues speculated that large effect size pathogenic deletions may be attributable to the sum of individual effects of genes encompassed in each CNV (6). They introduced a new framework to estimate the effect of pathogenic deletions on IQ whereby CNVs were annotated in two general population cohorts and a linear regression was performed to predict IQ using ten functional annotations scores of genes encompassed in the CNVs. The authors identified that the probability of being loss-of-function intolerant score (pLI (188)) best explained the effect of n=1713 deletion carriers on IQ measure. This cognitive measure was affected by 2.74 points per unit of pLI (6).

Overall, this study showed that haploinsufficiency of a large proportion of the coding genome was decreasing IQ. This finding is consistent with omnigenic models that speculate variants to be spread across the genome in the aetiology of complex pathogenic conditions.

To date, only one study investigated a potential linear effect of NP-CNVs on imaging features. Drakesmith and colleagues recently posit the existence of shared MRI patterns of alterations across a wide range of CNVs risk factors for SZ and neurodevelopmental conditions (189). Authors annotated 21 carriers of either 22q11.2, 15q11.2, 1q21.1, 16p11.2 and 17q12 CNVs and 15 non-carriers using estimates of CNV penetrance for the development of SZ and ID/ASD. They reported that the macro and microstructural properties of the cingulum bundles were associated with penetrance scores. Effects were stronger for curvature along the anterior-posterior axis and intracellular volume fraction, as well as for the ratio of volumes in the body and splenium of the corpus callosum (189). The authors suggested that alterations in brain development may manifest through an increase in forces applied parallel to the anterior-posterior axis. Alterations in the corpus callosum is one of the most consistent findings reported by structural connectivity in ASD (93). The fact that the distribution of axons encompassed in the corpus callosum was correlated to CNVs score is therefore consistent with this observation in ASD. The authors argue that this may lead to a change in forces applied to the cingulum during brain development.

These results allude to a linear effect of CNVs associated with NPs in imaging phenotypes. Larger sample size, combined to new modalities of investigation (such as functional connectivity) will help to validate such speculation.

Knowledge gap and hypothesis

Intermediate brain phenotypes of psychiatric conditions have mainly been studied by adopting a *top-down* approach, starting with a clinical diagnosis and moving to underlying neural substrates and further down to genetic factors. Altered brain networks do not appear to be disorder-specific and have been reported across several disorders that may be related to shared genetic contribution across diagnoses. Bottom-up approaches build models from NP-associated genetic proxies to brain endophenotypes and further up to behaviour and diagnosis, offering an alternative framework to disentangle multidimensional complexity of NPs.

Individually rare but collectively frequent, CNVs are among the most severe genetic risk factors for neuropsychiatric disorders, and might serve as a magnifying glass to study general mechanisms of psychiatry. Almost nothing is known about the effect of these rare variants on brain function.

In this dissertation I will investigate 1) how these mutations alter connectivity in humans, and 2) whether these patterns are related to brain signatures of traditional neuropsychiatric conditions.

I posit that entire classes of genetic mutations associated with neuropsychiatric conditions may converge upon common brain alterations that could reflect the polygenic nature of psychiatric conditions.

Overarching goal

Mapping the effects of rare variants on functional connectivity to identify connectivity dimensions contributing to neuropsychiatric conditions.

Aims and methods

Table I-1 Objectives, methods, and hypotheses

Abbreviations: copy-number variants (CNV), connectome-wide association studies (CWAS), deletion (DEL), duplication (DUP), effect-size (ES), functional connectivity (FC), idiopathic psychiatric conditions (IPCs), probability of being loss-of-function intolerant score (pLI), Schizophrenia (SZ).

Aims	Objectives	Hypotheses	Methods
AIM1. **One mutation at a time** Characterize the impact of CNVs on functional connectivity	1.1 Describe the gene dosage effect of CNVs on whole-brain connectivity	Gene dosage modulates FC in a mirror fashion	*CWAS: Linear model contrasting CNV carriers with controls* *Figure 8 a-c*
	1.2 Describe the gene dosage effect of CNVs on regional connectivity	CNV severity is correlated to CNV effect-size on FC	*CWAS at the regional level, adjusting models for mean connectivity.* *ES correlation with pLI per CNV*
	1.3 Characterize the effect of IPCs on FC, and compare with the effect of CNVs on FC	CNVs have a larger effect on FC than ASD, SZ, and ADHD	*CWAS: Linear model contrasting cases of each psychiatric groups (n=3) with IPCs controls.*
AIM2. **Enrichment in psychiatry** Test if CNV-FC profiles are observed in idiopathic psychiatric conditions	2.1 Investigate similarities between whole-brain CNV-FC profiles and those of IPCs	High-risk CNV-FC profiles are enriched in IPCs	*Pearson R between beta maps obtained from CNVs CWAS and individual connectomes of IPCs*
	2.2 Identify brain regions that contribute most to the similarities of CNVs and IPCs	A subset of brain regions are driving similarities identified in 2.1	*The same method used in 2.2 applied to each of the 64 regional FC patterns* *Figure 8 d-e*
	2.3 Understand how brain regions identified in 2.3 are linked to clinical severity scores	Similarity to deletion FC-profiles is associated with symptom severity	*Pearson R computed in 2.3 correlated to IQ, SRS, PANSS, ADOS, CPRS-LV of each individual*
AIM3. **Beyond case-control** Investigate the shared effect of rare mutations on FC	3.1 Investigate relation across high-risk deletions at the connectivity and gene expression level	Deletions converge on shared patterns of altered FC and gene expression	*Similarity across CNV-FC profiles (as 2.1).* *Pearson R between expression patterns of genes encompassed inside and outside CNVs*
	3.2 Investigate the effect of the intolerance to mutation of the genes involved in CNVs on FC	pLI is associated with a profile of connectivity shared across CNV	*Linear model testing the effect of pLI scores on FC in the CNVs carriers and non-carriers population*
	3.3 Test the relationship between regions identified in 3.2 and clinical severity scores	Similarity to pLI FC-profile is associated with symptom severity	*Correlation between similarity to pLI-FC-profile and IQ, ADOS, SRS measures at the individual level*
	3.4 Identify latent components shared across CNVs and IPCs	A set of FC dimensions underlie the relation between CNVs and IPCs	*Exploratory factor analysis across 15 FC-profiles (identified in 1.2-1.3)*

Specific Objectives

Aim 1: Delineate the effects of neuropsychiatric variants on functional connectivity

Rare CNVs associated with NPs provide an unbiased insight into the genetic architecture and the molecular mechanisms underlying mental disorders. They can be used to disentangle idiopathic psychiatric conditions. Almost nothing is known on the effect of these genetic variants on brain organization, and no investigation of the functional connectivity in reciprocal 16p11.2, 22q11.2 and 1q21.1, deletions and duplications have been conducted to date. I posit that CNVs alter functional brain organization, and that the effect size of connectivity alteration is correlated to the mutation burden.

Results at the clinical and anatomical level suggest a mirror gene-dosage effect of high-risk psychiatric CNVs. I posit that gene dosage also modulates connectivity features in a mirror fashion, with a stronger effect in deletion compare with duplication.

Moreover, and because a complex landscape of rare variants is known to confer elevated risk for a wide range of NPs (suggesting pleiotropy effect), I posit that connectivity signatures of high-risk NPs-CNVs will converge on shared connectivity patterns.

Aim 2: Relationship between the connectivity alterations of neuropsychiatric variants and brain architecture of individuals with psychiatric conditions

Because a large number of rare variants confers elevated risk for a spectrum of NPs, alterations conferred by NPs-CNVs may be enriched with brain organization underlying psychiatric conditions.

I aim to assess whether connectivity-profiles of NP-CNVs may represent dimensions observed in idiopathic ASD, SZ, or ADHD. I posit that seemingly distinct CNVs and idiopathic psychiatric conditions have overlapping patterns of dysconnectivity, which may help identify FC dimensions, providing insight into the complex connectivity organization involved in psychiatric conditions.

Aim 3: General effects of genome-wide deletions on connectivity

Previous steps (aims 1 & 2) were performed one mutation at a time, with the notion that CNVs would shed light on the relationship between molecular mechanisms and imaging phenotypes. This can only be applied to a few rare recurrent CNVs that are frequent enough to use a case-control study design. The effect of the vast majority of rare deleterious CNVs remains largely undocumented. How can we pursue the investigation of rare variants beyond the handful of CNVs and SNV frequent enough to establish an individual association study? How can we close the gap between the exponentially expanding landscape of rare genetic variants identified in psychiatry and the knowledge of their effects on intermediate brain phenotypes? To tackle these challenges, a complementary approach is to explore together recurrent CNVs based on their individual characteristics at the gene level. I will use annotation constraint scores of individual coding genes encompassed into any recurrent CNVs to extend this approach to other NP-CNVs at the individual level, moving beyond the typical case-control approach. The aim is to investigate the relationship between measures of intolerance to mutation and connectivity across genomic loci. I speculate that entire classes of genetic mutations will fall into common functional dimensions, which may be related to emerging properties of the genome. In other words, changing gene dosage at any node (hub) of the genomic network may alter system efficiency, leading to a measurable effect on brain functional architecture and associated psychopathology.

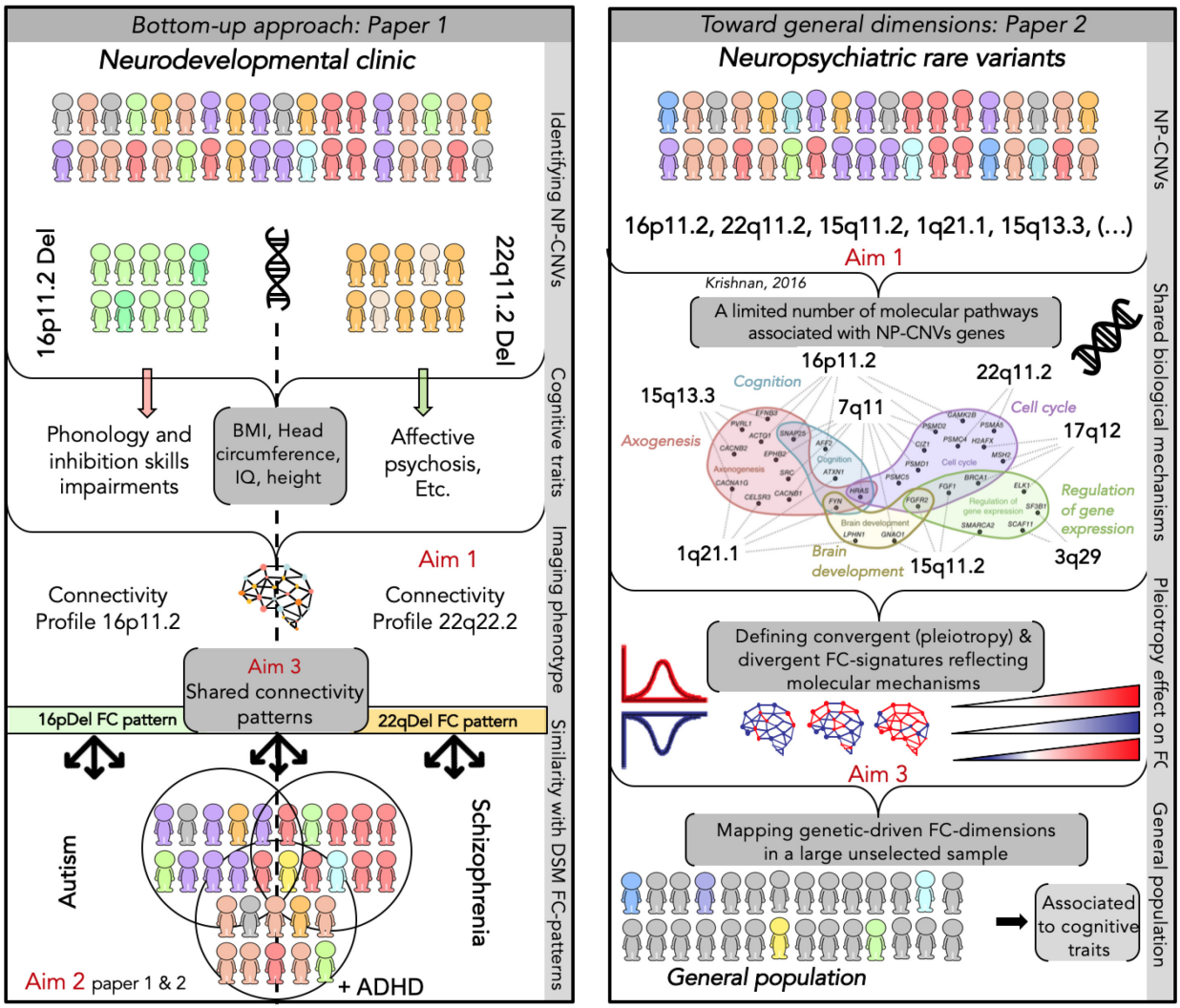

Figure I-7 Paper 1 and Paper 2 theoretical framework

Legend: Box 1 (left): General overview of the first paper, from 2 high-risk neuropsychiatric CNVs to psychiatric conditions; Box 2 (right): General overview of the second paper, from entire classes of CNVs to functional dimensions in the general population.

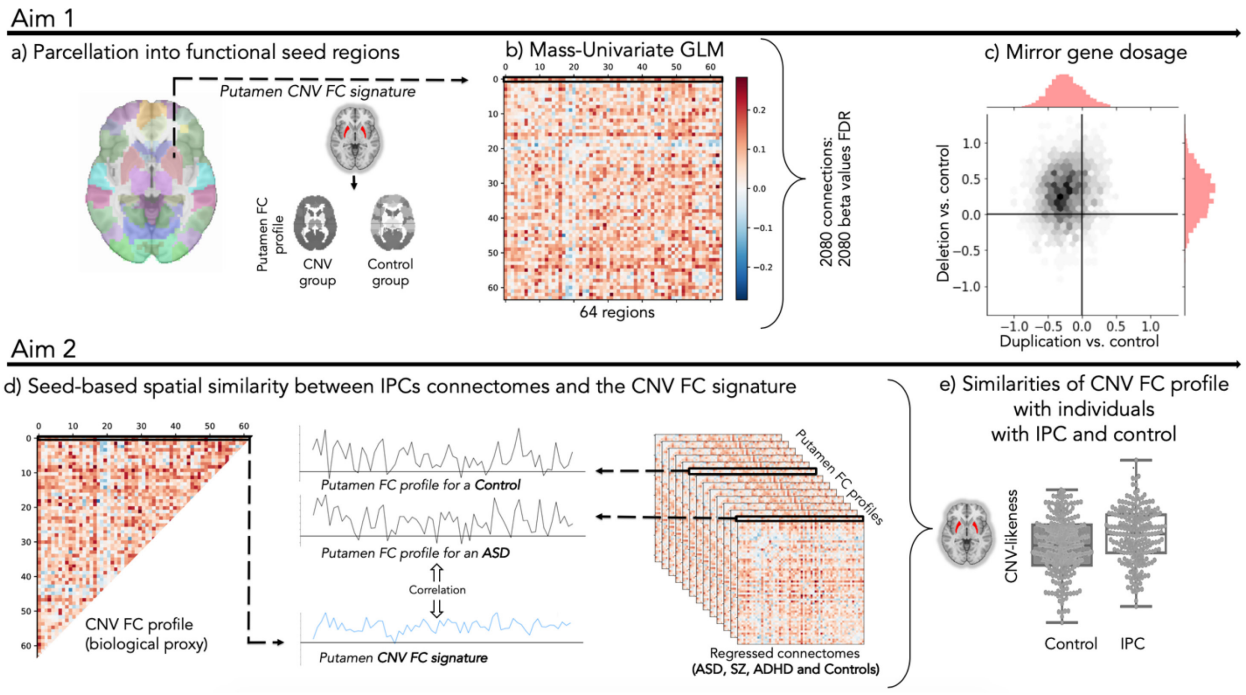

Figure I-8 Method overview for Aim 1 and Aim 2

Legend: a) We segmented the brain into 64 functional seed regions defined by the multi-resolution MIST brain parcellation b) Connectome-wide association studies (CWAS) were conducted by linear regression at the connectome level, in which z-scored FC (based on the control group) was the dependent variable and clinical status the explanatory variable. This test was applied independently for each of the 2,080 functional connections (corrected for the number of tests). c) We tested whether connections were affected by gene dosage in a mirror fashion. Scatterplot (hexagonal plot) show estimates (beta values) from connectome-wide association studies (CWAS) performed between CNVs and their respective controls. d) Similarities of CNV-FC-profiles across this study were computed by correlating (Pearson's r) a CNV group level FC-profile (matrix of 2080 beta values, on the left side, obtained from b) with individual connectomes of psychiatric cases and individual connectomes of psychiatric controls. The r values obtained for all cases and all controls were compared using a Mann Whitney test (e). Analyses were performed at the whole-brain level (2080 connections) and at the regional (64 brain regions) level.

II. Paper 1: Neuropsychiatric mutations delineate functional brain connectivity dimensions contributing to autism and schizophrenia

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Abstract

16p11.2 and 22q11.2 Copy Number Variants (CNVs) confer high risk for Autism Spectrum Disorder (ASD), schizophrenia (SZ), and Attention-Deficit-Hyperactivity-Disorder (ADHD), but their impact on functional connectivity (FC) networks remains unclear.

We analyzed resting-state functional magnetic resonance imaging data from 101 CNV carriers, 755 individuals with idiopathic ASD, SZ, or ADHD and 1,072 controls. We used CNV FC-signatures to identify major dimensions contributing to complex idiopathic conditions.

CNVs had large mirror effects on FC at the global and regional level, and their effect-sizes were twice as large as those of idiopathic conditions. Thalamus, somatomotor, and posterior insula regions played a critical role in dysconnectivity shared across deletions, duplications, idiopathic ASD, SZ but not ADHD. Individuals with higher similarity to deletion FC-signatures exhibited worse behavioral and cognitive symptoms.

Similarities between FC-signatures of both deletions could be related to the non-specific association of gene expression patterns with CNVs FC signatures.

Introduction

Copy number variants (CNVs) are deletions or duplications of DNA segments and represent an important source of genetic variation. An increase in rare CNV burden has been linked to a range of neurodevelopmental and psychiatric conditions (190,191). Twelve recurrent CNVs have been individually associated with autism spectrum disorder (ASD) (192), eight with schizophrenia (SZ) (136), and eight with attention deficit hyperactivity disorder (ADHD) (193) but the mechanisms by which they lead to neuropsychiatric disorders remain unclear. Although they have large impacts on neurodevelopment, their effect alone does not lead to a psychiatric diagnosis. CNVs could therefore be leveraged to identify major dimensions contributing to complex idiopathic conditions.

CNVs at the proximal 16p11.2 and 22q11.2 genomic loci are among the most frequent large effect-size genomic variants and alter the dosage of 29 and 50 genes, respectively (169,194). They confer high risk for ASD (10-fold increase for the 16p11.2 deletion and duplication) (192), SZ (>10-fold increase for the 22q11.2 deletion and 16p11.2 duplication) (136), and ADHD (4,156–158,176). Gene dosage (deletions and duplications) affect the same neuroimaging measures in opposite directions (mirror effect). Structural alterations of the cingulate, insula, precuneus and superior temporal gyrus overlap with those observed in meta-analytical maps of idiopathic psychiatric conditions including ASD and SZ.(4,176)

Large effect-size mutations can shed light on pathways connecting genetic risk to brain endophenotypes, such as functional connectivity (FC). FC represents the intrinsic low frequency synchronization between different neuroanatomical regions. It is measured by means of resting state fMRI which captures the covariance of BOLD fluctuations across brain areas when no explicit task is performed (26,27). Robust functional brain networks measured by rsfMRI are also recapitulated by spatial patterns of gene expression in the adult brain (195,196).

Few studies have investigated the effect of ‘neuropsychiatric’ CNVs on FC. Dysconnectivity of thalamic-hippocampal circuitry (197) has been reported in 22q11.2 deletion carriers, with prominent under-connectivity of the default mode network (DMN), which was predictive of prodromal psychotic symptomatology (179,198). Impaired connectivity of long-range connections within the DMN has also been reported by other studies (199). A single 16p11.2 study has shown a decrease in connectivity of fronto-temporal and -parietal connections in deletion carriers (165). These initial studies have focussed on regions of interest but connectome-wide association studies (CWAS) analysing all connections without a priori

hypotheses have not yet been performed in CNV carriers. Furthermore, their relation with idiopathic conditions has not been investigated.

Brain intermediate phenotypes of psychiatric conditions have mainly been studied by adopting a top-down approach, starting with a clinical diagnosis and moving to underlying neural substrates and further down to genetic factors (1). Studies applying this analytical strategy in ASD have shown reproducible patterns of widespread under-connectivity with the exception of overconnectivity in the thalamo-cortical regions (12,111). SZ also exhibits a general under-connectivity profile, mainly involving the medial prefrontal cortex, the cingulate and the temporal lobe (117), with over-connectivity of the thalamus (119). These altered networks do not appear to be disorder-specific and have been reported across several disorders, including ASD, ADHD, and SZ (123). These similarities seem to be distributed across several continuous dimensions (200) which may be related to shared genetic contribution across diagnoses, which is documented for common (142) and rare (201) variants, including the 16p11.2 and 22q11.2 CNVs.

We posit that seemingly distinct genetic variants and idiopathic disorders have overlapping patterns of dysconnectivity, which may help identify FC dimensions, providing insight into the complex connectivity architecture involved in psychiatric conditions.

We aimed to 1) characterize the FC-signatures of four high-risk neurodevelopmental CNVs, 2) explore whether FC-signatures of CNVs represent dimensions observed in idiopathic ASD, SZ, or ADHD and 3) investigate the relationship between deletions at the FC and gene expression level.

To this end, we performed CWAS studies on 101 carriers of a 16p11.2 or 22q11.2 CNV, 122 of their respective controls, 751 individuals with idiopathic ASD, SZ, or ADHD and 948 of their respective controls. To our knowledge, this is the first connectome-wide study to compare rare genomic variants and idiopathic psychiatric conditions.

Materials and Methods

Samples

We performed a series of CWAS using individuals from five data sets (Table 1 and Supplementary Materials and Methods).

1-2) Two genetic-first cohort (recruitment based on the presence of a genetic variant, regardless of any DSM diagnosis):

16p11.2 deletion and duplication carriers (29.6-30.1MB ; Hg19), and extrafamilial controls from the Simons Variation in Individuals Project (VIP) consortium (202).

22q11.2 deletion and duplication carriers (18.6-21.5MB ; Hg19) and extrafamilial controls from the University of California, Los Angeles.

3) Individuals diagnosed with ASD and their respective controls from the ABIDE1 multicenter dataset (12).

4) Individuals diagnosed with SZ (either DSM-IV or DSM-V) and their respective controls. We aggregated fMRI data from 10 distinct studies.

5) Individuals diagnosed with ADHD (DSM-IV) and their respective controls from the ADHD-200 dataset(203,204).

Imaging data were acquired with site-specific MRI sequences. Each cohort used in this study was approved by the research ethics review boards of the respective institutions. Signed informed consent was obtained from all participants or their legal guardian before participation. Secondary analyses of the listed datasets for the purpose of this project were approved by the research ethics review board at Sainte Justine Hospital. After data preprocessing and quality control, we included a total of 1,928 individuals (Table 1).

Dataset	Status	n	Age	FSIQ	Sex	FD*	ASD	ADHD	SZ
SVIP 16p11.2 Cohort (2 sites)	Del Carriers	20	12.7 (6.8)	92.5 (16.1)	12M	0.18 (0.03)	4	6	0
	Controls	79	26.7 (14.7)	103.6 (14.8)	46M	0.17 (0.04)	0	0	0
	Dup Carriers	23	28.2 (12.8)	94.1 (15.1)	12M	0.19 (0.05)	1	1	0
UCLA 22q11.2 Cohort (1 site)	Del Carriers	46	16.8 (6.1)	77.2 (13.8)	20M	0.17 (0.06)	18	20	3
	Controls	43	13.0 (4.6)	111.9 (17.6)	22M	0.14 (0.04)	0	2	0
	Dup Carriers	12	16.74 (13)	95.7 (19)	7M	0.17 (0.1)	3	4	0
ASD Cohort (ABIDE 10 sites)	Cases	225	15.9 (6.5)	103.7 (17.4)	221M	0.18 (0.05)	225	-	-
	Controls	234	15.7 (6.1)	110.63 (12.1)	232M	0.17 (0.04)	0	-	-
Schizophrenia Cohort (10 sites)	Cases	241	33.62 (9.2)	-	179M	0.16 (0.06)	-	-	241
	Controls	242	32.3 (9.6)	-	181M	0.14 (0.05)	-	-	0
ADHD Cohort (7 sites)	Cases	289	11.5 (2.8)	106.8 (13.7)	227M	0.15 (0.04)	-	289	-
	Controls	474	12.2 (3.3)	114..2 (13.1)	250M	0.14 (0.04)	-	0	-

Table II-1 Cohort characteristics

Legend: Description of the cohorts after filtering for quality criteria. SVIP: Simons Variation in Individuals Project; UCLA: University of California, Los Angeles; ASD: autism spectrum disorder; ABIDE: Autism Brain Imaging Data Exchange; SZ: schizophrenia; ADHD: attention deficit/hyperactivity disorder; Del: deletion; Dup: duplication; Age (in years); FSIQ: Full Scale Intelligence Quotient; M: male; FD: framewise displacement (in mm). Quantitative variables are expressed as the mean ± standard deviation. *More information regarding the remaining number of time frames for each group, and the percentage of motion censoring, is provided in Supplementary Materials and Methods. Sensitivity analyses investigating sex bias in the 3 idiopathic cohorts are presented in Supplementary Results. Sensitivity analysis investigating medication effect in ASD cohort is presented in Supplementary Results. Sensitivity analyses also showed that the FC-signature of 22q11.2 deletions is not influenced by a diagnosis of ASD or ADHD (Supplementary Figure VI-1). Columns ASD, SZ, and ADHD represent the number of subjects with those diagnoses. One subject may have several diagnoses. For example, 9 subjects with ASD have also an ADHD diagnosis.

Preprocessing and quality control procedures

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 (205). Preprocessed data were visually controlled for quality of the co-registration, head motion, and related artifacts by one rater (Supplementary Materials and Methods).

Computing connectomes

We segmented the brain into 64 functional seed regions defined by the multi-resolution MIST brain parcellation (206). FC was computed as the temporal pairwise Pearson's correlation between the average time series of the 64 seed regions, after Fisher transformation. The connectome of each individual encompassed 2,080 connectivity values: (63x64)/2 = 2016 region-to-region connectivity + 64 within seed 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 functional connectivity alterations in neurodevelopmental disorders such as ASD.(37)

Statistical analyses were performed in Python using the scikit-learn library (207). Analyses were visualized in Python and R. Code for all analyses and visualizations is being made available online through the github platform https://github.com/surchs/Neuropsychiatric_CNV_code_supplement.

Statistical analyses

All of the following analyses are summarised in Supplemental Materials and Methods.

Connectome-wide association studies

We performed seven CWAS, comparing Functional Connectivity (FC) between cases and controls for four CNVs (16p11.2 and 22q11.2, either deletion or duplication) and three idiopathic psychiatric cohorts (ASD, SZ, and ADHD). Note that controls were not pooled across cohorts. Within each cohort, FC was standardized (z-scored) based on the variance of the respective control group. CWAS was conducted by linear regression at the connectome level, in which z-scored FC was the dependent variable and clinical status the explanatory variable. Models were adjusted for sex, site, head motion, and age. We determined whether a connection was significantly altered by the clinical status effect by testing whether the β value (regression coefficient associated with the clinical status variable) was significantly different from 0 using

a two-tailed t-test. This regression test was applied independently for each of the 2,080 functional connections. We corrected for the number of tests (2,080) using the Benjamini-Hochberg correction for FDR at a threshold of $q < 0.05$ (208), following the recommendations of Bellec *et al.* 2015 (32).

We defined the global FC shift as the average of the β values across all 2,080 connections and tested for significant case-control differences in average global FC by a permutation test, shuffling the clinical status labels of the individuals included in each CWAS (using 10,000 replications). For example, we randomly permuted the clinical status of 16p11.2 deletion carriers and their respective controls in the 16p11.2 deletion *vs* control CWAS. We then estimated a valid permutation-based p-value associated with the observed average FC shift (209).

Gene dosage mirror effects on functional connectivity

We tested whether networks are affected by gene dosage in a mirror fashion by computing the product of the β values obtained in each genetic group contrasts: "Deletions *vs* Controls" and "Duplications *vs* Controls" (separately for 16p11.2 and 22q11.2). Negative values indicate mirror effects of deletions and duplications on FC. Positive values indicate effects in the same direction for deletions and duplications. The obtained products of the β values were grouped into 12 canonical functional networks using information from the multi-resolution brain parcellation (Supplementary Table S1.9).

Similarity of whole brain FC-signatures between idiopathic psychiatric conditions and CNVs.

We tested the similarity between dysconnectivity measured across idiopathic psychiatric conditions and CNV. This similarity was tested by correlating individual whole brain connectomes of cases and controls of one group to the whole brain FC-signature (group level) of another group (Figure II.1). The group-level FC-signature was defined as the 2,080 β values obtained from the contrast of cases vs. controls. This was repeated 21 times between all CNVs and conditions and in both directions (n=42 similarity tests).

Individual connectomes of case and their respective controls were used after independently adjusting for sex, site, head motion, age, and average group connectivity for each of the datasets.

Similarity scores were derived by computing Pearson's correlations between the whole brain connectomes. We asked whether cases compared to their respective controls had significantly higher (or lower) similarity to whole brain FC-signature of another group using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 42 tests ($q < 0.05$).

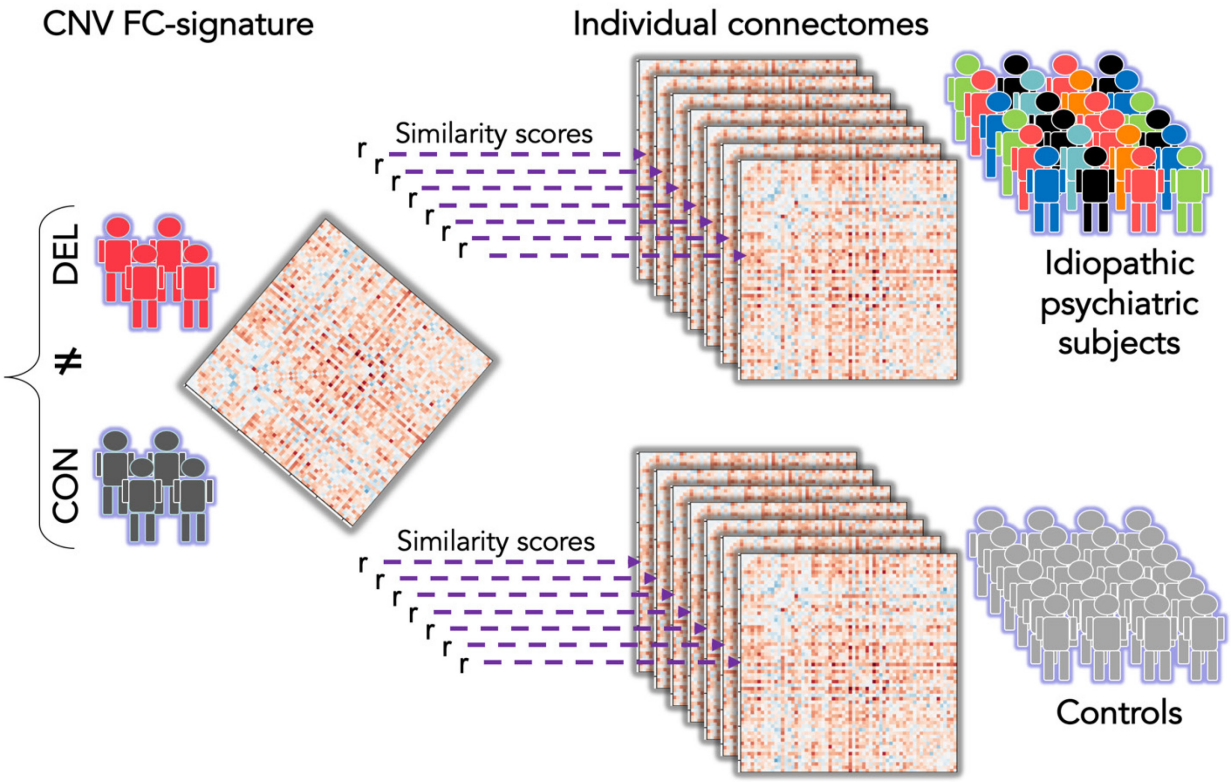

Figure II-1 Testing similarities across CNVs and idiopathic conditions

Legend: Similarities of FC-signatures across this study were characterized by correlating (Pearson's r) a group level FC-signature with individual connectomes from either cases and controls. The r values obtained for all cases and all controls were compared using a Mann Whitney test. Here, the group level connectome is represented by a matrix of 2080 beta values, on the left side. It is obtained by contrasting deletion cases (red) and controls (dark grey). The beta map is correlated to 7 individual connectomes of psychiatric cases and 7 connectomes of controls. The different colors used for the psychiatric cases represent phenotypic heterogeneity.

Similarity of regional FC-signatures between idiopathic conditions and CNVs

The same approach described above was performed at the regional level. Each of the 1705 connectomes of individuals with idiopathic psychiatric conditions and their respective controls were independently adjusted for sex, site, head motion, age, and average group connectivity for each dataset. We calculated a similarity score between these individual connectomes and the FC-signatures of the 16p11.2 and 22q11.2 deletions and duplications. The FC-signatures were broken down into 64 region-level FC-signatures and similarity scores were derived by computing Pearson's correlations between the 64 β values associated with a particular region. For each region, we tested whether individuals with a psychiatric diagnosis had significantly higher (or lower) similarity to 16p11.2 or 22q11.2 deletion FC-signatures than their respective controls using a Mann-Whitney U test. We reported significant group differences after FDR correction ($q < 0.05$) for the number of regions (64).

We investigated the relationship between symptom severity and similarity with deletions. The similarity of individuals with deletion FC-signatures were correlated (Pearson's r) with cognitive and behavioral measures. Those included the ADOS and FSIQ in the autism sample and the PANSS in the SZ sample. The p-values associated with these correlations were corrected for multiple comparison (FDR, $q < 0.05$).

Similarity between 16p11.2 and 22q11.2 deletions at the regional level

We correlated the 22q11.2 group-level deletion-FC-signature with individual connectomes of 16p11.2 deletion carriers and their respective controls. We correlated as well the 16p11.2 group-level deletion-FC-signature with individual connectomes of 22q11.2 deletion carriers and their respective controls. For each region, we tested whether individuals with a deletion had significantly higher (or lower) similarity to the other deletion FC-signatures than their respective controls using a Mann-Whitney U test. We reported significant group differences after FDR correction ($q < 0.05$) for the number of regions (64).

Gene expression analyses

We aligned the gene expression maps from AHBA to the MIST64 functional parcellation following the guidelines in (210) and adapting the abagen toolbox (211) (supplementary methods). For all analyses, we used a dataset including 1 expression value per gene and per functional region. These values were compared to the average connectivity alteration values of each region (mean of all 64 beta values of each region).

PLSR method was used to investigate the association between spatial patterns of gene expression (of the 37 and 24 genes encompassed in the 22q11.2 and 16p11.2 genomic loci) and the 16p11.2 and 22q11.2 FC signatures. PLSR is a multivariate approach, which has previously been applied to investigate the relationship between neuroimaging phenotypes and spatial patterns of gene expression(212–215). PLSR was performed separately for 16p11.2 and 22q11.2 genes. Components defined by PLSR were the linear combinations of the weighted gene expression scores (predictor variables) that most strongly correlated with FC-signatures of deletions (response variables). To assess significance, we recomputed PLSR using 5000 null FC-signature maps and counted the number of times the explained variance was higher than original observation. Null FC-signatures were obtained by computing 5000 times the contrast between CNVs and controls after label shuffling for 16p11.2 and 22q11.2 separately.

To investigate the association between FC alterations and expression patterns of individual genes, we computed Pearson correlations. The null distribution was defined by the same 5000 random FC-signatures described above.

To test the specificity of the relationship between gene expression and FC, we randomly sampled 10000 gene sets (n=24 for 16p11.2 genes and n=37 for 22q11.2 genes) from 15633 genes and re-computed the PLSR 10000 times. The explained variance (R-squared) was used as test-statistics for the null distribution, and the p-value was calculated as the number of times the explained variance of the random gene-set exceeded the variance explained by 16p11.2 or 22q11.2 genes. A similar approach was performed for the individual gene correlations using median correlation as test-statistics.

Results

16p11.2 and 22q11.2 CNVs have large effects on connectivity at the global and regional level.

The 16p11.2 deletion showed a global increase in FC of 0.31 z-scores (based on the variance of the respective control group, Supplementary Table S1.1) when compared with control subjects (p=0.011, permutation test, Figure II.2a,c). We observed over-connectivity in 88 connections (FDR, $q < 0.05$), with beta values ranging from 0.76 to 1.34 z-scores. Overconnectivity predominantly involved the fronto-parietal, somatomotor, ventral attention, and basal ganglia networks (Figure II.2c). Regions showing the strongest mean connectivity alterations included the caudate nucleus, putamen, lateral frontal pole, anterior middle frontal gyrus, and dorsal anterior cingulate cortex (Supplementary Table S1.8).

The 22q11.2 deletion was associated with a global decrease in connectivity (z-scores = -0.25, Supplementary Table S1.3), with 68 connections surviving FDR correction (beta values ranging from -0.59 to -1.69 z-scores, Figure II.2b, d). Underconnectivity predominantly involved the anterior and lateral DMN, and limbic network (Figure II.2d). The temporal pole, the ventral anterior insula and peri-insular sulcus, the amygdala-hippocampal complex, the dorsal anterior cingulate cortex, and perigenual anterior cingulate cortex showed the strongest changes in connectivity (see Supplementary Table S1.8).

16p11.2 duplication carriers showed a mean reduction of connectivity (z-score = -0.25, Figure II.2a and Supplementary Table S1.2) relative to controls ($p = 0.034$, permutation test), but none of the individual connections survived FDR correction. A sensitivity analysis showed that results are unaffected by differences in age distribution between deletions and control groups (see Supplementary Results).

22q11.2 duplications showed an overall increase in connectivity (z-score = 0.23, Figure II.2c and Supplementary Table S1.4), but only 16 connections survived FDR correction involving the posterior medial and lateral visual network, the cerebellum I-V, and the lateral fusiform gyrus (see Supplementary Table S1.8).

Deletions and duplications at both loci showed a mirror effect at the global connectivity level. 16p11.2 deletions and duplications also showed mirrors effects at the network level ($p = 0.006$, two-sided). This was not the case for 22q11.2 (Supplementary Results).

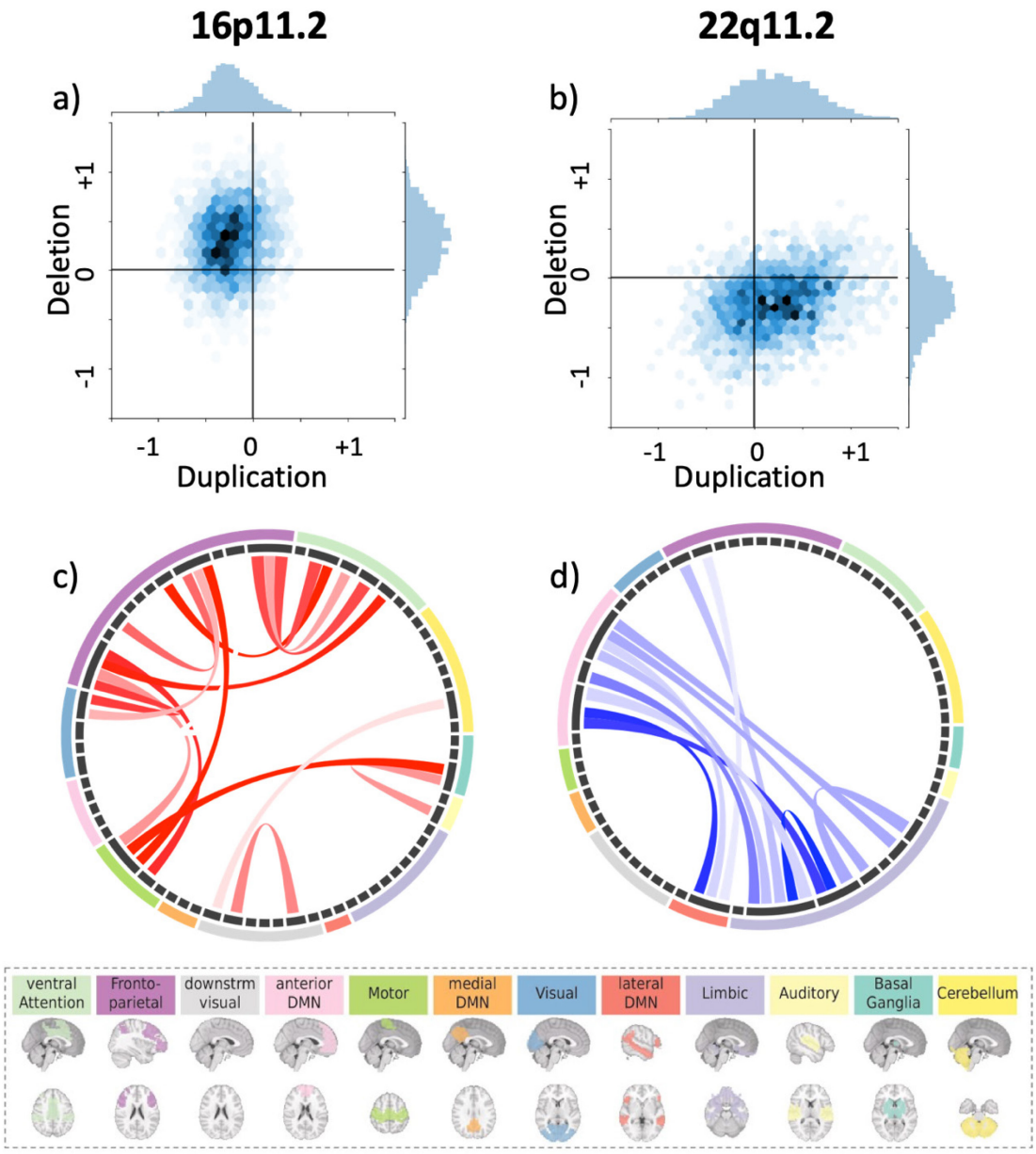

Figure II-2 Connectome-wide effects of CNVs

Legend: (a-b): Scatterplot (*hexagonal plot*), showing estimates (beta values) from connectome-wide association studies (CWAS) performed between 16p11.2 (a) and 22q11.2 (b) CNVs and their respective controls. In total, 2,080 beta estimates were obtained from a linear model computed from z-scored connectomes based on the variance of the respective controls. The color hue represents the number of beta estimates in the hexagon bin. Y axis: beta values associated with deletions (CWAS comparing deletions *vs* controls). X axis: beta-values associated with duplications (CWAS comparing duplications *vs* controls).

(c-d): Each chord diagram shows the top 20% of connections surviving FDR correction ($q < 0.05$) from the 16p11.2 deletion (c) and 22q11.2 deletion (d) CWAS. Each chord represents a significantly altered connection between two functional seed regions. All 64 seed regions are represented in the dark grey inner circle. The width of the seed region in the grey inner circle corresponds to the number of altered connections. Seed regions are grouped into 12 functional networks (outer ring, Supplementary Table S1.9). Networks are represented in 12 brains below the two diagrams. Red chords represent overconnectivity and blue chords underconnectivity.

The effect sizes of deletions are twice as large as the effects of idiopathic SZ, ASD, or ADHD

We performed three independent CWAS, comparing FC between patients with ASD, SZ, ADHD, and their respective controls. Idiopathic SZ showed overall underconnectivity affecting 835 connections, in line with previous reports (116,119) (Figures II.3a, II.3c, Supplemental Results and Tables S1.6 and S1.8). Over-connectivity was restricted to 24 connections (FDR, $q < 0.05$).

Idiopathic ASD also showed overall underconnectivity (73 under and 2 overconnected survived FDR, $q < 0.05$, Figures II.3b, II.3c, Supplemental Results and Tables S1.5 and S1.8).

For ADHD, none of the individual connections survived FDR correction (Supplemental Results and Tables S1.7 and S1.8). Sensitivity analyses excluding females from the SZ and ADHD cohorts showed identical results (Supplementary Results).

Among idiopathic conditions, the effect size of connectivity alteration was the highest in SZ (largest beta value = -0.56 std of the control group), followed by autism (largest beta value = -0.46), and ADHD (largest beta value = +0.26). Effect sizes observed for both deletions were approximately two-fold larger (beta values = +1.34 and -1.69 for 16p11.2 and 22q11.2 respectively) than those observed in idiopathic SZ, ASD, and ADHD (Figure II.3c). The largest effect size among the 16 connections surviving FDR for the 22q11.2 duplication was Cohen's d= 1.87.

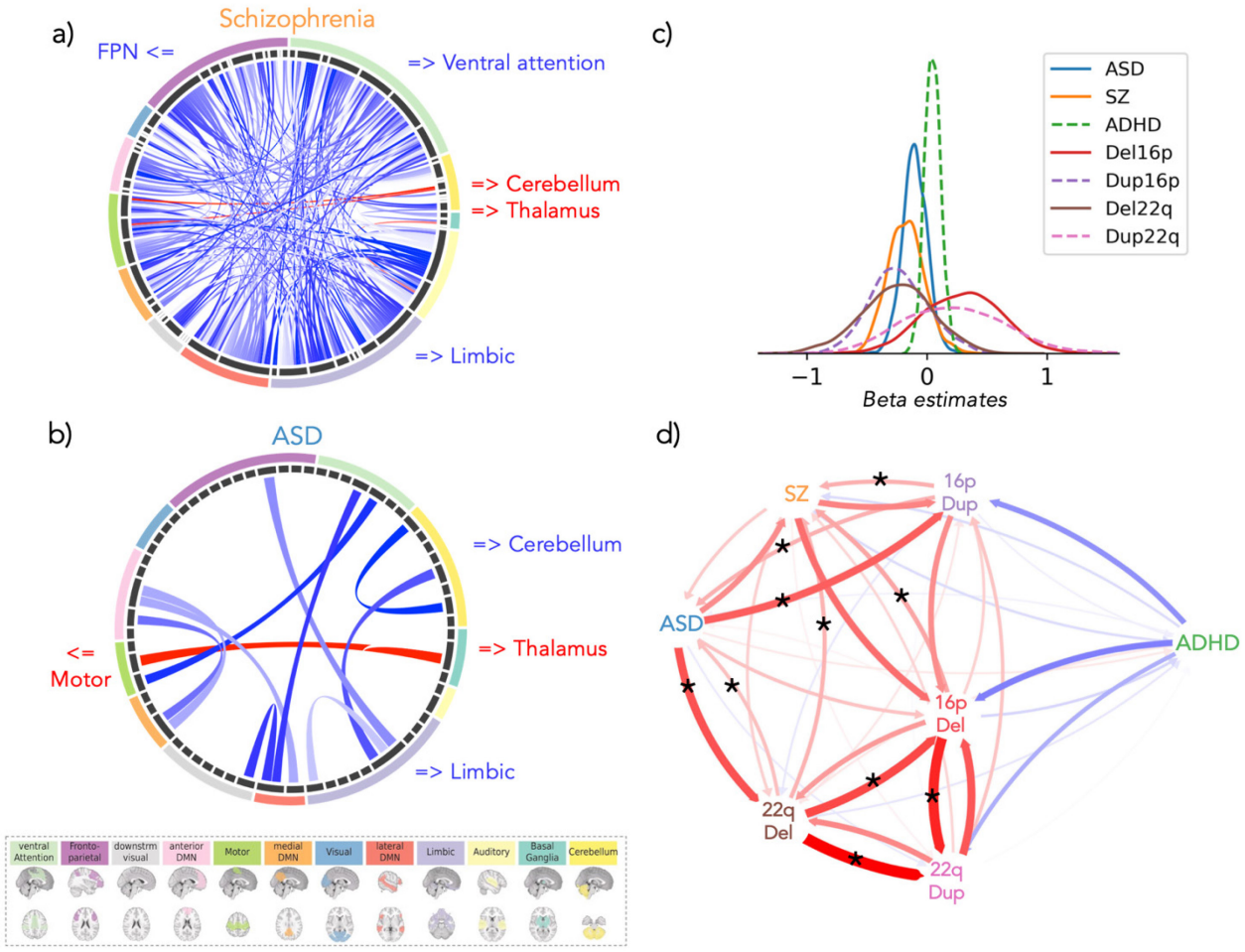

Figure II-3 Similarities at the connectome-wide level across ASD, SZ, and deletion FC-signatures

Legend: (a, b): Each chord diagram shows the top 20% connections surviving FDR correction ($q < 0.05$) from the SZ (a) and ASD (b) CWAS. Each chord represents a significantly altered connection between two functional seed regions. All 64 seed regions are represented in the dark grey inner circle. The width of the seed region in the grey inner circle corresponds to the number of altered connections. Seed regions are grouped into 12 functional networks (outer ring, Supplementary Table S1.9). The network colors correspond to the legend below. Red chords represent overconnectivity and blue chords underconnectivity. (c) Density plots represent the distribution of 2080 beta estimates for the CWAS (whole brain contrast of cases versus controls) for the SZ, ASD, ADHD, deletion and duplication groups. X axis values = z-scores of Beta estimates, which were obtained from linear models computed using z-scored connectomes based on the variance of the respective controls. (d) Spatial similarity of whole-brain FC-signatures between CNVs and idiopathic psychiatric conditions. Arrows represent the correlation between group level FC-signatures, and

the individual connectomes of either cases or controls from another group. The correlation was computed in both directions. Red and blue arrows represent positive and negative correlations respectively. Arrow thickness represents the effect size of the Mann-Whitney test. Stars represent similarities (Mann-Whitney tests) surviving FDR.

ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder; FPN: fronto-parietal network; 16pDel: 16p11.2 deletion; 22qDel: 22q11.2 deletion, 16pDup: 16p11.2 duplication; 22qDup: 22q11.2 duplication

Individuals with ASD and SZ relative to controls, show similarities with whole brain FC signatures of CNVs

We tested the spatial similarity between whole-brain FC-signatures across CNVs and idiopathic psychiatric conditions. To this mean we computed the similarity (Pearson R) between group level FC-signatures, and the individual connectomes of either cases or controls from another group (Figure II.1). This was repeated 42 times between all CNVs and conditions and in both directions. Most of the significant whole brain FC similarities were observed between individuals with either idiopathic ASD, SZ and 4 CNVs (Figure II.3d). ADHD did not show any significant similarities with any other group.

Thalamus and somatomotor regions play a critical role in dysconnectivity observed across CNVs and idiopathic psychiatric conditions

We asked if whole brain FC similarities between individuals with ASD, SZ and CNVs may be driven by particular regions. We thus repeated the same similarity analysis presented above at the level of the FC signatures of each of the 64 seed regions. Individuals with SZ showed increased similarity with 28 out of the 64 regional FC-signatures of the 16p11.2 deletion than controls (FDR, $q < 0.05$). They also showed increased similarity with 18 region-level FC-signatures of the 22q11.2 deletion (Figure II.4, Supplementary Tables S2.3 and S2.4, and Results). Deletion FC-signatures did not show any similarity with controls. We ranked the effect size of each seed region and compared them for both deletions. The seed regions with the highest similarity between SZ and 16p11.2 were also those with the highest similarity between SZ and 22q11.2 (adjusted $R^2 = 0.3709$, p = 6e-08) (see Supplementary Results).

Individuals with autism showed greater similarity with six regional FC-signatures of the 16p11.2 deletion compared to controls (FDR, $q < 0.05$). They also showed greater similarity with six region-level FC-signatures of the 22q11.2 deletion (Figure II.4, Supplementary Tables S2.1 and 2.2, and Results). Deletion FC-signatures did not show significant similarities with controls for any of the 64 seed regions. Of note, individuals with SZ and ASD showed higher similarity with the thalamus FC-signatures of both deletions (Figure II.4). None of the similarities correlated with motion or sex. Regions driving similarities between psychiatric conditions and deletion FC signatures were also those with the highest number of connections altered by each deletion individually. Eight and six out of the top 10 regions altered by 22q11.2 and 16p11.2 respectively were driving similarities with psychiatric conditions (Supplementary Table 1.8).

Despite lower power, we investigated similarities with duplication FC-signatures. The number of significant regional similarities was smaller. Out of the 28 regions showing a similarity between idiopathic conditions and duplications, 17 regions also showed similarities with deletions (See Supplementary Results). Individuals with ADHD, did not show higher similarities with the regional FC-signatures of any CNVs except for 2 regional FC-signatures of the 16p11.2 duplication (Supplementary Tables S2.5 and S2.6).

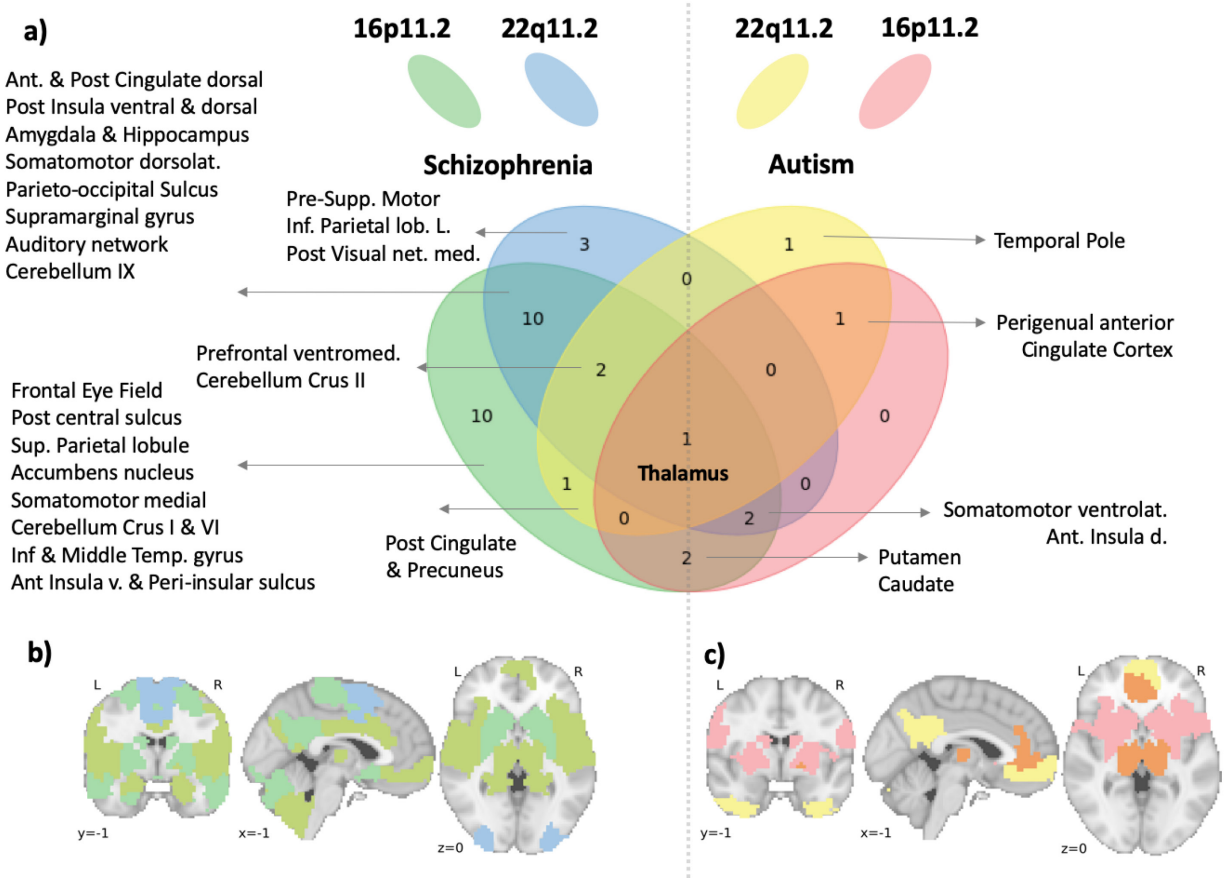

Figure II-4 Regional similarity between the individual FC profiles of subjects with a psychiatric diagnosis and FC-signatures of 16p11.2 and 22q11.2 deletions

Legend: The FC-signatures of both deletions are decomposed into 64 seed-regions. Deletion FC-signatures are correlated to the individual connectivity profile of subjects with a psychiatric diagnosis and their respective control subjects. Of note, the correlation is equivalent to the mean centering of all region-based FC-signatures. Significantly higher similarities of patients with either ASD and SZ were present in 33 seeds regions (FDR) and are presented on the right and the left side of the diagram, respectively (a) and also in the corresponding right and left brain maps. At the intersection of all ellipses, the thalamus FC-signatures of both deletions showed increased similarity with individuals who have a diagnosis of ASD or SZ compared to their respective controls.

16pDel: 16p11.2 deletion, 22qDel: 22q11.2 deletion; Ant: anterior; Post: posterior; dorsolat: dorsolateral; Inf: inferior; L.: left; v.: ventral; net.: network; med: medial; Supp: supplementary; lob: lobule (Full-name labels are provided in Supplementary Table S1.9).

Similarity to deletion FC-signatures is associated with symptom severity

We investigated whether regional FC similarities with deletions described above are associated with symptom severity among individuals in idiopathic psychiatric cohorts. Symptom severity was assessed using the Autism Diagnostic Observation Schedule (ADOS, (216)), in ASD, Positive and Negative Syndrome Scale (PANSS, (217)) in SZ, and Full Scale Intelligence Quotient (FSIQ) in ASD. The 10 seed regions with significant FC similarity between ASD and either deletion were those showing the strongest association with the ADOS symptom-severity score (two regions passed FDR correction $q < 0.05$: the caudate nucleus and temporal pole) and FSIQ (Figure II.5 and Supplementary Tables S3.1-3.4). Among the seed regions contributing to the similarity between SZ individuals and deletions, none were significantly associated with PANSS measures after FDR correction. FSIQ data was not available in the SZ cohorts.

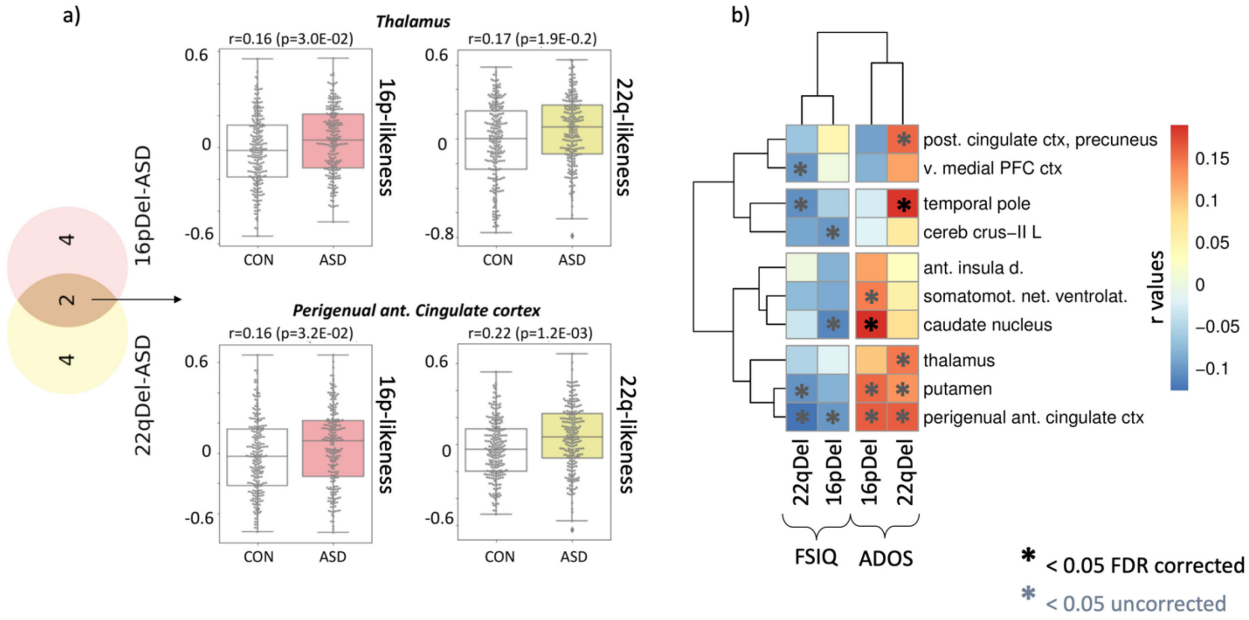

Figure II-5 Relationship between the deletion FC-signatures and behavior

Legend: a) Boxplots represent the connectivity similarity for two seed regions (thalamus and perigenual anterior cingulate cortex). Each data point represents one individual: r value of the Pearson correlation between the deletion FC-signatures and the FC-profile of an individual with ASD (n = 221 in the colored boxplots) or a control subject (n = 232 in the non-colored boxplots). For the two seed regions, individuals with ASD show significantly higher similarity (FDR, $q < 0.05$) with the 16p11.2 (pink) and 22q11.2 (yellow) deletion FC-signatures than the individual controls. All seed regions showing significantly higher similarity

with ASD are represented in the Venn diagram on the left. b) We investigated the relationship with cognitive scores and found that stronger individual similarity with the deletion FC-signature was associated with more severe symptoms measured by FSIQ and ADOS. Heatmaps show the level of correlation between behaviour scores and the similarity with deletion FC-signatures

16pDel: 16p11.2 deletion, 22qDel: 22q11.2 deletion; FSIQ: full-scale intelligence quotient; ADOS: autism diagnostic observation schedule; ant.: anterior; post: posterior; v.: ventral; PFC: prefrontal cortex; cereb: cerebellum; d.: dorsal; L: left; ctx: cortex; net.: network. (Full-name labels are provided in Supplementary Table S1.9).

16p11.2 and 22q11.2 deletions show regional FC similarities

Although the two deletions showed opposing effects on global connectivity (Figure II.3c), their connectomes were positively correlated (Figure II.3.d). We, therefore, sought to identify the main regions that contributed to this connectome-wide correlation.

Using the same approach as above (Figure II.1), we correlated the 22q11.2 deletion group-level FC-signature with individual connectomes of 16p11.2 deletion carriers and their respective controls. The 22q11.2 deletion FC-signature showed significant similarities with 16p11.2 deletion carriers for 12 regions (FDR, $q<0.05$), mainly involving the frontoparietal, ventral attentional, and somatomotor networks. The reverse test showed significant similarity of the 16p11.2 deletion FC-signature with 22q11.2 deletion carriers in 10 regions within the anterior and lateral DMN, frontoparietal and basal ganglia networks. Four seed regions were observed in both tests (Figure II.6a). We reasoned that the FC-similarity between CNVs may be informed by the spatial patterns of gene expression within both genomic intervals.

Association between gene expression spatial patterns and deletion FC-signatures

We performed Partial Least Squares Regression (PLSR) to investigate the association between FC-signatures of each deletion and the expression patterns of 37 and 24 genes encompassed in the 22q11.2 and 16p11.2 genomic loci respectively. The 2 components required to reach a significant association explained 24.2% of the variance of the 16p11.2 deletion FC profile ($p=0.041$, 5000 random FC profiles). For the 22q11.2 deletion, either one or 2 components were significant ($p<0.0002$, 5000 random FC profiles). The 2 components explained 43.2% of the variance of the 22q11.2 deletion FC signature. Similar PLSR analyses performed for each of the 64 regions showed that 18 and 32 regional FC-signatures were significantly associated (5000 random FC-signatures, FDR 64 regions) with spatial patterns of gene expression at the

16p11.2 and 22q11.2 loci respectively (Figure II.6b-c). However, this relationship was not specific because 22q11.2 genes were also associated with n=20 regions of the 16p11.2 FC signature. Conversely, the 16p11.2 genes were associated with n=19 regions of the 22q11.2 FC signature (Figure II.6c, Supplementary Table S4.2).

To further investigate the low specificity of the connectivity/gene expression relationship, we tested the individual correlation (Pearson) of all 15663 genes with available expression data with deletion FC signatures (Figure II.6d-e). Correlations with the 16p11.2 and 22q11.2 FC signatures were observed for 421 and 3883 genes respectively (5000 random FC-signatures). After genome-wide FDR correction, the expression of 1834 genes remained spatially correlated with 22q11.2 and none with the 16p11.2 deletion FC signature. The median correlation values for the n=24 16p11.2 genes and the 16p11.2 FC signature was not higher than the median correlation of 10000 randomly sampled gene sets of the same size (n=24, p=0.31). The same was true for 22q11.2 genes (n=37, p=0.36). However, both deletions were enriched in genes with correlations ranking higher than the genome-wide 98th percentile: *MVP* and *KIF22* showed correlations (r_{MVP}=0.33, r_{KIF22}=0.26) ranking at the 99.76th and 98.76th percentile genome-wide (p=0.03; null:10000 random gene sets). For 22q11.2, *AIFM3, TBX1* and *P2RX6* showed correlations in the 99.5, 98.84, 98.33th percentile (p=0.04).

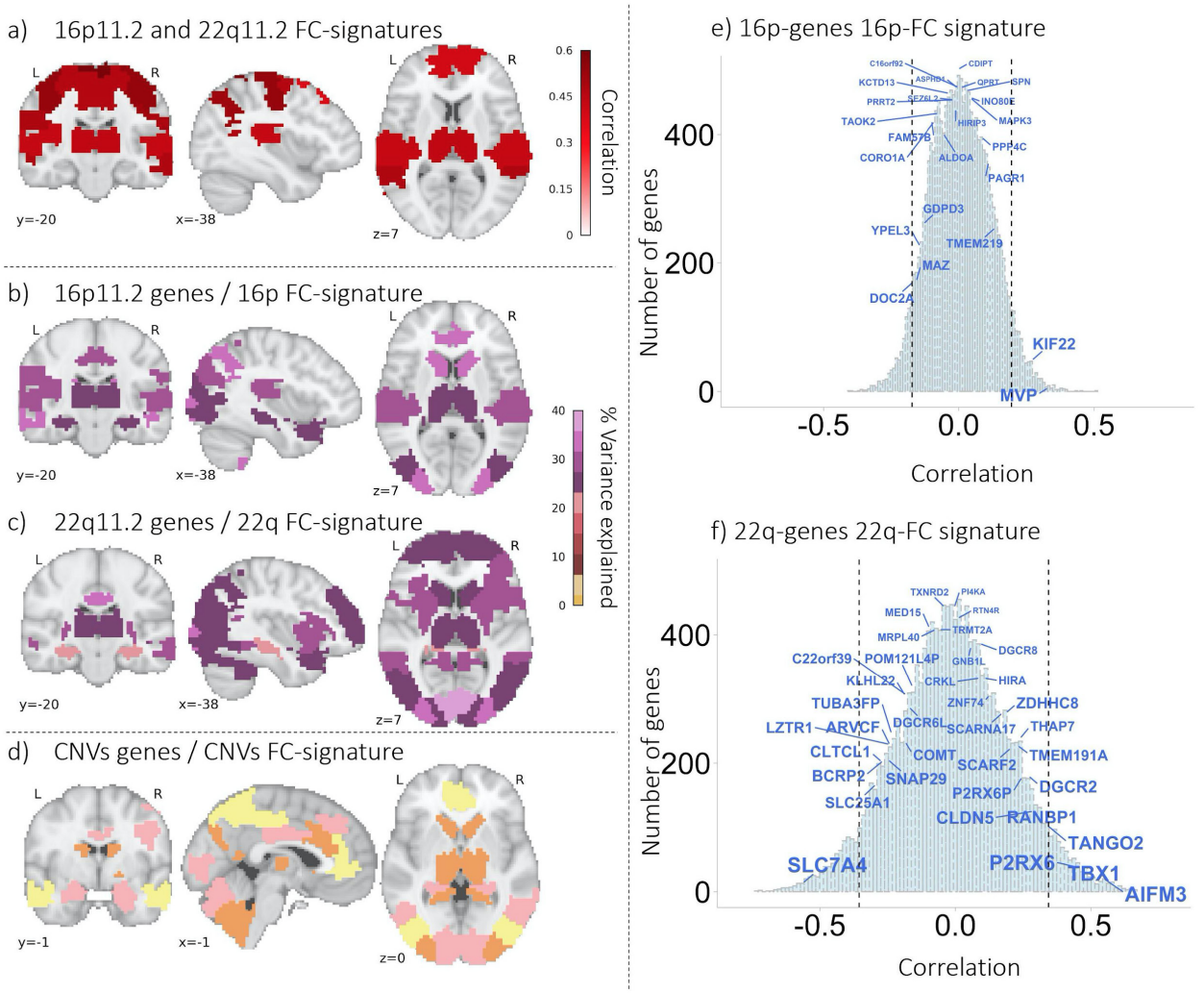

Figure II-6 FC similarities between 16p11.2 and 22q11.2 and relationship with gene expression

Legend: (a) FC similarities between both deletions at the regional level. The values in the brain map represent the level of the FC similarity between deletions (rank biserial correlation, Mann Whitney test). The values are thresholded (FDR, 64 regions): 18 out of 64 regions are similar between deletions.

(b) Relationship between spatial patterns of gene expression within the 16p11.2 locus and regional FC signatures of the 16p11.2 deletion. A partial least square regression (PLSR) was conducted for each of the 64 regions. Maps are thresholded (FDR corrected for 64 regions) and color code represents the percentage of variance explained by gene expression using 2 components in the PLSR. Eleven regions overlapped across PLSR maps (b,c): thalamus, caudate, anterior insula and posterior insula sulcus, cerebellum 9 and right crus-2, medial posterior visual network, lateral posterior visual network, dorsal anterior cingulate, left inferior parietal lobule, amygdala and hippocampus, dorsal visual network. Three (over the 18) regions

identified in the between deletion similarity analysis (a) are also present in the gene expression/FC-signature association maps (b,c): Thalamus, dorsal anterior cingulate and left inferior parietal lobule. c) The same analysis was conducted for 22q11.2 genes and the 22q11.2 deletion FC signature.

(d) Low specificity for the relationship between spatial patterns of gene expression and regional FC deletion signatures. In pink: the 16p11.2 regional FC associated with the expression patterns of both the 16p11.2 and the 22q11.2 genes. In yellow, the 22q11.2 regional FC associated with the expression patterns of genes in both genomic loci. PLSR was performed for each of the 64 regions. Maps are thresholded (FDR, correcting for 64 regions).

(e-f) Expression patterns of genes within and outside CNVs correlate with FC-signatures of 16p11.2 (b) and 22q11.2 deletions (c) The light blue histogram is the distribution of correlations for 15663 genes with available gene expression data from the AHBA. Genes within the CNVs have font-size scaled based on p values. X-axis values : Pearson coefficients. Y-axis values: number of genes. Dotted lines represent the 5th and 95th percentiles of the correlation distribution genome-wide.

Discussion

This proof of concept study provides the first connectome-wide characterization of four CNVs that confer high risk for psychiatric disorders. Deletions and duplications at the 16p11.2 and, to a lesser extent, the 22q11.2 locus were associated with mirror effects at the connectome-wide level. Overconnectivity in the 16p11.2 deletion predominantly involved the ventral attention, motor, and frontoparietal networks. Underconnectivity in the 22q11.2 deletion involved the anterior and lateral DMN and the limbic network. Regional FC-signatures of deletions and duplications, in particular, those implicating the thalamus, somatomotor, posterior insula and cingulate showed significant similarities with the complex architecture of idiopathic ASD, SZ but not ADHD. Seemingly distinct, rare neuropsychiatric mutations may converge on dimensions representing mechanistic building blocks shared across idiopathic conditions. The spatial expression pattern of genes encompassed in both genomic loci was associated with FC-signatures of the corresponding deletion but many genes outside these 2 loci show similar levels of association. This redundancy may represent a factor underlying shared FC signatures between both deletions.

22q11.2 and 16p11.2 CNVs showed large effect sizes on FC that are similar to those previously reported for structural neuroimaging measures, cognition, and behaviour (4,158,176). In sharp contrast, there is a significant discordance between the severe clinical manifestations observed in idiopathic ASD and SZ, and the small effect-size observed in case-control studies at the FC level. Previous structural neuroimaging studies of the same idiopathic psychiatric conditions have also reported small effect sizes (34,100). This discordance may be due to the heterogeneity of these idiopathic conditions and hints at the presence of subgroups or latent dimensions associated with larger effect sizes (200).

The FC-signatures of both deletions (and to a lesser extent those of both duplications) showed similarities with autism and schizophrenia, but not ADHD. Regions contributing to these similarities were also those with the highest number of connections altered by each deletion individually. The FC-signature of the same seed regions also showed the highest association with ASD severity scores and general intelligence in the idiopathic autism sample.

Among the regions, results highlighted overconnectivity between the thalamus and sensory-motor, auditory and visual networks as a common alteration across CNVs and individuals with idiopathic autism or schizophrenia who do not carry CNVs. This is in line with recent rsfMRI studies performed across psychiatric illnesses (200). Sensory processing and perceptual dysfunction are core features of SZ and ASD (8). Those include auditory and visuals hallucinations in SZ (218,219), impairments in gestalt visual perception and discrimination of visual motion (220), disturbances in auditory and tactile discrimination

tasks in Autism. Impairments in phonology (161) as well as visual and auditory deficits have also been demonstrated in 16p11.2 and 22q11.2 deletion carriers (221–223). A general thalamo-sensory disturbance may, therefore, be central across psychiatric diagnoses and genomic mutations. Further studies are required to investigate genome-wide, the genetic determinants of thalamo-sensory disturbance. Because it appears ubiquitous across conditions, the genetic basis is likely to be very broad. FC similarities between idiopathic psychiatric disorders, deletions and duplications is also in line with an emerging body of literature that points to common neurobiological substrates for mental illness (102). Evidence includes the genetic correlation between psychiatric disorders (142,224), and pleiotropic effects of CNVs associated with several conditions (141,191).

Recent work has shown that many genes share similar spatial patterns of expression (195) organized along broad spatial gradients across the brain that are closely related to functional connectivity networks (225,226). In line with these spatial trends, we show that FC-signatures of deletions are associated with expression patterns of genes within as well as outside the genomic loci of interest. The FC profile of the thalamus, dorsal anterior cingulate, and left inferior parietal lobule were associated with expression patterns of genes at both loci and may explain, in part, the FC similarities between both deletions. Expression data were derived from 6 adult brains of the AHBA and results should be interpreted with caution. Nevertheless, they suggest that FC alterations in deletion carriers may in part be related to postnatal processes involved in neuro-maintenance.

Functional connectivity studies using a top-down case-control approach (eg. autism versus control) have characterized large-scale brain network changes associated with diseases, but this framework is unable to describe the directionality of this relationship (227). FC-changes may not necessarily represent an intermediate brain phenotype but rather a secondary impact of psychiatric illnesses. Our strategy integrating top-down and bottom-up approaches shows that individuals with idiopathic ASD or SZ as well as CNV carriers who do not meet diagnostic criteria for these conditions share regional FC alterations. This suggests that the risk conferred by genetic variants and the associated FC-patterns represent important dimensions that are necessary but insufficient to cause disease. Additional factors and associated FC-patterns are required (incomplete penetrance (5)). Bottom-up approaches studying rare variants have almost exclusively been performed individually. Our results suggest, however, that they likely converge on overlapping intermediate brain phenotypes, consistent with a recent study showing overlapping effects on subcortical structures across 12 different CNVs conferring risk to SZ (187).

Limitations

Reproducibility of rs-fMRI in psychiatry has been challenging. However, when studies using similar methodologies analytical strategies are compared, there are consistent results. In SZ and ASD, global decrease in FC has been reported by most studies except for those adjusting for global signal (111,114). Increased thalamocortical connectivity is also repeatedly reported in both conditions (111,116,119). These previous findings are consistent with our results (see Supplementary Results). Our 22q11.2 deletion FC signature was also consistent with the literature including 1) underconnectivity of the DMN (228,229), 2) thalamocortical overconnectivity and the hippocampus underconnectivity (197). The only rsfMRI study previously published for the 16p11.2 deletion focused on the dmPFC (165). Using the same approach and regressing global signal, we also found underconnectivity of the dmPFC with the same set of regions. This highlights the fact that many seemingly discrepant results can be reconciled once methodologies are aligned.

There is no available genetic data for any of the three idiopathic cohorts. However, the frequency of 16p11.2 and 22q11.2 CNVs in ASD or SZ is < 1% (136,192). Therefore our results suggest that other ASD and SZ causal factors share FC similarities with CNVs.

The results on duplications should be interpreted with caution due to our limited power to detect changes in connectivity. The limited phenotypic data in the SZ group did not allow to investigate the relationship between deletion FC-signatures and cognitive traits in this sample. Lack of similarity observed for ADHD is line with the small association between 16p11.2 CNVs and ADHD but is discordant with the association reported for 22q11.2 (193). ADHD has a smaller effect size than SZ and ASD, which may have limited our analysis (230). Several confounding factors may have influenced some of the results. Those include sex bias, which is present across all 3 psychiatric cohorts, age differences in the 16p11.2 deletion group, diagnosis of ASD and ADHD in 22q11.2 deletion carriers, and medication status in the idiopathic ASD and SZ groups. However, carefully conducted sensitivity analyses, investigating all of these confounders did not change any of the results.

Conclusion

Deletion and duplication at several genomic loci result in mirror effects across many human traits (149,163,178,182), including brain connectivity. Haploinsufficiency may define functional connectivity dimensions that represent building blocks contributing to idiopathic psychiatric conditions. Our results show that it is becoming increasingly difficult to justify the study of psychiatric conditions or rare genetic variants in isolation. Large scale studies simultaneously integrating a top-down approach across diagnostic boundaries, and a bottom-up investigation across a broad set of genomic variants are required to improve our understanding of specific and common psychiatric outcomes associated with genetic variants and FC signatures.

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Author contributions

C.M., S.U., S.J., and P. B., designed the overall study and drafted the manuscript.

C.M. and S.U. processed the data and performed all imaging analyses.

P.O. preprocessed the SZ data and reviewed the manuscript.

C.S. performed the statistical analyses and drafted the manuscript.

K.K. and G.D. performed the gene expression analyses.

A.L., E.D. , PO, and G.H. contributed to interpretation of the data and reviewed the manuscript.

A.L. and L.K. provided the UCLA fMRI data.

A.E. contributed to interpretation of the data and reviewed the manuscript.

S.G., D.L., A.M., S.P., and E.S. provided the SZ data.

CE.B. provided the UCLA fMRI data, contributed to interpretation of the data and drafted the manuscript.

The Simons Variation in Individuals Project Consortium provided the 16p11.2 data.

All authors provided feedback on the manuscript.

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Data in the schizophrenia dataset were accessed through the SchizConnect platform (http://schizconnect.org). As such, the investigators within SchizConnect contributed to the design and implementation of SchizConnect and/or provided data but did not participate in the data analysis or writing of this report. Funding of the SchizConnect project was provided by NIMH cooperative agreement 1U01 MH097435. SchizConnect enabled access to the following data repository: The Collaborative Informatics and Neuroimaging Suite Data Exchange tool (COINS; http://coins. mrn.org/dx). Data from one study was collected at the Mind Research Network and funded by a Center of Biomedical Research Excellence (COBRE) grant, (5P20RR021938/P20GM103472) from the NIH to Dr. Vince Calhoun. Data from two other studies were obtained from the Mind Clinical Imaging Consortium Database. The MCIC project was supported by the Department of Energy under award number DE-FG02-08ER6458. MCIC is the result of the efforts of co-investigators from the University of Iowa, University of Minnesota, University of New Mexico, and Massachusetts General Hospital. Data from another study were obtained from the Neuromorphometry by Computer Algorithm Chicago (NMorphCH) dataset (http://nunda.northwestern.edu/nunda/data/projects/NMorphCH). As such, the investigators within NMorphCH contributed to the design and implementation of NMorphCH and/or provided data but did not participate in the data analysis or writing of this report. The NMorphCH project was funded by NIMH grant RO1 MH056584.

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III. Paper 2: The general impact of haploinsufficiency on brain connectivity underlies the pleiotropic effect of neuropsychiatric CNVs

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Abstract

Copy number variants (CNVs) are among the most highly penetrant genetic risk factors for neuropsychiatric disorders. Their impact on brain connectivity remains mostly unstudied. Because they confer risk for overlapping conditions, we hypothesized that they may converge on shared connectivity patterns.

We performed connectome-wide analyses using resting-state functional MRI data from 436 carriers of neuropsychiatric CNVs at the 1q21.1, 15q11.2, 16p11.2, 22q11.2 loci, 4 “neutral effect” CNVs, 66 carriers of scarcer neuropsychiatric CNVs, 756 individuals with idiopathic autism spectrum disorder (ASD), schizophrenia, attention deficit hyperactivity disorder, and 5,377 controls.

Neuropsychiatric CNVs showed global shifts of mean connectivity. The effect size of CNVs on relative connectivity (adjusted for the mean) was correlated with the known level of neuropsychiatric risk conferred by CNVs. Individuals with idiopathic schizophrenia and ASD had similarities in connectivity with neuropsychiatric CNVs. We reported a linear relationship between connectivity and intolerance to haploinsufficiency measured for all genes encompassed by CNVs across 18 loci. This profile involved the thalamus, the basal ganglia, somatomotor and frontoparietal networks and was correlated with lower general intelligence and higher autism severity scores. An exploratory factor analysis confirmed the contribution of these regions to three latent components shared across CNVs and neuropsychiatric disorders.

We posit that deleting genes intolerant to haploinsufficiency reorganize connectivity along general dimensions irrespective of where deletions occur in the genome. This haploinsufficiency brain signature opens new avenues to understand polygenicity in psychiatric conditions and the pleiotropic effect of CNVs on cognition and risk for neuropsychiatric disorders.

Introduction

Genomic copy number variants (CNVs) are deletions (DEL) or duplications (DUP) of more than 1000 base pairs of DNA. Rare CNVs with large effects have been associated with a range of neurodevelopmental and psychiatric conditions (190,191). Twelve recurrent CNVs have been individually associated with autism spectrum disorder (ASD) (192), eight with schizophrenia (SZ) (136), and eight with attention deficit hyperactivity disorder (ADHD) (193) but studies have shown that ultra-rare CNVs at many more genomic are also associated with these conditions (5,136).

Functional connectivity (FC) studies have provided critical insight into the architecture of brain networks involved in neuropsychiatric disorders (NPs), but only a few studies have investigated networks modulated by CNVs (165,176,231). These large effect-size mutations can shed light on pathways connecting genetic risk to brain endophenotypes, such as FC. In a previous study, we characterized the connectome-wide effects of four CNVs that confer high risk for NPs (NP-CNVs). Deletions and duplications at the 16p11.2 and, to a lesser extent, at the 22q11.2 locus were associated with mirror effects on global FC (231). For 16p11.2 deletion carriers, overconnectivity predominantly involved the ventral attention, motor, and frontoparietal networks relative to controls. 22q11.2 deletion carriers showed global underconnectivity, involving the anterior and lateral default mode network (DMN) and the limbic network. Connectivity profiles of the thalamus, somatomotor, posterior insula and cingulate showed significant similarities between NP-CNVs and idiopathic ASD, SZ but not ADHD.

Previous studies were mainly performed one mutation at a time, with the notion that the function of genes would shed light on the relationship between molecular mechanisms and phenotypes. Results from this approach have raised several questions including 1) How specific are the effects of CNVs, and are there any general rules linking the gene content of CNVs to intermediate brain phenotypes? 2) How can one pursue the study of rare variants beyond the handful of CNVs and single nucleotide variants (SNV) frequent enough to conduct an individual association study? The hypothesis of shared neuroimaging alterations across NP-CNVs was recently investigated in 21 carriers of CNVs across the 22q11.2, 15q11.2, 1q21.1, 16p11.2 or 17q12 loci (189). Analysis of diffusion-weighted imaging (DWI) measures from the cingulum bundles suggested that macro- and microstructural properties were associated with the level of risk for psychiatric disorders conferred by CNVs. Using T1-weighted data, Warland and colleagues showed that the volumes of three subcortical brain regions (thalamus, hippocampus, and nucleus accumbens) were significantly

reduced in a group of 49 carriers of 4 SZ-associated CNVs in the UK Biobank (16p11.2 duplication, 22q11.2 deletion, 15q11.2 deletion, and 1q21.1 deletion) (187).

In the current study, we asked two questions: 1) Do previous observations of connectivity alterations associated with 16p11.2 and 22q11.2 extend to other genomic loci? and 2) How can we close the gap between the exponentially expanding landscape of rare neuropsychiatric variants and the knowledge of their effects on intermediate brain phenotypes? We recently tackled a similar question by investigating the statistical relationship between the coding gene content of rare CNVs and their effect on intelligence quotient (IQ). We showed that around 75% of the effect-size of any CNV on IQ can be explained by linear models using the sum of the "probability of being loss-of-function intolerant" (pLI) scores (188) of all genes encompassed in the CNV (6). The pLI (probability loss-of-function intolerant) score is the probability that a given gene is intolerant to "protein loss of function" (pLoF). The score measures selective pressure and is based on lower-than-expected rates of variants leading to haploinsufficiency in the general population (188).

We aimed to 1) characterize the connectivity-profiles of CNVs at genomic loci previously associated with neurodevelopmental disorders (1q21.1, 15q11.2, 16p11.2 and 22q11.2), 2) assess whether connectivity-profiles of NP-CNVs may represent dimensions observed in idiopathic ASD, SZ, or ADHD, and 3) investigate the relationship between measures of pLI and connectivity across genomic loci. We gathered rs-fMRI data on 502 carriers of deletions or duplications at the 1q21.1, 2q13, 15q11.2 (BP1-BP2), 15q13.3, 16p11.2 proximal, and 22q11.2 genomic loci as well as 66 carriers of scarcer NP-CNVs at 8 additional genomic loci (5). Among these carriers were included 4 "neutral effect" CNVs without prior association to neuropsychiatric conditions (2q13 CNVs, 15q13.3 and TAR-1q21.1 duplications) (5,136,232). Three out of the five genetic-first cohorts used in this study have not yet been published. We also analyzed 756 subjects with idiopathic ASD, schizophrenia, or ADHD, and 5,377 controls (Table 1).

CNV (hg19)	**Status**	**n tot /clin**	**Age**	**Sex (M)**	**Motion**	**Sites**	OR ASD	OR SZ
15q11.2 chr15: 22.81-23.09	DEL	66 / 1	63 (7.6)	42%	0.18 (0.06)	3	n.s	2 (b)
	DUP	71 / 1	62.5 (6.9)	45%	0.18 (0.06)	3	n.s. (a)	n.s. (a)
15q13.3 31.08–32.46	DUP	40 / 0	62.6 (6.7)	37%	0.18 (0.05)	2	n.s. (a)	n.s. (a)
2q13 chr2: 110.86-110.98	DEL	36 / 0	63.3 (7.3)	31%	0.18 (0.06)	2	-	-
	DUP	30 / 0	62.8 (7)	40%	0.17 (0.05)	2	-	-
1q21.1 chr1: 146.53-147.39	DEL	25 / 9	42.4 (20.4)	56%	0.18 (0.06)	7	3 (a)	4 (b)
	DUP	16 / 7	42.36 (21)	31%	0.2 (0.06)	7	5 (a)	4 (b)
145.39-147.39	DUP-TAR	18 / 0	58.6 (7.9)	56%	0.17 (0.05)	2	-	-
22q11.2 chr 22: 19.04-21.47	DEL	43 / 43	17 (7)	55%	0.18 (0.07)	1	32 (a)	68 (b)
	DUP	19 / 11	36 (23.1)	42%	0.18 (0.09)	4	n.s. (a)	0.15 (b)
16p11.2 chr 16: 29.65-30.20	DEL	41 / 37	18.8 (19)	58%	0.22 (0.08)	6	14 (a)	12 (a)
	DUP	31 / 29	30.5 (17)	64%	0.21 (0.09)	4	14 (a)	9 (b)
Additional CNVs for pLI analysis		66 / 12	57 (16)	45%	0.18 (0.06)	5	-	-
CNVs Controls		4427 / 0	61.31 (11)	47%	0.19 (0.06)	7	-	-
Idiopathic Psychiatric Conditions	**SZ**	242 / 242	33.6 (9.24)	73%	0.16 (0.06)	9	-	-
	ASD	225 / 225	16 (6.5)	100%	0.18 (0.05)	12	-	-
	ADHD	289 / 289	11.5 (2.8)	78%	0.15 (0.04)	6	-	-
IPCs Controls		950 / 0	18.8 (10)	70%	0.15 (0.04)	27	-	-

Table III-1 CNV carriers, individuals with idiopathic psychiatric conditions and controls after MRI quality control

Legend: Chr: chromosome number, coordinates are presented in Megabases (Mb) according to Hg19. DEL: deletion; DUP: duplication; IPCs: Idiopathic Psychiatric Conditions; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity-Disorder n = tot /clin: total number of participants /number of participants clinically ascertained. Age (in years); M: male; Motion: framewise displacement (in mm). Quantitative variables are expressed as the mean ± standard deviation. All sites

scanned controls and sensitivity analyses were performed to investigate the potential bias introduced by differences in site, age and sex. Odd-ratios for the enrichment of CNVs in ASD and schizophrenia were previously published (a (5), b (136)). OR for the enrichment of CNVs in ADHD were not available. The four 'Neutral-effect CNVs' are highlighted by a light grey background. Additional NP-CNVs (n=66) included in the pLI analysis include NRXN1 (n=2 deletion), 13q12.1 (n=5 deletion, n=2 duplication), 16p12.1 (n=1 deletion, n=3 duplication), 16p13.11 (n=4 deletion, n=6 duplication), 17p12 (n=5 deletion; n=1 duplication), TAR (n=2 deletion), 22q11.2 [B-D] (n=3 deletion, n=23 duplication), 2q11.2 (n=1 deletion, n=2 duplication), 16p11.2 distal (n=1 duplication), 7q11.23 distal (n=1 duplication), 15q13.3 (n=1 deletion), 14q32 (n=1 deletion) and 2 carriers of multiples CNVs. Detailed information relative to diagnosis, IQ, and motion, are available in Supplementary Tables 2-3.

Materials and Methods

Samples

We analyzed 6,635 individuals from nine datasets (Table 1, Supplementary Materials and Methods).

CNVs carriers and controls

Genetic-first cohorts were recruited based on the presence of a CNV, regardless of symptomatology, by five consortia (three out of five have never been published before): the Simons Variation in Individuals Project (VIP) consortium data (16p11.2 and 1q21.1 CNVs carriers) (202), the University of California, Los Angeles (22q11.2 CNVs carriers), the Brain Canada cross NP-CNVs project (CHU Sainte Justine, Montreal, Canada), the Define cross NP-CNVs Project (Cardiff, UK), and the Lausanne Prisma project (16p11.2 and 1q21.1 CNVs carriers) (see Supplementary Materials and Methods for individual dataset description).

CNVs were also identified in an unselected population (UK Biobank) (see Supplementary Materials and Methods for the CNV calling procedure and final sample description).

Idiopathic psychiatric conditions and respective controls

Individuals with idiopathic ASD and their respective controls were sampled from the ABIDE1 multicenter dataset (12). Individuals with idiopathic SZ and their respective controls were obtained from aggregated fMRI data of 10 studies. Individuals diagnosed with ADHD (DSM-IV) and their respective controls were obtained from the ADHD-200 dataset (203,204)(see Supplementary Materials and Methods for individual dataset description).

Imaging data were acquired with site-specific MRI sequences. Each cohort analyzed in this study was approved by the research ethics review boards of the respective institutions. Signed informed consent was obtained from all participants or their legal guardian before participation. Secondary analyses of the listed datasets for the purpose of this project were approved by the research ethics review board at Sainte Justine Hospital. After data preprocessing and quality control, we included a total of 6,635 individuals (Table 1).

Preprocessing and QC procedures

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 (205). Preprocessed

data were visually controlled for quality of the co-registration, head motion, and related artefacts by two raters (Supplementary Materials and Methods).

Computing connectomes

We segmented the brain into 64 functional seed-based regions defined by the multi-resolution MIST brain parcellation (206). 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 functional connectivity alterations in neurodevelopmental disorders such as ASD (Supplementary Table 10) (37). We corrected for multiple comparisons using a false discovery rate strategy (208).

Statistical analyses were performed in Python using the scikit-learn library (207). Analyses were visualized in Python and R. Code for all analyses and visualizations is available online through the GitHub platform with Jupyter notebook: https://github.com/claramoreau9/NeuropsychiatricCNVs_Connectivity.

Statistical analyses

All of the following analyses are summarised in Supplemental Materials and Methods (Objective and methods, Supplementary Table 1).

Connectome-wide association studies (CWAS)

We performed fifteen CWAS: comparing FC between cases and controls for five CNVs (15q11.2, 1q21.1, 2q13, 16p11.2 and 22q11.2, for deletion and duplication carriers), for TAR-1q21.1 and 15q13.3 duplications carriers, and for three idiopathic psychiatric cohorts (ASD, SZ, and ADHD). Controls were pooled across all CNV cohorts (n=4,427). Controls were separately pooled across the three idiopathic groups (IPCs, n=950, Table 1). FC was standardized (z-scored) based on the variance of the respective control group. CWAS was conducted by linear regression at the connectome level, in which z-scored FC was the dependent variable and clinical status the explanatory variable. Models were adjusted for sex, scanning site, head motion, mean connectivity, and age. We determined whether a connection was significantly altered by the clinical status effect by testing whether the β value (regression coefficient associated with the clinical status variable) was significantly different from 0 using a two-tailed *t*-test. This regression test was applied independently to each of the 2,080 functional connections. We corrected for the number of tests (2,080) using the Benjamini-Hochberg correction for FDR at a threshold of $q < 0.05$ (208), following the recommendations of Bellec *et al.* 2015 (32).

We defined the global FC shift as the average of the β values across all 2,080 connections. We tested whether the observed global FC shifts were significantly different from zero by conducting a permutation test, shuffling the clinical status labels of the individuals included in each CWAS (using 10,000 replications). We thus estimated a valid permutation-based *p*-value associated with the observed global FC shift (209).

Two additional CWAS were performed to assess the linear effect of pLI deletion and duplication scores on FC. The CNV pLI annotation is described in the Supplementary Materials and Methods. This analysis was performed only among the CNVs cohorts, controlling for sex, scanning site, head motion, mean connectivity, and age. FC was standardized (z-scored) based on the variance of the entire sample.

Similarity of whole-brain connectivity-profiles between idiopathic psychiatric conditions and CNVs

We tested the similarity between dysconnectivity measured across the 3 IPCs and the 12 CNVs. This similarity was tested by correlating, at the whole-brain level, individual connectomes of cases and controls of IPCs to the CNVs-connectivity-profiles (group level; Figure 2cd). Controls used to compute the similarity with psychiatric conditions have not been used to compute the CNVs-FC profiles in the first place. The group-level FC-profile was defined as the 2,080 β values obtained from the contrast of cases vs. controls (aim1.2). This was repeated between all CNVs (n=12) and the 3 conditions (n=36 similarity tests).

Individual connectomes of IPC cases and controls were used after independently adjusting for sex, scanning site, mean connectivity, head motion, and age. Similarity scores were derived by computing Pearson's correlations between the whole brain connectomes. We asked whether IPC cases compared to the IPC controls had significantly higher (or lower) similarity to whole-brain CNV-profile using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 36 tests ($q < 0.05$).

Similarity of regional connectivity-profiles between idiopathic conditions and CNVs

The same approach described above was performed at the regional level. We calculated a similarity score between individual adjusted connectomes and the 12 CNVs FC-profiles. FC-profiles were broken down into 64 region-level FC-profiles and similarity scores were derived by computing Pearson's correlations between the 64 β values associated with a particular region. For each region, we tested whether individuals with a psychiatric diagnosis had significantly higher (or lower) similarity to CNVs FC-profiles than controls using a Mann-Whitney U test. We reported significant group differences after FDR correction ($q < 0.05$) for the number of regions (n=64). We investigated the relationship between severity scores and similarity with pLI-FC profile. Similarities of individuals with pLI FC-profiles were correlated (Pearson's r) with severity scores. The p-values associated with these correlations were corrected for multiple comparisons (FDR, $q < 0.05$).

Exploratory factor analysis

Exploratory Factor Analysis (EFA) was performed using the maximum likelihood (mle) method. Factors were allowed to rotate. Analyses were performed using the *psych* and the *stats* packages in R 3.4.1 (233). Factor models were fit iteratively and compared using three criteria: TLI ≥ 0.90, RMSEA ≤ 0.10 and a smaller Bayesian Information Criteria relative to other models. The model with the best fit has been retained.

We used FC-profiles of 12 CNVs and 3 IPCs obtained by CWAS (aim 1.2). The EFA identified 3 latent components (LC) to obtain a non-significant p-value (test for the null hypothesis that 3 factors were sufficient). We extracted standardized EFA loading scores per LC. We used the Nilearn package (207) to report the 64 standardized loading scores per LC into 3 brain maps. We computed the Pearson correlation between the pLI deletion FC-profile and each of the three LCs.

Results

Neuropsychiatric CNVs cause global shifts of functional connectivity

Deletions and duplications of several genomic loci showed a shift in mean FC (Figure 1a-e). There was a positive association between the number of genomic copies (deletion=1, duplication=3) and global connectivity for the 22q11.2 and 1q21.1 CNVs, and negative gene dosage effect for the 16p11.2 CNVs (Figure 1a, 1d-e, Supplementary Tables 4-5). A negative shift was observed for both 15q11.2 and 2q13 duplications (Figure 1b, 1c). In all subsequent analyses, we investigated relative FC, which is computed by adjusting for mean whole-brain connectivity (mC-adjusted).

CNV severity is linked to the effect-size on relative connectivity

We previously showed that the severity of a CNV's impact on cognition is strongly associated with measures of intolerance to haploinsufficiency such as the pLI (6). We, therefore, tested the relationship between pLI scores and the size of a CNV's effect on FC across the 7 genomic loci (listed in Table 2). We showed a significant correlation between pLI scores and effect sizes of deletions (r=0.89, p=0.03). There was no significant relationship for duplications.

Relative regional connectivity is robustly altered by high-risk neuropsychiatric CNVs

The 16p11.2 deletion significantly altered 160 connections (76 positives, 84 negatives, FDR, q<0.05) with beta values ranging from -0.8 to 1.4 z-scores (z-scores based on the variance of the control group, Table 2, Figure 1.k, Supplementary table 6). The altered connections mostly involved the ventral and dorsal posterior insula, the pre-supplementary motor cortex, the putamen, dorsal precuneus, and the left inferior parietal lobule. The 16p11.2 duplication significantly altered 4 connections (1 positive, and 3 negatives), with beta values ranging from -0.9 to 0.7 z-scores). The altered connections mostly involved the amygdala-hippocampus complex, the cerebellum crus-II and VIIIab, and the caudate and accumbens nuclei (Table 2, Figure 1.l, Supplementary Table 6).

The 22q11.2 deletion was associated with over-connectivity in 25 connections and underconnectivity in 21 connections (FDR, q < 0.05), with beta values ranging from -0.95 to 0.8 z-scores. The regions showing the strongest FC alterations included the thalamus, the dorsal anterior and posterior cingulate cortices, the lateral fusiform gyrus, the temporal pole, and the anterior insula (Table 2, Figure 1.m, Supplementary Table 6). The 22q11.2 duplication did not show FC alterations that survived FDR.

15q11.2 and the 1q21.1 CNVs have mild effects on relative connectivity.

The 15q11.2 deletion was associated with overconnectivity of one connection (FDR, $q < 0.05$) between the thalamus and the ventrolateral somatomotor network (Figure 1i, Table 2, Supplementary Table 6). In the 15q11.2 duplication carrier group, 27 connections were significantly altered (16 negatives, and 11 positives, beta values [-0.51; 0.36], Table 2). Altered connections primarily involved the supramarginal, inferior temporal, occipitotemporal gyri, and the temporal pole (Figure 1.j, Supplementary Table 6).

The 1q21.1 deletion was associated with underconnectivity of three connections (FDR, $q < 0.05$) between by the lateral fusiform gyrus, the dorsal precuneus, the lateral occipitotemporal gyrus, the dorsal visual stream, and the dorsal posterior cingulate cortex, with beta values ranging from -1.0 to 0.67 z-scores, (Table 2, Supplementary Table 6, and Figure 1.g). The 1q21.1 duplication showed 13 connections that were significantly altered (4 negatives, and 9 positives, FDR, $q < 0.05$), with beta values ranging from -0.98 to 1.0 z-scores. Altered connections mostly involved the caudate nucleus, the posterior lateral visual network, the temporal pole, the cerebellum Crus-I, and the putamen (Figure 1.h, Table 2, Supplementary Table 6).

We did not detect any significant effects of the 4 neutral effect CNVs (Tar 1q21.1 duplication, 15q13.3 duplication and 2q13 deletion and duplication) on connectivity (Supplementary Table 6).

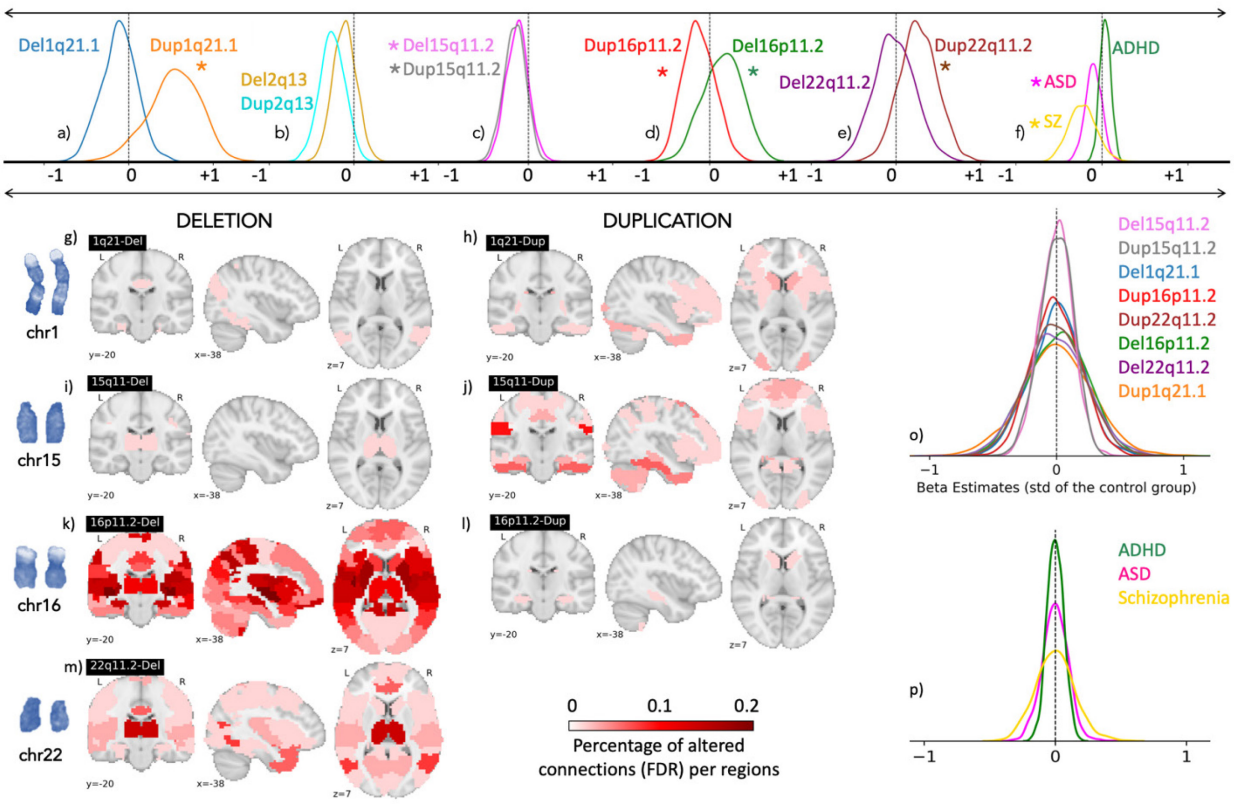

Figure III-1 Global and regional effects of CNVs on connectivity

Legend: (a-e) Global effects of CNVs on connectivity. Density plots represent the distribution of the 2,080 beta estimates for the connectome wide association study (CWAS, whole-brain contrast of cases versus controls) of the CNVs, SZ, ASD, ADHD groups. Stars represent a significant global shift in mean FC. The same density plots are shown after adjusting for mean connectivity (o-p). X-axis values of all density plots represent z-scores of the Beta estimates, which were obtained from linear models computed using z-scored connectomes based on the variance of the control group. Brain maps (g-n) represent the percentage of altered connections (FDR corrected) per region. Del=Deletion, Dup=Duplication, ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder; chr=chromosome.

Loci / ∑ pLI	CNV	n pos	n neg	min-max	var
1q21.1 *1.7*	DEL	0	3	[-1; 0.7]	0.04
	DUP	9	4	[-1; 1]	0.08
TAR (*3.4*)	DUP	0	0	/	0.04
2q13 *0*	DEL	0	0	/	0.02
	DUP	0	0	/	0.02
15q11.2 *1.7*	DEL	1	0	[-0.4; 0.5]	0.02
	DUP	11	16	[-0.5; 0.4]	0.02
15q13.3 (*1.6*)	DUP	0	0	/	0.02
16p11.2 *7.06*	DEL	76	84	[-0.9; 1.4]	0.06
	DUP	1	3	[-0.9; 0,7]	0.04
22q11.2 *10.5*	DEL	25	21	[-0.9; 0.8]	0.06
	DUP	0	0	[-0.7;0.8]	0.05
ADHD		0	0	/	0.01
ASD		21	9	[-0.3; 0.4]	0.01
Schizophrenia		203	233	[-0.4; 0.6]	0.02

Table III-2 The number of significantly altered connections (FDR corrected) for each connectome wide association study (n=15) after adjusting for mean connectivity

∑ pLI: sum of pLI of all genes encompassed in each CNVs. pLI: the **p**robability of being **L**oss of function **I**ntolerant is a measure of gene's intolerance to haploinsufficiency. DEL: deletion; DUP: duplication; ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder. min-max: minimum-maximum of z-scored beta values; var: variance of z-scored beta values; n pos: number of positive connections; n neg: number of negative connections.

Neuropsychiatric CNVs and idiopathic psychiatric conditions show whole-brain FC similarities

We compared (Mann-Whitney) spatial similarities between CNV FC-profiles and IPC, with spatial similarities between CNV FC-profiles and controls (Figure 2c-d). This was performed for all 12 CNVs and 3 IPCs (Figure 3a). Out of the 36 correlations, 12 survived FDR. Of those, most were observed between large effect-size neuropsychiatric CNVs, SZ and ASD. Neutral CNVs (2q13 CNVs and 15q13.3 and TAR-1q21.1 duplication) did not show similarities with FC-profiles of individuals with IPC.

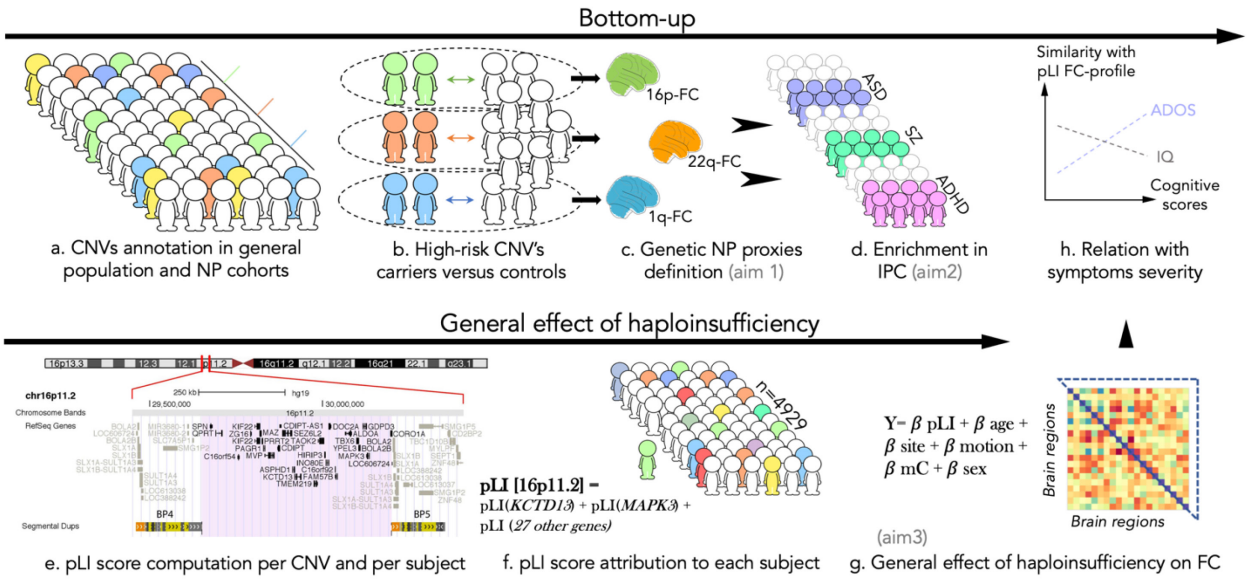

Figure III-2 Method overview

Legend: a) CNVs are identified in unselected and neuropsychiatric populations. b) Connectome wide association studies (CWAS) between CNVs carriers and controls define a CNV-FC-profile (c) for each CNV (aim 1). d) Comparing (Mann-Whitney) 1] the spatial similarity between CNV FC-profile and individuals with IPCs, and 2] the spatial similarity between CNV FC-profile and controls (aim 2).

e) To investigate the general effect of pLI on FC, we used CNVs at 18 genomic loci. We computed the sum of pLI of all genes encompassed within each genomic loci. f) Each carrier obtains a score corresponding to the gene content of his CNV. g) Mass univariate linear models draw a relationship between the pLI score (X) of each individual, and each of the 2080 functional connections (Y). h) Correlation at the regional level between pLI FC-profile and symptoms severity scores.

NP: neuropsychiatric conditions; 16p: 16p11.2; 22q: 22q11.2; 1q:1q21.1; ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder; mC: mean-connectivity adjustment.

Connectivity similarities between neuropsychiatric CNVs and idiopathic psychiatric conditions involve the thalamus, the basal ganglia and the posterior cingulate cortex

We investigated whether whole-brain FC similarities between individuals with SZ, ASD, ADHD and CNVs were driven by particular regions. To do so, we applied the same approach as described above at the regional level by decomposing the FC-profiles of each CNV into 64 seed regions. We found that a set of regions

including the thalamus, the caudate, the putamen, the posterior cingulate, temporal pole, and anterior insula exhibited high degrees of similarity between all neuropsychiatric CNVs FC-profiles and individuals with IPC (figure 3b, red regions, Supplementary Table 7, and Supplementary Figure 3). Only a few regional-level CNVs FC-profiles showed higher similarities with controls (Figure 3b, blue regions, Supplementary Figure 3). Individuals with SZ and ASD demonstrated the highest level of similarity with all neuropsychiatric CNVs compared to their respective controls. We did not detect significant similarities between the FC-profiles of "neutral" CNVs (2q13 deletion and duplication, and TAR-1q21.1 duplication) and individuals with IPC (Figure 3, Supplemental Figure 3, Supplementary Table 7). None of the similarity was correlated with motion.

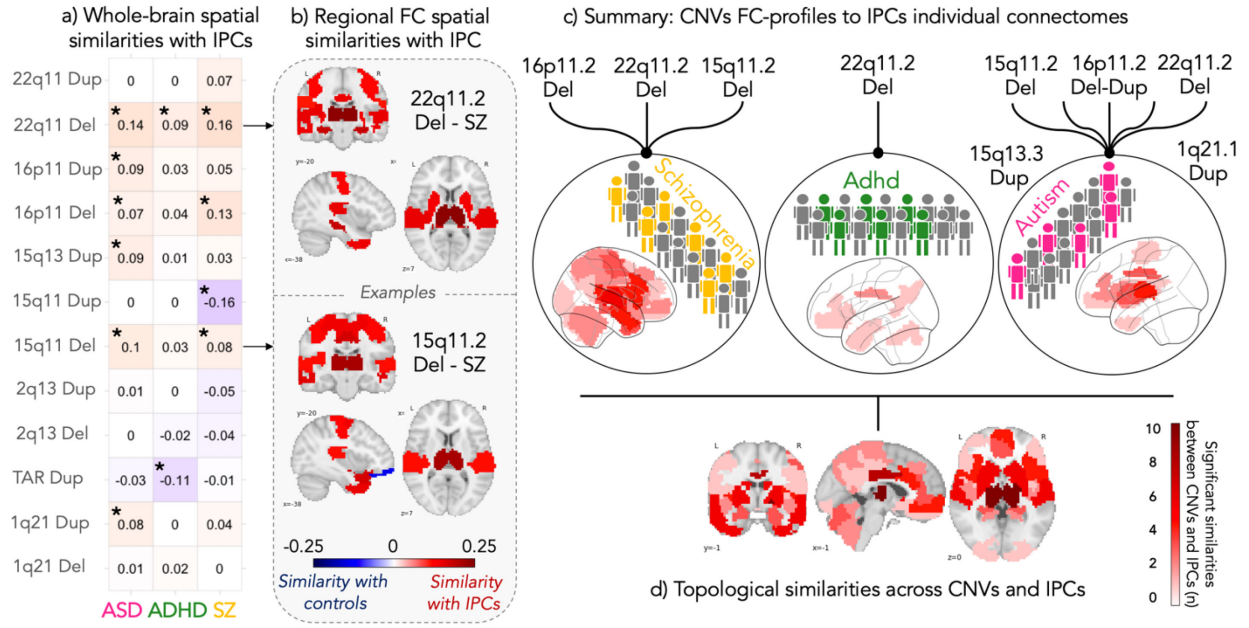

Figure III-3 Spatial similarities between FC-profiles of CNVs and idiopathic psychiatric conditions at the regional and connectome-wide level

Legend: (a) The whole-brain FC-profiles of CNVs were correlated to the individual FC-profiles of subjects with a psychiatric diagnosis, and their respective controls. The effect size (Mann-Whitney test statistic, rank biserial correlation) of the spatial similarity between the CNVs-FC-profiles and individuals with IPC are detailed in the table. Positive (red) reflects higher similarity between CNVs-FC-profiles and individuals with IPC, while negative (blue) reflects higher similarity with controls. Stars represent significant similarities after FDR correction for 36 tests. (b) The whole-brain FC-profiles of CNVs were decomposed into 64 seed-based regions and compared to the individual FC-profiles of subjects with a psychiatric

diagnosis, and their respective controls. Regions with higher similarities between CNVs and IPC are presented in red hues for 2 examples: 15q11.2 deletion-FC-profile (left side) and 22q11.2 deletion-FC-profile (right side) to individual connectomes of SZ and controls. Colors reflect the effect size (rank-biserial correlation) of the similarity between CNV and idiopathic patients (all the 36 brain maps are available in Supplementary Figure 3, with corresponding statistical values in Supplementary Table 7). (c) The spatial similarity between the whole-brain FC-profiles of CNVs and connectomes of IPC individuals. Connectors represent significant similarities between group-level CNVs-FC-profiles and the individual connectomes of either IPC cases or controls. Brain maps summarize FC similarities at the regional level between CNVs and ASD (right), ADHD (middle) and SZ. The color scale represents the number of times a region shows significant similarities between CNV FC-profiles and IPCs. (d) Brain map summarizes the frequency of regions involved in FC similarities between all NP-CNVs and all IPCs. Eg. the thalamus showed significant similarities in 9 comparisons:15q11.2 deletion and ASD; 15q11.2 deletion and SZ; 16p11.2 deletion and ASD; 16p11.2 deletion and SZ; 22q11.2 deletion and ASD, 22q11.2 deletion and SZ; 1q21.1 duplication and SZ; 15q13.3 duplication and ASD; 22q11.2 duplication and SZ. ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder; Del: deletion; Dup: duplication; 22q11: 22q11.2, 16p11: 16p11.2; 1q21: 1q21.1, TAR: 1q21.1-TAR, 15q11: 15q11.2, 15q13: 15q13.3.

Haploinsufficiency is associated with a profile of dysconnectivity shared across genomic loci

To investigate the potential general effects of haploinsufficiency on FC, we used a model previously developed to estimate the effect size of any CNVs on general cognitive abilities (6). This model used as an explanatory variable the sum of pLI scores of all genes encompassed in all deletions and duplications carried by an individual to explain FC (Figure 2g) (188). We analyzed all CNVs available: 502 CNVs carriers at 18 genomic loci and 4,427 individuals who did not carry a detectable CNV and thus had a pLI score of zero (Table 1, Figure 2g, Supplementary methods).

The pLI-associated profile for deletions (hereinafter referred to as haploinsufficiency profile) was characterized by a higher FC in 60 connections mainly involving the thalamus and a lower FC in 58 connections in the anterior cingulate, the pre-supplementary motor area, and the dorsomedial prefrontal cortex (Figure 4a-b, Supplementary Table 6). Since this linear model may be influenced by CNVs with the largest pLI scores, we performed a sensitivity analysis and showed that removing the 16p11.2, and the 22q11.2 deletions did not substantially impact the observed pattern of dysconnectivity (haploinsufficiency profile before and after exclusion were correlated at r=0.77, r=0.72, respectively). Our results suggest that

this haploinsufficiency FC profile is present across genomic loci with an effect size correlated to pLI. We were likely underpowered to detect a pLI-associated FC-profile for duplications (only 3 connections survived FDR).

We investigated the relationship between the haploinsufficiency FC-profile and general intelligence, autism, schizophrenia and ADHD severity measures (Figure 2.h). Individuals with lower general intelligence scores showed similarity with 20 out of the 64 regions of the haploinsufficiency FC-profile (Figure 4d-f, Supplementary Table 8). This negative association was significant across all 3 cohorts with general intelligence measures (UKBB non-carriers, ABIDE autism and controls, ADHD cases and controls). Autism severity scores (ADOS and SRS) also increased in individuals with higher similarities to pLI-FC-profile in 11 and 3 regions respectively (Supplementary Table 8). Regions driving correlation with intelligence and autism measures were partially overlapping (figure 4d). None of these similarities was correlated to motion.

A parsimonious set of FC dimensions may underlie the dysconnectivity observed across CNVs and idiopathic psychiatric conditions

We asked if dysconnectivity profiles across all CNVs and IPCs could be summarized by latent components (LCs). We used the FC-profiles of 12 CNVs delineated in aim 1 (those with sample size allowing CWAS) and 3 IPCs obtained by CWAS (Figure 1o-p, Supplementary results). We performed an exploratory factor analysis (EFA) using maximum likelihood as a fitting procedure across all CNVs and IPC FC-profiles. The EFA identified 3 LCs that explained 28% of the variance between FC-profiles (Tucker-Lewis Index (TLI) of factoring reliability = 0.93, Root Mean Square Error Approximation index (RMSEA) =0.01, p=0.42 for the null hypothesis that 3 factors were sufficient). Regions contributing the most across LCs included the thalamus, the temporal pole, the anterior cingulate, and the ventromedial prefrontal cortex (Supplementary Table 9). The third LC showed a high spatial similarity with the haploinsufficiency FC-profile (r=0.57) (Figure 4c).

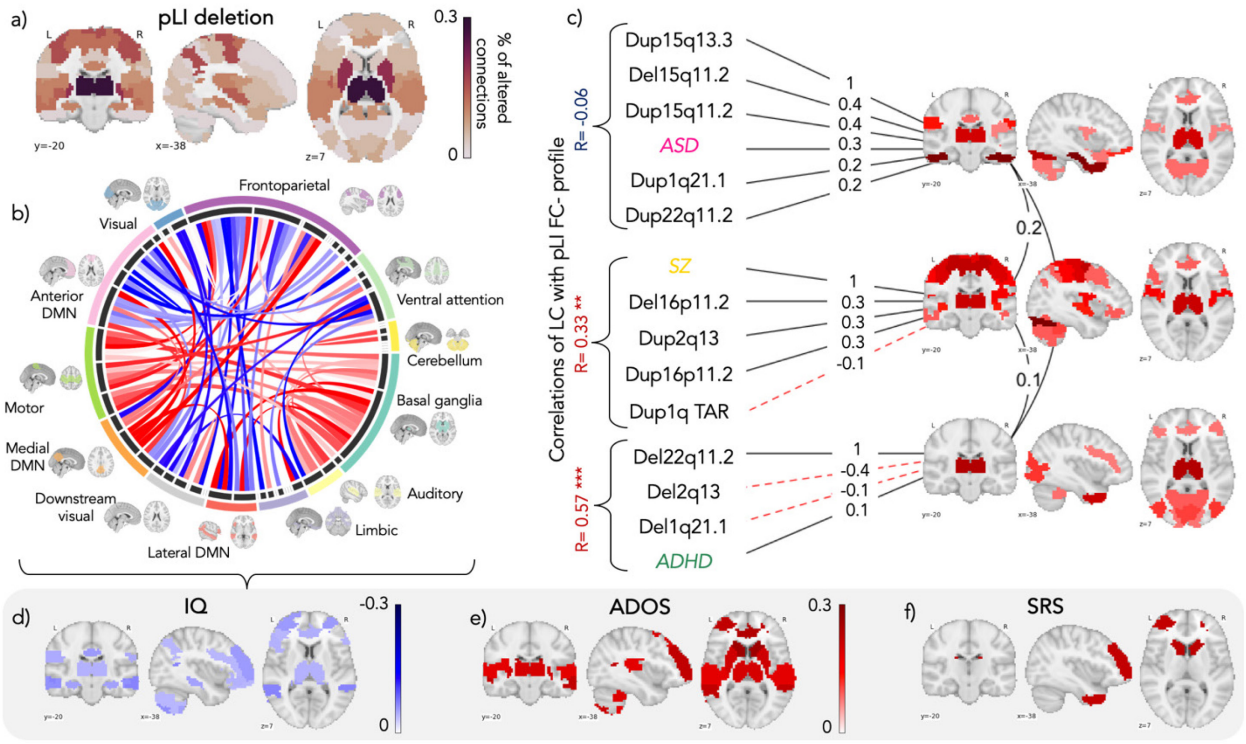

Figure III-4 Haploinsufficiency connectivity profile and latent dimensions across CNVs

Legend: (a-b) Relationship between dysconnectivity and haploinsufficiency measured by pLI across genomic loci. (a) Brain map represents the percentage of altered connections (FDR corrected) per region. (b) Each chord represents a functional connection between 2 regions that are significantly associated with intolerance to haploinsufficiency (measured by pLI). All 64 seed regions are represented in the dark grey inner circle of the chord diagram. The width of the seed region in the grey inner circle corresponds to the number of altered connections. Seed regions are grouped into 12 functional networks (outer ring). Networks are represented in 12 brains around the diagram. Red chords represent overconnectivity and blue chords underconnectivity. Full names are available in Supplementary Table 10. (c) Exploratory Factor Analysis results across 15-FC profiles of alterations converging on 3 latent components (LCs). Value on each arrow represents standardized EFA loading (see Supplementary Method). We reported the 64 values for the corresponding 3 LCs into the 3 brain maps (red: positive contribution, blue: negative contribution, Supplementary Table 9). (d) Individuals with higher similarity to the haploinsufficiency FC-profile have lower measures of general intelligence and higher autism severity measures. Colour codes represent Pearson r computed between the 64 regions of the haploinsufficiency FC-profile and the regional profiles of

individuals based on their cognitive and behavioural measures. IQ: Intelligence Quotient, ADOS: Autism Diagnostic Observation Schedule, SRS: Social Responsiveness Scale.

Discussion

Main findings

We provided the first connectome-wide characterization of CNVs at the 1q21.1 and 15q11.2 loci and conducted a systematic comparison across 8 neuropsychiatric CNVs. Deletions and duplications at 6 out 8 CNVs were associated with a global shift in mean connectivity with the largest effect at the 1q21.1 duplication locus. The effect size of CNVs on relative FC (mean-connectivity adjusted) was correlated with the known level of NP-risk conferred by CNVs. We identified connectivity architecture similarities between high-risk NP-CNVs and individuals with ASD, SZ and to a lesser extent ADHD. These similarities were driven by the thalamus, the posterior cingulate cortex, and the anterior insula. Four neutral control CNVs exhibited far less similarities with idiopathic psychiatric conditions than large effect size NP-CNVs. Intolerance to haploinsufficiency measured by pLI score was related to a FC profile characterized by increased connectivity in the thalamus, basal ganglia, the somatomotor network and medial DMN, and decreased connectivity in the limbic, frontoparietal and anterior DMN. This haploinsufficiency profile was associated with lower measures of intelligence across three cohorts and an increase in autism severity scores. Using exploratory factor analysis, we validated these regions by showing their contribution to three latent components explaining 28% of FC variance across CNVs and neuropsychiatric conditions.

Bottom-up genetic-first versus top-down approaches

The effect sizes of rare variants on functional neuroimaging traits are concordant with effects previously measured for the same variants on brain structure, cognitive and behavioural traits (4,6). This is in striking contrast with neuroimaging studies of behaviorally defined groups of patients that have required very large samples to reach reproducible results. On average, the effect sizes observed for FC and brain structure in SZ, ASD and ADHD range from 0.3 to 0.15 and lower (2,34) which is discordant with the severity of those conditions that lie well beyond 2 standard-deviation with respect to their impact on behavioural and adaptive traits. Therefore, while intermediate brain endophenotypes remain elusive in heterogeneous psychiatric

conditions, genetic first strategies have the potential to provide key insights into underlying biological mechanisms.

Pleiotropic effects in neuropsychiatric CNVs on brain connectivity

GWAS studies have shown that the same set of SNPs confer risk for a range of different conditions, suggesting pleiotropic effects (144). Similarly, CNVs increase risk for a range of psychiatric disorders including ASD, SZ, ADHD, as well as obsessive-compulsive, oppositional defiant, and tic disorders (234). Mechanisms underlying these apparent pleiotropic effects are unclear. Recent systematic cross-CNV analyses reported that impairments in many behavioural and cognitive traits were broadly similar for 12 NP-CNVs (234). There were only moderate qualitative profile differences in cognitive and behavioral measures between NP-CNVs(234). Consistent with these findings, we showed that CNVs present similarities with several idiopathic psychiatric conditions at the connectivity level. This may be related to connectivity-dimensions such as the FC profile defined by intolerance to haploinsufficiency associated with increased risk across several psychiatric conditions and cognitive deficits (6,235). In line with these observations, cross-psychiatric diagnoses studies have delineated FC dimensions very similar to those associated with haploinsufficiency and involving the somatosensory motor network, DMN, thalamus and subcortical structures (200). This is consistent with our current and previous findings showing that the FC patterns shared between CNVs and IPC were correlated to IQ and SRS(231).

Haploinsufficiency reorganizes brain connectivity according to a general FC-profile.

We extended to connectivity some models which were initially developed to estimate the effect size of CNVs on IQ (6). This approach showed that deleting genes intolerant to haploinsufficiency (measured by pLI) may lead to a pattern of dysconnectivity irrespective of where the deletion occurs in the genome. This haploinsufficiency profile was associated with a decrease in intelligence measures in the general population and disease cohorts and increased severity on autism assessments. Such findings may help decipher why the same linear model using pLI as an explanatory variable can explain 75% of the effect of deletions on IQ irrespective of genomic location and point to mechanisms explaining why 70%–100% of any 1-MB windows in the human genome contributes to increased risk for SZ and ASD (235,236). Intolerance to haploinsufficiency measured by pLI reflects a negative selection pressure unrelated to a particular molecular function. Non-specific effects of haploinsufficiency on cognition, behavior and FC could be related to emerging properties of the genome, rather than a limited set of biological pathways (237). In other words, the hypothesis is that changing gene dosage at any node of the genomic network may alter its efficiency

leading to a measurable effect on brain organization and behavior. Such efficiency remains dependent on several constraint scores and is probably modulated by common variant background and environmental factors.

The Thalamus is a central hub across psychiatric disorders and rare neuropsychiatric variants

Recent models of thalamic functions revealed a far more complex contribution than a simple passive relay with extensive connections to the entire cerebral cortex. Functional MRI studies have demonstrated that thalamocortical and corticothalamic pathways are engaged in memory, attention, and mental representations through specific thalamic subdivisions (238,239). fMRI studies have reported involvement of the thalamus across several NPs including ASD, SZ, and major depression (116,240,241). Our study also highlighted the thalamus as a functional hub highly sensitive to altered gene dosage across loci. The thalamic connectivity-pattern in high-risk NP-CNVs carriers also showed the highest similarities with those of ASD, SZ, and ADHD. Finer parcellation of the thalamus (238) will provide insight into the relationship between functional alterations related to CNVs and idiopathic psychiatric conditions.

Limitations

Previous studies have shown that the effect size of duplications is 2 to 3 fold smaller than deletions for cognitive (235) and neuroanatomical measures (4,178). A similar phenomenon was observed in this study and much larger samples of duplication carriers will be required to accurately characterize their effects on FC.

Our study was designed to search for shared effects but we are not implying that most of the FC alterations are common across CNVs. It will require much more data on many more genomic loci to delineate the potential specific effects of any given genomic variant.

This multisite study associating clinically and non-clinically ascertained cohorts may have introduced biases. Several confounding factors including sex bias, age differences, and medication status may also have influenced some of the results. However, carefully conducted sensitivity analyses, investigating all of these confounders, and performing sensitivity analyses matching control group for sex, site, age, motion and excluding IDP with medications provided similar results. Finally, we could not perform EFA with all 2,080 connections due to the insufficient number of CNV carriers. By moving to regional patterns, directionality is no longer taken into account. Larger samples are required to confirm and further characterize these latent components.

Conclusion

Our results suggest that deletions and duplications across the genome may converge upon a parsimonious set of connectivity dimensions involved in cognition and idiopathic NPs. Such findings raise the question on the nature of the relationship between the molecular functions of genes included in CNVs and functional changes of large scale brain networks. General haploinsufficiency connectivity profiles will likely extend to a large number of genomic loci and may help decipher why broad groups of genomic variants confer risk to the same neuropsychiatric conditions.

Acknowledgements

Author contributions

C.M., S.J., and P. B., designed the overall study and drafted the manuscript.

Analyses

C.M. and S.U. processed 90% of all the fMRI data and performed all imaging analyses.

G.H., J-L. M., and E. D. performed the CNVs calling and pLI annotations

P.O. preprocessed the SZ data.

A.L. contributed to the computation and the interpretation of the EFA data

H.S. performed 3/4 of the UKBiobank fMRI preprocessing.

AE.J., C.M., K.K, C.G., and S.M-B. contributed to the interpretation of the data and reviewed the manuscript.

Data collection

D.L. and A.D.S. provided the Cardiff Define CNV fMRI data.

S.L., K.J, C.O., P.T., N.Y. recruited/scanned patients for the Brain Canada Montreal CNV project.

C.E.B., A.L. provided the UCLA 22q.11.2 fMRI data.

A.M. provided the Lausanne CHUV fMRI data.

D.L., M.O., M. V.d.B., J.H, and A.I.S. provided the Cardiff CNV fMRI data

The Simons Variation in Individuals Project Consortium provided the 16p11.2 data.

All authors provided feedback on the manuscript.

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Data and materials availability: Processed connectomes are available through request to the corresponding authors.

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IV. Discussion

The general hypothesis tested in this thesis was that entire classes of rare neuropsychiatric variants may converge upon shared functional connectivity dimensions contributing to mental illnesses.

My first aim was to test how neuropsychiatric variants change functional brain connectivity in humans during rest. To do so, I performed the largest connectome-wide characterization of CNVs to date. Findings showed that deletions and duplications of high-risk genomic loci had strong effects on connectivity, and that the level of brain dysfunction was associated with the known levels of risk conferred by mutations.

My second aim was to investigate whether the alterations of functional brain organization associated with neuropsychiatric variants were also found among idiopathic neuropsychiatric populations. I showed that this was the case since CNV connectivity signatures were enriched in individuals with autism, SZ and to a lesser extent with ADHD at the functional connectivity level. The level of similarity was associated with mutation severity, and stronger in schizophrenia and autism. Interestingly, enrichment was driven by a set of networks previously identified as hubs in transdiagnostic studies. Beyond categorical diagnoses, I also showed that these CNV-connectivity profiles were correlated with autism severity metric and FSIQ.

These results raised questions about pleiotropy mechanisms, as well as general effects of deletions and duplications shared across genomic loci. This motivated the investigation of the relationship between haploinsufficiency in general, and connectivity changes.

My third aim was, therefore, to test whether deleting genes intolerant to haploinsufficiency reorganizes connectivity along general dimensions, irrespective of where deletions occur in the genome.

In paper#1, we performed a simple comparison showing that deletions at the 16p11.2 and 22q11.2 loci exhibit similarities of functional architecture, which may partially reflect the similar topological co-expression patterns of genes encompassed in both loci.

In paper#2, we extended this approach to all deletions available for analysis. The severity of deletions was scored using the pLI, a measure of intolerance to haploinsufficiency. We showed that a particular connectivity profile is positively associated with the pLI. This profile involved the thalamus, anterior cingulate, and somatomotor networks and was correlated with lower general intelligence and higher autism severity scores in 3 unselected and disease cohorts. An exploratory factor analysis confirmed the contribution of these regions to three latent components shared across CNVs and NPs.

These results open new avenues for understanding polygenicity in psychiatric conditions, and the pleiotropic effect of CNVs on risk for NPs. Such approaches also provide novel strategies to estimate the effect of undocumented CNVs identified in the neurodevelopmental disorder clinic.

Contributions

Aim 1. One mutation at a time: brain fingerprints of neuropsychiatric variants

Mirror gene dosage of NP-CNVs at the connectome-wide level

In paper#1, I characterized the effect of four CNVs, that confer high-risk for NPs, on functional brain connectivity. Deletions and duplications at the 16p11.2 and, to a lesser extent, the 22q11.2 genomic loci were associated with mirror effects at the connectivity level during rest (n=101 carriers, n=122 controls). Deletions at both loci have been classified as 'pathogenic of high-effect size CNVs'. These findings were replicated in paper#2 with a larger dataset.

Analyses were extended to four loci associated with a wide range of NPs (classified as 'mild-effect size CNVs': 1q21.1 and 15q11.2 deletion and duplication, n=178), and to four additional loci without any association to mental illness (classified as "neutral CNVs": 2q13 deletion and duplication, 15q13.3 duplication, and 1q21.1 TAR duplication, n=124). A gene dosage effect on global functional brain organization had never been described before for any of these loci.

I identified a positive association between the number of genomic copies (i.e., deletion=1, control=2, duplication=3) and global connectivity for the 22q11.2 and 1q21.1 CNVs, and a negative association for the 16p11.2 CNV. Deletion and duplication at the 15q11.2 locus were associated with underconnectivity. Neutral-CNVs, which served as controls, did not have any effect on FC. Interestingly, the effects on global connectivity all occurred in the same direction as previously reported effects on total brain volume (see paragraph on brain volume below). After adjusting for these mean effects on connectivity (global signal regression), I conducted in paper#2 a systematic comparison across the eight NP-CNVs (four high and four mild-effect size variants) and the four neutral CNVs. Beyond global effects, I showed for the first time that the effect size of the FC-profiles of high-risk CNVs was correlated to the known CNV severity.

Take-home messages

Mirror gene dosage effects of neuropsychiatric CNVs extend to global connectivity.

The severity level of 12 neuropsychiatric variants is correlated to their effect-size on connectivity.

Dysconnectivity involves brain regions associated with psychiatric conditions

I investigated brain regions and networks most affected by CNVs. On the haploinsufficiency side (deletion vs. controls), I identified in paper#1 and confirmed in paper#2, that 16p11.2 mostly altered the insula, the pre-supplementary motor area, the putamen, and the precuneus, while the 22q11.2 predominantly altered the thalamus, the cingulate cortex, the lateral fusiform gyrus, the temporal pole, and the insula.
The 1q21.1 FC alterations were driven by the lateral fusiform gyrus, the dorsal precuneus, the visual network, and the dorsal posterior cingulate cortex. Effect sizes of deletions on FC reported in paper#1 and 2 are concordant with effects previously measured for the same variants on brain structure, cognitive and behavioural traits (4,6). Effect sizes were systematically smaller for duplications compared to deletions in both papers. This is in line with previous studies showing that duplications have a smaller effect on cognitive and neuroanatomical traits (4,235) compared to deletions. The study was therefore underpowered to properly characterize duplication FC patterns.

CNVs have a larger effect-size than idiopathic psychiatric conditions on FC

Throughout the analyses reported in Aim 1 of my thesis, I observed alterations of functional connectivity in a recurrent set of brain regions: the thalamus, the cingulate cortex, the insula, and the basal ganglia, and somatomotor networks, which have also previously been identified in case-control studies of autism and SZ.
I, therefore, extended CWAS analyses to individuals with idiopathic ASD, SZ, and ADHD conditions (n=756) and controls (n=950). I replicated in paper#1 the previously identified general underconnectivity alteration profile in SZ (38), and an association of over and under-connectivity alteration profiles in ASD (110). Among idiopathic conditions, I showed that the effect size of connectivity alteration was the highest in SZ, followed by ASD, and ADHD, which is concordant with previously reported heterogeneity in ASD and ADHD (37,242). I finally validated that effect sizes of the two high-risk deletions on FC, studied in paper#1, were larger (by approximately two-fold) than effect sizes observed in idiopathic SZ, ASD, and ADHD.

Take-home messages

Deletions FC alteration profiles are driven by brain regions disconnected in psychiatric conditions.
Duplications have a smaller effect size on FC than deletions, concordantly with results on cognition.
Effect-sizes of CNVs are twice as large as the ones reported in idiopathic psychiatric conditions.

Aim 2. Genetic proxies to address the clinical heterogeneity of psychiatric conditions

Neuropsychiatric CNV connectivity profiles are enriched in psychiatric conditions

Using a genetic-first strategy, I characterized CNV-connectivity profiles in Aim 1 using functional imaging data. In Aim 2, I tested how these connectivity profiles may explain observations higher up in the hierarchy (association with a diagnosis and severity scores).

I tested the contribution of neuropsychiatric variants to alterations of the functional brain architecture observed in idiopathic psychiatric conditions. To do so, I investigated similarities between biological proxies at the group-level, and individuals with idiopathic psychiatric conditions and controls.

I showed in paper#1 FC similarities between individuals with SZ and ASD, and the 16p11.2 and 22q11.2 CNVs. Individuals who showed higher similarities with deletion connectivity profiles were the most severely affected based on the ADOS and IQ.

Using a larger sample of CNVs carriers and controls, I was able to replicate and extend these results in paper#2 investigating less penetrant CNVs. Paper#2 demonstrated stronger functional relations between deletions, ASD and SZ individuals, and the similarities were extended to ADHD (for 4 out of the 12 CNVs). Variants not associated with neuropsychiatric conditions (2q13.3 CNVs, TAR duplications and 15q13.3 duplications) exhibited far fewer similarities with idiopathic conditions than large effect size mutations.

Similarities are driven by the thalamus, the cingulate, the insula, and the basal ganglia

The thalamus, the posterior cingulate cortex, the basal ganglia, the anterior insula, and the temporal pole exhibited the highest degrees of similarity between all neuropsychiatric CNVs connectivity-profiles and individuals with idiopathic psychiatric conditions.

These similarities at the connectivity level may explain the known association between these CNVs and idiopathic neuropsychiatric conditions.

Take-home messages

Connectivity profiles of individuals with SZ, ASD, and ADHD show similarities with those observed in high-risk neuropsychiatric CNVs.

Similarities are driven by the thalamus, the basal ganglia, and the posterior cingulate cortex.

Similarities are associated with clinical severity metrics.

Aim 3: Toward general mechanisms of haploinsufficiency on connectivity

Results across CNV and psychiatric conditions obtained in Aim 1 and Aim 2 further encourage to study rare variant in the same model. I, therefore, asked if rare neuropsychiatric variants are associated with common changes in the functional brain architecture.

I hypothesised that CNVs of a large proportion of the genome converge on a limited number of shared dysconnectivity patterns.

Deletions disorganize similar brain nodes and have gene co-expression similarities

I reported in Aim 1 an opposing mirror effect of gene dosage at 16p11.2 and 22q11.2 loci. CNVs were however enriched with similar idiopathic psychiatric conditions (Aim 2). I therefore investigated the relationship between the 22q11.2 and the 16p11.2 deletion FC-signature. Analyses identified similarities at the global and regional level between both haploinsufficiency FC profiles. Similarities were driven by the frontoparietal network, the basal ganglia, and the somatomotor network.

Recent work has shown that the brain transcriptome is following broad spatial gradients that are closely related to the functional architecture. I tested the hypothesis that these functional similarities may be driven by the co-expression profiles of genes encompassed in both loci. I showed shared topological co-expression patterns across both CNVs, involving visual, limbic and cingulate regions.

Take-home messages

Alteration profiles of two seemingly different deletions present similarities at the connectivity level.

Functional overlap may be related to the shared topological transcriptomic organization.

Latent dimensions summarise dysconnectivity observed in CNVs and psychiatric conditions.

Effect-size of CNVs on connectivity can be statistically estimated based on coding characteristics of the affected genomic region. Using a gene's intolerance to variation score, I extended a model previously developed to estimate the effect of any CNVs on general cognitive abilities (6), to connectivity. After genes annotation for constraint score at the individual level, I analyzed all CNVs available (502 CNVs carriers at 18 genomic loci and 4,427 individuals who did not carry a detectable CNV). I showed a linear relationship between haploinsufficiency constraint score and connectivity of the dorsal anterior cingulate, the thalamus, the pre-supplementary motor area, and the dorsomedial prefrontal cortex. This connectivity profile was

associated with higher symptom severity scores in ASD and ADHD, and lower intelligence measures in the general population. These results suggest that deleting genes intolerant to haploinsufficiency may reorganize connectivity along general dimension(s), irrespective of where deletions occur in the genome.

Finally, I posited that not one but several dimensions were altered by rare variants. I addressed this question with an exploratory factor analysis across 12 mutations and 3 idiopathic conditions.

I identified three latent dimensions explaining a third of the variance. The thalamus, the anterior cingulate, and the prefrontal cortices were again the major contributors of the latent components. One dimension was highly correlated to the haploinsufficiency signature. These patterns may represent a substantial part of the essential dimensions implicated in idiopathic conditions.

Take-home messages

Deleting any gene intolerant to haploinsufficiency results in a stereotypical pattern of brain connectivity. This Haploinsufficiency connectivity profile is associated with lower intelligence measures in the general population and increased autism severity.

Other contributions

Multi-scale characterization of the 16p11.2 CNVs

I participated in a broader characterization of the 16p11.2 CNVs effect on intermediate brain phenotypes (CT, voxel-based morphometry) using anatomical data (4,243).

Using diffusion-weighted imaging data, I first replicated tract-based spatial statistics findings in 16p11.2 (244) and showed a positive gene dosage effect of white matter fractional anisotropy. I then investigated mean diffusivity alteration in subcortical material and reported an overall higher major depression in both deletion and duplication compared to controls in the caudate, the thalamus, and the amygdala. Alterations in deletion were correlated with higher severity score (SRS), and lower IQ. Interestingly, major depression has previously been reported as altered (higher) in the hippocampus, thalamus and accumbens nucleus in SZ (245). This study was supervised by J.D. Lewis at the Montreal Neurological Institute and presented at OHBM 2016. I extended this work to other CNVs at the Imaging Genetic Centre (USC, CA) in 2019 (poster at SOBP 2020 and OHBM 2020). These results have not been included in my thesis, but will be published during my postdoc.

Large international consortium on rare variants

To my knowledge, our two resting-state fMRI papers were the largest characterization of the effect of rare neuropsychiatric variants on functional connectivity in the human brain. The majority of available fMRI data on CNV carriers worldwide has been included in these two studies. It relied on several years of intense scanning, in Montreal and Lausanne, as well as collaborations with Cardiff University, UCLA, and SFARI consortium. I participated in establishing the Lausanne rare-variant cohort during my first year in Switzerland (I travelled to different hospitals through Europe to collect phenotypic data on CNV carriers, I developed websites to inform and recruit families), and the scanning component of the Montreal rare-variant cohort during my PhD at the Sainte-Justine hospital. The ENIGMA consortium has been developed simultaneously to study common variants and is now being extended to also include rare variants. This collaborative work has resulted in four additional publications on the 15q11.2 BP1-BP2 (184,185), the 16p11.2 BP1-BP3 (246), and the 1q21.1 CNVs (under-review in Molecular Psychiatry). These results highlighted the fact that only large international collaborations can provide the large amounts of data required to improve our understanding of rare genomic variants on the brain.

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General limitations

Top-down approach

Comorbidities and medical background

Psychiatric comorbidities are major caveats in diagnostic-first studies. As an example, a patient with diagnosed ASD has a high probability of comorbid OCD, ADHD, intellectual disabilities, or eating disorders (9,52,247). CNVs carriers are associated with several confirmed and suspected diagnoses, including ID, dyslexia, motor delay, speech delay. In my thesis, ASD, SZ and ADHD case-control analyses were conducted without taking into account any knowledge about comorbidities. The similarity between CNV connectivity profiles and idiopathic conditions could, therefore, be mediated by such comorbidities. I did not have information on comorbidities for individuals with idiopathic SZ data, but prior findings show that a small number of them may have suspected mood disorders (9).
Continuous cognitive and behavioural traits provide a more fine-grained appreciation of individual symptoms and therefore allow more granular analyses. I investigated several scales including the ADOS and SRS (ABIDE), PANSS (SZ), CPRS-LV (ADHD-200), and general intelligence (WASI, WISC, and fluid intelligence score) for all datasets except SZ. The limited cognitive data available per dataset, the lack of harmonisation of neuropsychological tests across cohorts, and the large age range and diagnoses included in my thesis did not allow me to use other scales.

It is more the rule than the exception to have several diagnoses at the same time. A patient with a DSM-V label of ASD has a high probability of comorbid OCD, ADHD, or eating disorders (9,52,247). Clinicians decide which diagnosis is going to be the “first-hit”. This label will be assigned to the individual and will serve to guide treatment. If this individual is enrolled in a research project, then the designated diagnosis group will ignore any of the comorbidities. This group is, therefore, potentially misleading to answer subsequent research questions on the diagnosis. That is why alternative nosographic stratification strategies are particularly important (biologically driven, and dimensional).

More importantly, meaningless labelling will result in a self-identification to a concept of mental disease, built by psychiatrists and statisticians, that may have no actual relationship with what the subject is actually feeling, which could have repercussions on his entire life and at multiple levels.

Autism's sex ratio: the 'female-protective' effect and unsuitable screening tools

The largest meta-analysis conducted to date estimated a ratio of about 4.2 boys with autism for every girl (248). The origin of this sex-ratio imbalance is an ongoing question in autism research.

A genetic study investigated the molecular basis of this sex-based difference in a large cohort of probands ascertained for neurodevelopmental conditions and demonstrated an excess of deleterious autosomal CNVs in females compared to males (249). In other words, females carry a higher burden of deleterious mutations than males who receive an autism diagnosis. Jacquemont and colleagues also showed that deleterious mutations were preferentially inherited from mothers (CNVs and SNVs, 249). Such results suggest a 'female protective' effect with a gender-specific liability to neuropsychiatric mutations (250).

This sex-ratio imbalanced may also be related to unsuitable diagnostic instruments. There is growing evidence that girls with autism are not diagnosed as such because of a "camouflage" effect (251,252). Autistic features may manifest in a different way in girls, with a different developmental timeline, and early compensatory mechanisms. This "camouflage" effect may be particularly present among women without intellectual disability, which may affect performance on gold-standard diagnostic measures (251). This effect has been operationalized through a quantitative measure in adults with an autism diagnosis (252). Lai and colleagues reported that women with ASD had a higher camouflaging score than men. This camouflaging metric was positively associated with depressive symptoms in men and signal-detection sensitivity in women with autism (252).

Another explanation of the potentially under-estimated rate of women with ASD may be that in the presence of comorbidities, women with ASD may be more likely to be diagnosed with the comorbid mood, or eating disorder, or OCD, rather than ASD.

The sex-ratio imbalance is an important pitfall in transdiagnostic studies that include individuals with autism. A possible solution is to exclude females from cohorts, but such approaches will induce misrepresentation of the condition of interest. All the analyses performed in my thesis have been adjusted for sex. The sex ratio was well distributed in all cohorts except in ASD. We decided to exclude the few fMRI data of females with an ASD diagnosis from the ABIDE data ($n<30$). We performed sensitivity analyses excluding all the women from the SZ and ADHD cohorts and showed that results did not change. This does not demonstrate that the sex-ratio imbalance has no influence, but rather indicates that the main effects found in my thesis for ASD are not biased by this factor. Further analyses using more female data will help to validate our findings.

Versions of diagnostic manuals

Data included in my thesis were aggregated from several cohorts and some were collected before DSM-V. This is particularly relevant for ASD since the diagnostic criteria have been revised since then (58). Modern tools revisited the DSM-4 categories that were established in 1994, raising substantial concerns about their validity (58). The DSM-V introduced the "spectrum" concept in autism, aggregating the Asperger Syndrome, the pervasive developmental disorder–not otherwise specified, the Childhood Disintegrative Disorder and the Autistic Disorder from the fourth version of the DSM. A large number of individuals with a pre-existing DSM-IV autism diagnosis may fall into the DSM-V ASD classification (253). However, several "independent DSM-4 forms of autism" such as the Rett Syndrome driven by the MECP2 gene (known genetic origin as a specifier) have been excluded from the revised DSM version (DSM-V). I therefore expect some differences between results obtained with patients recruited using version 4 or 5 of the manual (or even ICD-10 in Europe) being an additional source of heterogeneity in ASD results.

Using several diagnostic tools and severity metrics (such as ADI-R or ADOS-2), large multisite cohorts managed to obtain clinical consensus across ICD-10, DSM-IV, and DSM-5 categories (254). Such observation encourages the use of continuous metrics (similar across as many disorders as possible, such as IQ with for example the WISC version for children, and the WAIS version for adults) in addition to the actual label, to re-harmonise the boundaries delineation of the diagnosis.

Difficulties in identifying neuroimaging alterations in ADHD

ADHD is a heterogeneous disorder, with a wide range of clinical manifestations, multifactorial etiological risk factors, and comorbidities (255,256). The case-control analyses on individuals with ADHD and controls in paper#1 and, with a substantially larger sample in paper#2, did not allow us to identify any significant differences. The small effect size of overconnectivity (+0.2 z-scores) detected in ADHD likely reflects heterogeneous mechanisms involved in this condition. This is also concordant with results from previous studies in ADHD (242,257). Using the same publicly available dataset, Zhou and colleagues pointed out inconsistencies of results across scanning sites, as well as small effect size (242,256).

We were, however, able to report similarities between 16p11.2, 22q11.2 and 15q13.3 CNVs-FC profiles and individuals with ADHD in paper#2. These results were concordant with the association of these CNVs with ADHD (157,232,258), and encouraging for further studies. Analyses with a larger sample of

individuals with ADHD and data-driven methods will likely manage to detect differences between cases and controls, and to decompose with more granularity the similarities with neuropsychiatric CNVs. Top-down studies limitations reported in the latest part emphasised the need to work in parallel with neurobiological dimensions.

Bottom-up approach

Second hits and genetic background

Genetic datasets suffer from other challenges. It is almost impossible to build a rare variant cohort in humans while controlling for a second (and third) hit.

We studied the majority of the CNV carriers (Aim 1) without any knowledge of the presence of additional genomic variants.

While each primary pathogenic variant sensitizes the genome to varying extents, additional mutations may modulate the clinical manifestation (259). They constitute an uncontrolled source of variability in any human genetic-first framework.

To properly address this variability, we will need to use animal models (186,260,261). Knockout manipulations at the syntenic locus of interest provide the ability to control genetic and environmental backgrounds (262).

Studies identified that humans and animals share components of functional brain organization such as the default mode network (29,263,264), opening a potential avenue for the translation of findings obtained with mice models to human imaging results (186,265). Translational research remains particularly challenging for mice models of psychiatric conditions in general. The vast majority of mouse studies with rs-fMRI are furthermore employing sedation to minimise stress and motion during scanning.

One of the most appropriate ways of studying the effect of mutations in humans is to build models integrating genomic and functional constraint scores of genes included in any variation. Such frameworks require to have access to whole-exome information and will take additional hits into account (235).

The proof of concept framework used in Aim 3 was able to take into account any second hit and to properly code for variation of CNV's genomic locations across carriers (e.g. two carriers of 16p11.2 CNV may have slightly different coordinates). The pLI score is a binary measure of a gene's intolerance to haploinsufficiency that has been identified as the best metric to predict IQ compared to other constraint scores such as protein-protein interactions score (6). New continuous measures such as the LOEUF (Loss-of-function Observed/Expected Upper bound Fraction (266)) may better reflect the full spectrum of intolerance to pLoF in future studies. Our preliminary results on deletions are a motivation to extend our current framework to other constraint scores and more data (including SNVs and non-recurrent CNVs).

Several other scores will have to be investigated together and we will have to compare the accuracy of predictive results, with the literature on imaging results (for the few recurrent studied CNVs, eg. 16p11.2 and 22q11.2). This had been done by Huguet and colleagues to estimate PIQ using pLI but also, the differential stability metrics, and a protein-protein interactions score (6). Interestingly, many genes with a high pLI score do not express in the brain, and therefore have a differential stability score equal to 0 (score quantifying the stability and regional specificity of a gene expressed in the brain (196)). The opposite is also true (eg. with 16p11.2 genes: *KCTD13* has a high pLI and DS close to 0, while *KIF22* has a high DS and a pLI close to 0). Combining these scores (weighted, mean, or first principal component) and others will help us to fine-tune our model and to test our hypothesis about general mechanisms.

Hawrylycz and colleagues identified modules (cluster) of co-expressed genes that might also be implemented in further models. For example, module-4 (eigengene *GABARAPL1*) is a thalamocortical module, that encompassed *NRXN1* (196). Considering our results on thalamocortical overconnectivity, we might want to test this module.

Sample size and duplication effect-sizes

Carriers of large effect size CNVs are, by definition, rare in the general population (<1%). Building a genetic-first cohort is therefore extremely difficult. CNVs of interest studied in my thesis are associated with a wide range of neuropsychiatric conditions. Collecting sufficient usable fMRI data after quality control is another level of challenge.

CWAS have been, therefore, performed with small to medium sample sizes in both papers. By increasing the number of carriers in paper#2, I was able to replicate most of the signal. The only exception was the 22q11.2 deletion FC-signature that exhibited smaller overall FC alterations in paper#2. This is most likely related to the fact that the 22q11.2 deletion was the only mutation for which I did not increase the sample size (part of the UCLA cohort), combined with the fact that, as a large number of cohorts were included in paper#2, I took into account scanning sites as a confounding factor. By correcting for the scanning site effect, I therefore also partially regressed for the 22q11.2 deletion effect (collinearity). I still decided to do so, to keep the same number of controls, in order to compare and rank mutations effect-sizes on FC. Future work will use more advanced methods, such as *ComBat* harmonisation technique, in order to remove scanning site effects in our analytical framework from our large multi-site cohorts (267).

Another caveat was the small number of duplication carriers, in particular for the 1q21.1 CNV. Previous studies showed that duplications have a smaller effect on the cognitive and neuroanatomical levels (4,6,235) than deletions in general. For example, studies on 16p11.2 CNVs reported that deletion carriers exhibited more severe neuroanatomical alteration and phonology/inhibition skills impairments than duplication carriers (4,158,161). Douard and colleagues reported more recently that the effect of duplication is three-fold smaller than the effect of deletion on IQ (235). This is in line with my reported smaller effect sizes of duplications compared to deletions on connectivity in both papers. Determining the effects of duplications on connectivity would therefore likely require larger sample size.

Finally, we treated deletions and duplications separately because most of the connectivity alterations of deletions and duplications are not mirror effects and would not be detected in a model including the number of genomic copies (1 for deletion, 2 for control and 3 for duplication) as the main explanatory variable. In larger datasets exploring T1 weighted measures in the 16p11.2 CNVs, only the bilateral insula was detected using genomic copies as the main explanatory variable (4).

Limitations in both top-down and bottom-up approaches

Medications and functional MRI

Drugs such as antidepressants and antipsychotics are known to modulate the fMRI signal (268,269). Results are inconsistent but studies suggest an impact on the DMN and the striatum. For example, Wang and colleagues reported that antipsychotics may regulate the DMN and the salience networks (including the striatum) connectivity in early-phase SZ (269). Using a predictive model, Sarpal and colleagues reported that individual differences in striatal connectivity were predictive of response to antipsychotic drug treatment in psychotic patients including SZ (270). Consequently to these findings, the active medication status is often used as an exclusion criterion. However, studies doing so will collect only the less severe cases of the condition of interest. Such recruitment rules may induce bias, and the study may include an only partially representative sample of the condition. One of the challenges in the quest for reproducible biomarkers is to retain large sample sizes while also properly taking into account the impact of treatment on connectivity.

In my thesis, none of the psychiatric cohorts excluded individuals on the basis of medication status. In a sensitivity analysis to investigate the medication issue, I excluded from ASD and ADHD cohorts individuals with medication or without information about a potential medication.

The profile of alterations using non-medicated case and control was highly correlated to results obtained with all subjects. These sensitivity analyses suggest that results reported in this thesis were overall not strongly biased by medication in ASD and ADHD. I, unfortunately, did not have information about medication in SZ and CNVs carriers. Findings reported by previous studies (269,270) suggest that a part of my results on SZ may be mediated by the medication status. Future studies are needed to investigate this relationship in depth.

Age and disease trajectory

Positive symptoms of SZ are mainly becoming noticeable during adulthood (271). It is therefore highly difficult to recruit carriers of CNVs associated with SZ before adolescence (e.g. 22q11.2 deletion carriers). One way to tackle this issue is to test and include siblings of the proband (intra-familial controls) as the SFARI consortium did (202), and as we did in the Lausanne and the Montreal projects (data included in paper#2). My final dataset included controls under 15 years old. I, therefore, performed a sensitivity analysis

by restricting control groups to age-matched individuals in all CWAS. CNV-profiles were highly correlated with the CNV-profiles computed with all controls.

Age effect may also be a concern because I included carriers and controls from the UK Biobank cohort in paper#2 that includes older individuals (mean age = 60, sd=7). I performed a sensitivity analysis to ensure that my results were not related to age. By excluding the entire UK Biobank cohort, I showed that CNV-FC profiles with and without UK Biobank data were highly similar, and I reported a stronger signal without UK Biobank data.

Of note, in all analyses reported in this thesis, I controlled for the effect of age to build FC profiles (CWAS, in Aim 1), and I adjusted the individual connectomes of individuals with idiopathic psychiatric conditions for the effect of age (for similarities analyses, in Aim 2).

This set of findings suggest that results reported in my thesis were overall not strongly biased by age differences.

Age effects remain a major pitfall in developmental studies.

Functional MRI studies investigating the normative effect of ageing on connectivity during rest support the notion of network-specific effects in ageing (272–274). Reduced connectivity of the DMN is a stable finding in normal ageing across studies (272). This underconnectivity result has been replicated and extended to visual networks in a larger follow-up study (273), which also showed that the frontoparietal network was positively correlated with age. Such results emphasise the importance of understanding the age effect on brain functional architecture and underline the lack of age normative data for fMRI analyses. Such data would help to properly adjust for age. A recent developmental study that I was involved in used a large, normative neurodevelopmental dataset to investigate the onset of anatomical alterations in 16p11.2 carriers and whether they evolved with age (243). We reported that MRI alterations remained stable through childhood, adolescence and adulthood. Voxel-wise differences were already present at 4.5 years and were stable until the age of 23. Structural findings are encouraging and should be extended to functional data to properly estimate the age impact on our results. Findings for 16p11.2 carriers are consistent with previous developmental MRI findings in idiopathic ASD, suggesting an early development of neuroanatomical traits related to autism (such as brain overgrowth and cortical surface area occurring before 24 months) (92). Gene expression studies similarly showed that genes associated with ASD and SZ were specifically expressed during the perinatal windows of development (see paragraph further on in Perspective) (78). Early development of autism and schizophrenia traits are consistent with the alteration stability of 16p11.2 MRI

from 4 years old. Given this stability of findings in 16p11.2, my inability to properly account for age effects may be less of a concern.

Relationship of brain volume and connectivity in CNVs and neurodevelopmental studies

Because the effects of gene dosage on total brain volume have been well documented and given the large body of literature on the relationship between autism and increased brain volume, I was compelled to examine the general relationship between total brain volume and connectivity. Somewhat surprisingly, this has not yet caught the interest of the field. Studies using fMRI data do not typically account for brain size. Because of the high collinearity with our factor of interest (16p11.2 deletion and 22q11.2 duplication have macrocephaly, while 16p11.2 duplication and 22q11.2 deletion have microcephaly), and the lack of an established relationship between total brain volume and functional connectivity in the literature, analyses in this thesis have not been regressed for total brain volume.

To address the potential effect of brain volume on FC, I analyzed a large unselected population of 1,500 subjects (Brain Genomic Superstruct project, (275)). I reported a positive relationship between total brain volume and global FC. Regions most affected were the dorsal anterior cingulate cortex and insular regions (unpublished results). The effect size was however approximately one-fourth of that of the high-risk NPs deletions. We may thus conclude that the effect of deletions on FC may be partially related to their effect on total brain volume. I then showed that brain volume was correlated to mean connectivity. All statistical models in paper#2 were adjusted for mean connectivity.

I was able to replicate the general positive linear relation between total brain volume and FC in a larger unselected adult population (n=4600, >50 years, UK Biobank sample). Regions driving the relation involved more frontal areas in addition to the dorsal anterior cingulate cortex and the insula, compared to findings obtained in the adolescent sample. Connections from the thalamus were not affected by brain volume in both unselected cohorts. I finally did not find any correlation between the pLI-FC profile and total brain volume-FC profile. Given the relationship between increased and decreased brain volume in ASD and SZ respectively (see introduction), total brain volume may be partially mediating effects reported by functional connectivity studies. Because this finding has consequences for the interpretation of connectivity studies in the context of neurodevelopmental and genetic studies, further studies should provide a full characterization of the relationship between brain size and connectivity as well as collinearity with other variables such as intelligence measures (276,277).

Motion in pediatric and neuropsychiatric cohorts

Resting-state functional MRI is sensitive to several confounding factors, including head motion (273). Age and symptomatology are negatively correlated to motion (278). Younger, and lower-functioning individuals will therefore either not be able to comply with the MRI task instructions or will move too much and thus be excluded from the dataset (279). Different methods have been proposed to deal with such artefacts in fMRI (280). They are typically applied during preprocessing (scrubbing, global signal regression) and/or processing (adjusting for frame displacement, adjusting for global signal regression).

One of the most controversial debates in the fMRI field (task-based and resting-state) is whether to use or not to use a global signal regression procedure (281,282). Methodologists suggested that global signal is related to respiratory, head motion and vascular artefacts, and taking into account such "artefact" will improve the signal. Many studies decided to implement this procedure in their analytical pipeline, typically by removing the first component during preprocessing, or by regressing mean connectivity (voxel-wise or region-wise) during processing (eg. (110)). Some groups remove negative correlations (which are perceived as spurious correlations). On the other hand, several groups recently showed that global signal encompassed neural signal related to cognitive function (283). Many studies, therefore, do not use a global signal regression procedure. As experts are puzzled about global signal and best strategy, recommendations are for now to do both (with and without) because it seems that it depends on your conditions of interest and that both results contain important information. This on-going debate is, therefore, amplifying the challenge of comparing the directionality of the results across studies.

A much more accepted procedure is the scrubbing during preprocessing. The number of frames remaining after scrubbing is impacted by the scanning time, which varies from 5 to 10 min in a typical resting-state fMRI sequence, and criteria are not fixed about the minimum number. Furthermore, studies working in a pediatric population, and/or in psychiatric condition, do not always regress for motion artefacts because it is highly collinear with their condition of interest. This might induce false results. Head motion artefact has been also reported to affect long-distance and short-distance connections differently (284) and therefore induce false results (eg. in the orbitofrontal regions). Finally, many analytical frameworks so-called "whole-brain" analyses do exclude the cerebellum from their pipeline because their methods are designed for the neocortex and may be suboptimal for the analysis of cerebellar data (eg. field of view, poor signal)(285). This might be an issue to compare results across conditions. Indeed, cerebellar regions have been reported as preferentially affected in SZ, but as many ASD and ADHD studies decided to drop this structure (not

part of parcellation atlases), the uniqueness of this finding might be reconsidered. We did not exclude the cerebellum from paper#1 or paper#2, we performed analyses with and without global signal regression in paper#2, and we applied typical scrubbing and well as sensitivity analyses by removing subjects with a low number of frames available after scrubbing. We also carefully verified that none of our signal in the similarity analyses was correlated to motion.

Pediatric and neonatal fMRI may require sedation and different forms of anxiolytic to participate in fMRI studies (286), but medication, drowsiness, and sleep can introduce additional biases in the fMRI results. Ethical concerns have been raised and alternative strategies were suggested such as watching a movie or low-cognitive demand movies. Inscapes is such an abstract movie that was designed to provide enough stimulation to reduce head motion, increase wakefulness, and minimize cognitive load during the acquisition of the resting-state fMRI data (287). As we are working with children (with and without developmental delay), we decided to use the Inscapes movie as much as possible to collect functional imaging data for the Montreal project (data included in paper#2) (288).

Conclusion: compromise

Understanding the mechanisms underlying psychiatric conditions, and their operationalizations remain one of the profound mysteries in modern medicine. This is partially due to the multitude of pitfalls inherent to any existing framework. Several of these limitations for the bottom-up and the top-down approaches were laid out here.

Each of these limitations could however be useful to clear up underlying factors involved in psychiatry, and may guide further studies to a better understanding of these conditions. Therefore, there is room for both models, and others such as dimensional approaches. A model is, by definition, an abstraction of reality to make sense of a complex set of interactions (289). Any model is, therefore, “wrong”. What we should ask is not if it is true or false, but if this model is accurate enough to be useful to teach us something. Small case-control studies on ASD or SZ may be able to investigate patients without comorbidities and medication that are representative of a broad range of ages by balancing the sex-ratio, using matched controls, and scanning everyone at the same site with the same imaging sequence. But these studies will probably not have the statistical power to detect any relevant signal for the field because small samples cannot cover the inherent heterogeneity in neuropsychiatry. By selecting patients based on a homogeneous biological trait, the bottom-up approach used in my thesis may help to overcome some of these pitfalls. If they are properly implemented, I do think that both approaches can elucidate different aspects of the heterogeneity, and that they are highly complementary. Recent computational psychiatry discoveries finally emphasise the urgent need to aggregate multi-scale data, to perform broad phenotyping and genotyping, and to move to predictive models at the individual level.

Perspectives

From a pathognomonic hypothesis to a core set of vulnerable brain regions

Anterior cingulate cortex and insula

Dysconnectivity of the cingulate and insular regions has been repeatedly reported in case-control studies of several psychiatric conditions and cognitive deficit as well as across diagnoses. Both regions have also been found to be altered in several neuropsychiatric CNVs (4,177,185,290). For the 16p11.2 CNV, a negative gene dosage effect on the insula volume was reported (4). These converging results suggest that the cingulate cortex and the insula are core hubs of alterations linked to neuropsychiatric conditions (95,102,110,114,291–294). Throughout my thesis, both regions were consistently found to be altered across CNVs, ASD, and SZ. My findings thus further support the hypothesis of the critically important role of these regions in psychiatry. The results at the functional and anatomical level provided by neuroimaging studies raised questions about microstructural properties of cingulate and insular regions. The relationship between the functional connectivity of these two regions, which is a large-scale measure of brain synchronisation, and their observation at the cellular level remains mostly unstudied.

Large-scale discovery on brain functional architecture was provided by Margulies and colleagues in 2016 (295). This dimensional view introduced a new coordinate system with major gradients of brain organization, that locates sensory and motor networks at one end, and the transmodal DMN on the other end (296,297). Psychiatric conditions and CNVs may disturb such dimensional brain structure. This hypothesis has recently been tested by Hong and colleagues in ASD (298). They compared the first functional gradient (explaining 24% of the connectome variance) in ASD compared to control, using surface-based analytical models. They showed that both extremes of the rostrocaudal gradient were decreased in ASD. Interestingly, vertex-wise analyses revealed that diminution in ASD was driven by transmodal medial PFC and posterior cingulate regions (298). Similar to connectivity data, the dimensional hierarchy was captured by cortical microstructure and gene expression data (297,299). Such multi-scale mapping may provide insight into the biological relation across psychiatric conditions, and could be used to understand the recurrent involvement of a core set of brain regions in psychiatry.

Transcriptomic analyses are a recent technique promising to link our understanding of molecular changes in these two brain hubs with their role in psychiatric conditions. Velmeshev and colleagues performed RNA-

seq analyses at the single-cell level on post-mortem anterior cingulate and prefrontal cortex tissue samples from 15 patients with ASD and 16 controls (300). They identified 513 differentially expressed genes between ASD and control samples, predominantly in upper-layer cortical neurons. The dysregulation of a module of genes in cortico-cortical projection neurons was furthermore associated with a clinical severity measure of ASD. Their findings on the anterior cingulate and prefrontal cortex suggest that severity traits in autism may be related to molecular changes in upper-layer projection neurons, and in microglia.

Cytoarchitectonic studies revealed that von Economo neurons are found exclusively in layer Vb of the anterior cingulate cortex, and in the rostral portion of the insula in the human brain (301). These large bipolar neurons tend to be selectively vulnerable to a wide range of neuropsychiatric and neurodegenerative conditions (302,303). They have also been found to be specifically enriched in humans and great apes, but not in other primates (301,304). Several studies reported a decreased number of von Economo neurons in the ACC in psychiatric conditions such as schizophrenia (305,306). Postmortem analyses of frontoinsular and ACC areas have reported a higher ratio of von Economo neurons to pyramidal neurons in individuals with autism compared to controls (306). Authors suggested a relation between their results and cellular mechanisms involved in multiple neuropsychiatric conditions such as neuronal overgrowth (307,308). Overall, the cellular level investigation suggested that molecular mechanisms involved in neuropsychiatric conditions may target specific brain hubs, that may translate to an early loss in von Economo neurons in frontoinsular and ACC regions.

Future studies using modern cytoarchitectonic mapping and transcriptomic single-cell methods, combined with new large-scale functional properties knowledge will provide more insight into the nodal role of the ACC and the insula in neuropsychiatric conditions.

General thalamo-sensory disturbance

Altered connectivity of thalamus was one of the strongest findings across most of the conditions studied in my thesis (231). This region has been extensively identified as involved in multiple psychiatric conditions including ASD, SZ, major depression, epilepsy, and sleep disturbance (116,118,240,241,309), as well as in several CNVs at the neuroanatomical level (164,177,290,310). Dimension delineated by genomic constraint score in paper#2 also offered a nodal place to the thalamus, suggesting this functional hub as being highly sensitive to general gene-dosage and etiological mechanisms of psychiatric conditions.

This well-known gateway for sensory inputs (239) is disturbed in a similar way across conditions (Supplementary Figure IV.2): the thalamus was preferentially overconnected to somatomotor, visual, and auditory regions. This pattern is driving the similarities across conditions (see Venn diagram, Figure II.4) and could reflect sensory disturbance dimensions. Sensory processing and perceptual dysfunction is a core feature in SZ. Auditory and visuals hallucinations are experienced by more than 69% and 27% of patients with SZ (218,219). Kantrowitz and colleagues suggested that auditory deficits may contribute to the theory of mind impairment in SZ (311). Altered sensory and perceptual functions are also recognized as core features in ASD (8). Individuals with autism present several visual tasks impairment such as gestalt perception and discrimination of motion (220). They also present disturbances in auditory and tactile discrimination tasks (hypo and hypersensitivity, as well as outperformance). One theory is that individuals with ASD have deficits in perceptual integration: they are able to process stimuli but they fail to integrate them in a coherent manner (312,313). Sensory dysfunctions are also present in animal models of ASD (eg. drosophila (314)) suggesting a strong genetic component underlying these manifestations. In individuals with the 16p11.2 deletion, studies showed large impairments of speech motor control (315). Interestingly, Hippolyte and colleagues showed that deletion carriers present severe impairments of phonology, while duplication carriers outperform for the same task (161). Such results might recapitulate and mirror what is seen in autism (low vs. outperformance). Deletion at the 22q11.2 locus is finally also strongly associated with visual and auditory deficits (221–223).
The general thalamo-sensory disturbance may, therefore, be central across psychiatric diagnoses and genomic mutations. Comorbidities might be a consequence of such mechanistic dysfunction.

Decades of multi-scale studies have aimed to disentangle the link between properties of this central structure and clinical severity traits of neuropsychiatric conditions. The thalamus is part of the diencephalon, which is one of the earliest brain structures developed during human ontogenesis (316). Recent models of thalamic

functions highlighted a far more complex role than a passive relay for cognitive processes. By studying of thalamic projections to granular or subgranular layers of the cortex, and corticothalamic pathways, converging findings point to a general engagement of thalamic subdivisions in memory, attention, and mental representations (238,239,317). By recording neurons from the ventrolateral thalamus and across layers of the frontoparietal cortex, Redinbaugh and colleagues recently showed that neurons in the thalamus and deep cortical layers were most sensitive to changes in the level of consciousness, suggesting its critical role in the process of awareness (318). Using high-resolution resting-state MRI and Allen Institute cellular data, Muller and colleagues showed for the first time that the thalamocortical connectivity was concordant to the large-scale gradient of brain organization (317). They were able to recapitulate the primary cortical gradient with the core and matrix cellular thalamic populations that respectively project to granular and subgranular layers of the cortex (317,319). Further research on neuropsychiatric CNVs and relation with psychiatric conditions may, therefore, study thalamic subdivisions provided by alternative functional parcellation (238).

The previous paragraph offers several pieces of information that could be used in the future to disentangle the critical role played by the thalamus in psychiatry: an early maturation (that could be related to the early biological onset of multiple psychiatric conditions), a heterogeneous cellular architecture, a complex connectivity pattern to granular and subgranular layers of the cortex, and a central role in multiple cognitive functions and in consciousness processes. Complementary techniques will provide more granular information about thalamic involvement in psychiatry.

Limbic system and emotion regulation

The limbic system is the major centre of emotion regulation and memory. This network was found as massively disrupted in 22q11.2 deletion carriers, ASD and SZ, in particular, in amygdala-hippocampus regions (see Supplementary Figure VIII.3), ventral anterior insula, and the temporal pole. These regions were identified as under-connected with the frontoparietal network and the anterior DMN. Given the important role of these regions in emotion regulation and memory and the presence of emotion dysregulation symptoms in the studied conditions (see below), dissecting this signal might help us to disentangle the general dimensions altered across conditions.

Such dysconnectivity patterns have been previously reported in several conditions, including major depressive disorder (320), anxiety (321), and in patients with suicidal ideation (322). Drysdale and colleagues studied 1,118 subjects with a data-driven approach applied to fMRI. They showed that patients with major depressive disorder were falling into two components (anhedonia-related, and anxiety-related) defined by profiles of dysconnectivity in the limbic and the frontostriatal networks. The second one involved predominantly the amygdala, the ventral hippocampus, the subgenual cingulate, and the lateral prefrontal cortex (321). These regions were preferentially altered in the 22q11.2 deletion group, but also in ASD and SZ results. Patients with 22q11.2 deletion suffer from primary anxiety disorders and insomnia (323,324). This is also the case for individuals with autism and SZ (325,326). Such observation has not been reported as a core trait in subjects with the 16p11.2 deletion. Sleep deprivation has been associated with a reduction of connectivity between the amygdala and the prefrontal cortex during rest (327,328).

By studying specifically the connectivity profile of the amygdala-hippocampus region across conditions, we reported a shared profile of underconnectivity with the perigenual anterior cingulate cortex, the dorsomedial and ventromedial prefrontal cortices, and the anterior insula (see Supplementary Figure VIII.3). This was particularly the case in 22q11.2 deletion and duplication, ASD, and SZ but not in 16p11.2 deletion. Such results suggest that some of the similarities might be related to general anxiety - emotion regulation and sleep-disturbance dimensions, that could be an interesting avenue for future research.

How do common genetic variants modulate brain architecture?

Top-down GWAS

To date, top-down GWAS of neuroimaging measures have not yet been performed using rare variants because it would require massive samples (n>40,000) with CNVs or SNV data.

A first insight into the genetic architecture of the brain phenotypes was provided by Stein and colleagues in 2012. GWAS identified two SNPs (rs7294919 and rs10784502) associated with hippocampal and intracranial volumes (329). A follow-up study aggregated MRI data from 50 cohorts (n=30,717 individuals) to investigate volumes of subcortical brain regions and ICV (330). All volumes showed high heritability and the strongest effects were found for putamen and hippocampal regions. They discovered five novel common genetic variants related to the putamen and caudate nucleus volumes, and confirmed previously established (329) relations between 2 SNPs with ICV and hippocampal volume. A more recent GWAS study (38,000 individuals) extended these results to forty-eight common variants associated to the regional volumes of nucleus accumbens, thalamus, amygdala, brainstem, caudate nucleus, globus pallidus, and putamen (331). Common variants were involved in several developmental pathways including apoptosis, axon guidance and vesicle transport. The last update was recently published by the ENIGMA consortium on 51,662 individuals, with 175 loci identified showing association with SA and 10 with CT (332). Common genetic variants explained 34% of the variation in SA and 26% in CT. SA-associated SNP loci were enriched within regulatory elements active during prenatal cortical development. The same loci were clustered near genes in Wnt signalling pathways known to influence progenitor migration. Interestingly, SA and CT exhibited negative genetic correlation, while SA had a positive genetic correlation with educational attainment and cognitive functioning.
On the functional side, several studies identified that functional networks were heritable (333,334). Using rs-fMRI data of n=820 subjects from the human connectome project, Colclough and colleagues investigated the heritability of connectivity among 39 cortical regions. They showed that additive genetics accounted for 17% on average of the functional connectivity (335). Follow-up study showed that heritability was driven by high-order systems, including the frontoparietal and dorsal attention networks (333).

Overall, large GWAS studies showed intermediate to high heritability of subcortical area volumes and functional networks, and identified common variants associated with intermediate brain phenotypes.

Understanding genetic control of brain architecture may help to determine mechanisms involved in neuropsychiatric conditions dysfunction.

Bottom-up framework with polygenic risk scores

Although most of the genetic-first studies have been performed with rare variants, a small number of them have tested the effect of polygenic risk scores (PRS) of SZ and ASD on structural brain imaging phenotypes (336–338). PRS are increasingly being used to capture the aggregated common genetic effect from a set of trait-related SNPs that may not achieve significance at the individual level, but collectively may explain a substantial portion of the trait variance (16). Such results relying on common variants are however largely linked and constrained by the sample size of each original GWAS and will likely change. Predictive modelling suggested that the number of future discovery for anorexia will be the same as for SZ and that the number for ASD will be between those for SZ and major depression disorder (339).

Using 2864 participants from UK Biobank, a study reported negative associations between SZ-PRS and whole-brain CT, and between SZ-PRS and insular lobe CT ((336–338)). A larger follow-up study (n=12,490 UK Biobank) reported negative associations between SZ-PRS and frontotemporal CT (340). In addition, they showed that a higher SZ-PRS in healthy individuals was correlated with a smaller CA2/3 volume of the left hippocampus. Investigation of PRS for ASD, SZ, ADHD, BIP, and major depression in 1,139 children from Generation R (341) was unable to identify any association with brain measurements. As the power of GWAS studies increases leading to more informative PRS, larger neuroimaging genetic studies will be able to accurately characterize and compare the brain correlates of genetic scores. Such scores are able to capture individual-level variation and may be used to parameterize predictive models. We could, therefore, extend Aim 3 to predict the combined effect of common and rare genetic variants on several phenotypes related to psychiatry.

One gene at a time

Studies have sought to identify major genes driving phenotypic effects in CNV carriers to understand cellular mechanisms that give rise to the risk conferred by these variants. I hypothesise that a limited number of genes per CNVs (building blocks) are driving the phenotype by converging on a limited number of molecular pathways shared across conditions (Figure 1). Such mechanistic findings may help to understand why genetic risk factors for neuropsychiatric conditions present shared connectivity components (see paper#1).

First, we will review if key genes have been identified to drive the CNV-associated phenotype to date.

Genes encompassed in the 16p11.2 region

To study mechanisms at play in the 16p11.2 CNVs, several studies have phenotyped mice (morpholino-mediated knockdown) with heterozygous and homozygous deletions of genes with the 16p11.2 interval. The zebrafish embryo has emerged as an alternative in vivo model due to the high evolutionary conservation of key genes and pathways between humans and this organism. The 16p11.2 chromosomal region contains approximately 29 genes and none of them has been formally linked to 16p11.2-associated features (342). Human genetic findings, however, did suggest a smaller critical region of five genes that includes the *TAOK2* and *KCTD13* gene. Animal studies on *TAOK2* reported dosage-dependent effects including changes in brain size and neural connectivity (262). Richter and colleagues showed that loss of *TAOK2* activity was related to a reduction in RhoA activation, suggesting that this pathway is a mediator of Taok2-dependent synaptic development. Of note, *TAOK2* is interacting with *KCTD13* in the RhoA signalling pathway, and with *MAPK3* by activating MAPK pathway (343). *KCTD13* may therefore also be a major driver of neuroanatomical phenotypes.

Golzio and colleagues reported that overexpression of human *KCTD13* gene in zebrafish embryo induces microcephaly, whereas deletion of the zebrafish ortholog yields a macrocephalic phenotype. These results suggested mimicking the human phenotypes seen in 16p11.2 CNV carriers (194). Follow-up *KCTD13* mice and zebrafish study did not replicate the increase in brain size and neurogenesis results (342). Overall, the identification of a single gene within 16p11.2 locus responsible for phenotypical traits has not been conclusive.

Genes encompassed in the 1q21.1 region

Studies using animal models to investigate the ten genes within the 1q21.1 CNV have suggested the key role of the *CHD1L, PRKAB2,* and *AMPKβ.* Results on drosophila showed that *AMPKβ* loss leads to sleep disturbances and may be associated with neuropsychiatric conditions. Knock-out mice models of *CHD1L* resulted in a developmental arrest, with a specific impact of neuroepithelial differentiation of embryonic cells, suggesting an early critical role of this gene in the nervous system maturation (344). However, no direct link has been found, and no major contributors to the cognitive and behavioural phenotypes have been identified (345). Despite the smaller number of genes compared to 16p11.2 CNV, the contribution of individual genes to phenotypes observed in patients remains unknown.

Genes encompassed in the 22q11.2 region

Attempts have been made as well to associate SNP on single genes encompassed within the 22q11.2 CNV. *COMT, TBX1, SEPT5,* and *DGCR8* were identified as critical drivers of the phenotype but results remain inconsistent (346). Examining gene-candidate studies results on 22q11.2, the latest review conducted by Motahari and colleagues in 2019 concluded by the following statement: "Our 22q11.2 functional genomic assessment does not support current theories of single gene haploinsufficiency for one or all 22q11DS phenotypes" (167). Overall, the quest of nodal genes within 22q11.2 has not been conclusive (in particular in humans) (346).

Overall, the search for critical segments or single genes within CNVs has not been a simple task (346). These studies illustrate that relationships between phenotype and gene encompassed in CNVs does not automatically imply a single gene but rather request additional genes with smaller individual effect or even general mechanisms. The lack of established association with phenotype outcome raised concerns about the gene-candidate approach to understand general mechanisms underlying phenotypes in psychiatric conditions.

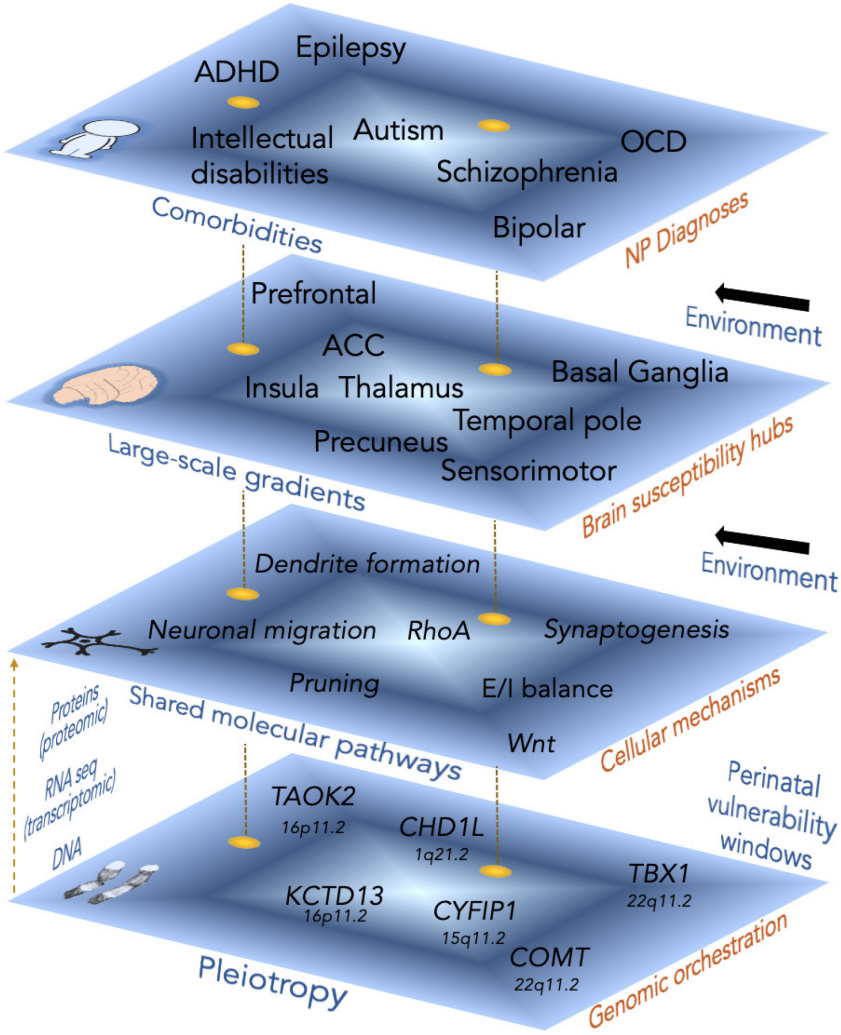

Figure IV-1 From candidate genes to psychiatric diagnoses: a cascade of shared mechanisms

Legend: Overview of the bottom-up approach with the example of several candidate genes, each being encompassed into one of the eight neuropsychiatric CNVs loci studied in paper#2, and a brief non-exhaustive summary of molecular mechanisms at play. This over-simplification of the potential nodes is to be interpreted with caution, the genome and the brain being both a network. I do believe that the major part of the coding genome (347), and that most of the brain, is involved and disturbed in this cascade underlying the emergence of traits associated with psychiatric conditions. E/I: excitatory/ inhibitory ratio

Toward a canonical organization of the genome

Genetic first studies have raised questions on the nature of the relationship between molecular functions of genes included in CNVs, and changes in large scale networks observed in neuroimaging studies. Results provided by candidate gene studies illustrate the multiplicity of molecular mechanisms involved in NPs. I reported in the previous paragraph the difficulty to find a causal association between a gene and an associated phenotype.

The transcriptional architecture of the human brain is providing an additional framework to characterize and model the effect of any genomic CNVs on intermediate brain phenotypes. A recent study supports the general idea that anatomical brain architecture underlying NPs is orchestrated by brain expression patterns of genes encompassed into neuropsychiatric CNVs (215). This work introduced a "transcriptional vulnerability framework" that could be used to predict regional vulnerability with measures of gene expression in human CNVs carriers. This proof of concept study started by defining the cortical organization of six CNVs, including both duplications (chromosomes X, Y and 21) and deletions (X-chromosome, 22q11.2, 11p13). The authors compared the anatomical CNV-profiles to corresponding gene expression maps. Anatomical profiles were preferentially linked to the spatial expression pattern of genes encompassed into the CNV (215). These findings are concordant with results from paper#1 where I showed an association between connectivity and gene co-expression CNV-profiles, but potentially discordant with the hypothesis of shared mechanisms and general dimensions across CNVs.

Considering that over 1000 loci and genes are expected to contribute to NPs, it is likely that they converge on a smaller set of altered neuroanatomical and functional patterns. The ASD and SZ case-control neuroimaging studies would have otherwise obtained no result at all. My findings on functional imaging phenotype level may reflect the fact that broad groups of genetic variants confer risk to the same psychiatric conditions. This suggests that the genome is organized in a canonical and dynamic way, going beyond the well-known spatial static 2-D coordinates.

Previous work from the Allen Institute suggested that a set of genes expressed in the brain constitutes the core transcriptional machinery of the human brain (196). Hawrylycz and colleagues introduced the differential stability metric that assesses the topographical specificity of expression of a gene in a brain region and the reproducibility of this pattern across individuals. They showed that genes with a high-DS were specifically associated with NPs and more preserved between human and mouse than genes with low-

DS. The top ten percent of genes build the so-called Default Gene Network. This canonical transcriptional organization of the genome (Default Gene Network) was correlated with the functional architecture of the brain (such as with the DMN), suggesting a link between gene expression and functional brain organization (Figure IV-2). The differential stability metric could be used as an additional constraint score to model linear effect of rare variants on intermediate brain phenotype (Aim 3).

Using the Default Gene Network, Hawrylycz and colleagues also highlighted thirty-two modules (cluster of genes related to anatomical patterns), that were enriched for specific cell types, intracellular components, and associated with specific developmental and degenerative conditions (196). These modules may be related to emerging properties of the genome and could underlie larger scale gradients of brain organization (297). Functional dimensions identified across CNVs and psychiatric conditions in paper#2 may also be distributed through these modules. Such general macro to micro-level of study will help to understand the genetic underpinnings of brain organization and provide a baseline to quantify association with NPs.

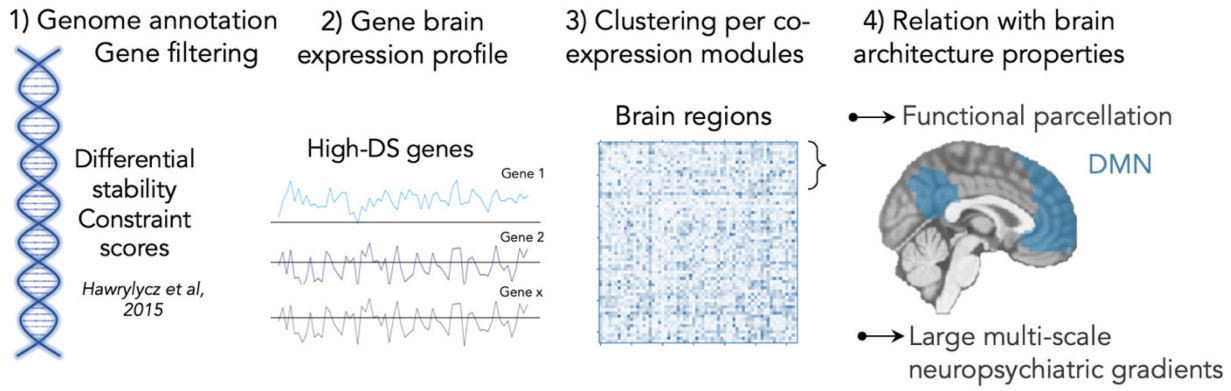

Figure IV-2 From the Default Gene Network to the Default Mode Network

Legend: By using annotations scores (DS), and by filtering the 10% of the genes expressed in the brain with high DS-score (1-2), Hawrylycz and colleagues identified relationship between co-expression profile (3) and functional network architecture (4).

Brain developmental windows and external factors

A gene is static, but its transcription to RNA and a protein is not. The transcription phase is highly sensitive to external factors. Recent discoveries in biology revealed a novel form of plasticity that refers to the biochemical environment, namely the epigenome, where genes are transduced to cellular commands (348). The epigenome is modulated by environmental conditions throughout the lifespan and has been identified as contributing to mental illnesses etiology.
A recent review on SZ suggested that environmental factors could lead to "molecular scars" that influence brain function throughout lifespan contributing to SZ symptomatology (349). These epigenetic scars could be related to the phenotypical heterogeneity found in SZ.

Models introduced in my thesis and proposed in the perspective section are therefore still "simplistic" views that omit to integrate environmental influence (epigenetic) and potential developmental windows of susceptibility. Maternal stress or toxins are two examples of environmental variables that may modulate biological insults, colouring the complexity of neurodevelopmental conditions etiology (348,350). Such factors mainly act during developmental windows of susceptibility (78). Identifying and taking into account these variables and vulnerable periods is a necessity to pursue such study on neurodevelopmental conditions.

Using developmental gene expression data, Bennett and colleagues recently highlighted three periods of susceptibility for ASD: neural differentiation (during the first trimester), cortical specification (mid-second trimester) and upper layers (UL, early third trimester) stages (78). Interestingly, expression of SZ's genes was starting at a later stage than ASD in general, occurring first at the UL. Results are going to the direction of potential time differences that may precipitate ASD onset compared to SZ. Postmortem samples used in the second part of this study (78) were restricted to one brain region per condition (frontal cortex and superior temporal gyrus respectively), and genes were limited to the top 200 candidates already associated with ASD and SZ. Further work on additional genes and brain regions will help to uncover differential windows of susceptibility. Finally, single-cell RNA-sequencing to test different cellular populations, and other analytical frameworks, testing gene co-expression patterns across brain regions (such as weighted correlation network analysis) could help to dissect such results.
By using expression data from brain tissues across five different developmental stages (351), I showed that 16p11.2 genes were the only genes preferentially expressed during the perinatal and infant stages in sensory and temporal brain regions, and during adolescence (hippocampus, V1, ACC, mediodorsal nucleus of the thalamus). Other CNVs studied in paper#2 did not show significant specificity for any developmental stage

(unpublished results). Such new findings will be integrated into further studies to understand converging mechanisms in a more representative manner. Windows of susceptibility may be one way to understand pleiotropy (one CNV could be involved in several NPs, according to the gene expression timeline) and to validate the neurodevelopmental continuum between ASD, ADHD, and SZ (76,77).

One note about neuropsychiatric (NPs) and neurodevelopmental terminology: It may appear that neuropsychiatric and neurodevelopmental disorders are terms used interchangeably throughout my thesis. The well-known early onset of the ASD symptomatology (and ADHD), compared to the later emergence of SZ (and BIP) clinical traits motivated researchers to separate ASD and ADHD (neurodevelopmental conditions group) from SZ and BIP (NPs group). Recent findings from transcriptomic studies (see above) suggest that SZ could also be considered as an neurodevelopmental condition, albeit with a later onset (76). As the terminology is still evolving, I decided to refer to NPs in both papers to prevent any misunderstanding with the SZ literature. Both terminologies are correct and depend on the level of observation.

Are neuropsychiatric conditions a by-product of human brain evolution?

Modern RNA-seq techniques are now able to compare genomes of hominins to other species in order to study the evolutionary history of the CNV contributing to psychiatric conditions.

NOTCH2NL encompassed in the 1q21.1 CNV has recently been identified as a human-specific essential determinant of number of neurons in the cortex, as well as necessary for radial glia stem cell proliferation (352). Using RNA-seq analyses, authors showed that under-expression (deletion) of *NOTCH2NL* accelerates the differentiation into cortical neurons. The opposite pattern was reported in duplication. The emergence of human-specific genes could have contributed to the rapid expansion of the human neocortex. However, genetic mechanisms causing cortical brain expansion in evolution remain mostly unclear. Interestingly, the 1q21.1 was the CNVs found with the largest effect on mean connectivity (paper#2).

BOLA2 gene (16p11.2 CNV) has been identified as exclusively duplicated in Homo Sapiens (353). The fact that the same set of genes contribute to the cortical expansion of the human brain and to neuropsychiatric conditions raise questions about potential relations between evolutionary mechanisms and psychiatry. One current hypothesis is that a part of genetic variants associated with neuropsychiatric conditions, such as gene dosage, may confer an evolutionary advantage by contributing to cortical expansion (354–356). Psychiatric manifestations could, therefore, result from a cascade of adaptive processes relative to the development of higher-level cognitive functions. Large-scale modifications in brain structure (such as brain size) and functional architecture (transmodal network) (357) have been identified as accompanying this process.

Reardon and colleagues identified a parallel between ontogenesis (from early childhood to adult) and phylogenesis (across species to hominins) by showing a greater expansion in DMN, frontoparietal, subcortical and dorsal attentional networks (including the anterior and posterior cingulate, and the thalamus) than in limbic and sensory-motor systems (negative scaling) during evolution (357). Multiple neuroimaging studies in psychiatry have identified alteration of regions subject to positive scaling during human brain evolution. Evolutionary pressure in service of high-level brain function may have also rendered brain hubs specifically vulnerable (355,358). We showed in this thesis that CNVs associated with neuropsychiatric conditions modulate similar gradients of brain regions as well as the whole-brain connectivity phenotype. Recent human brain evolution may, therefore, have contributed to the emergence of traits associated with autism and schizophrenia.

Further studies could implement evolutionary metrics (such as evolutionary pressure on protein-coding regions (ω, (359,360)) as additional constraint scores to predict the effect of any rare genetic variant associated to NPs on intermediate brain phenotypes.

Conclusion

Recent discoveries in neuroimaging, genomics, machine learning and neurobiology bring us to exciting crossroads in psychiatry. Uncovering genetic and imaging components underlying the emergence of cognitive dysfunctions does require large-scale studies. By simultaneously integrating a bottom-up framework across a broad set of rare variants associated with neuropsychiatric conditions, and a top-down approach across diagnostic boundaries, we have delineated genetic dimensions of dysconnectivity contributing to mental illnesses. By identifying the general effects of rare variants, we have also discovered that haploinsufficiency may reorganize connectivity along general dimensions, irrespective of where deletions occur in the genome. Such results suggest an underlying canonical organization of the genome that modulates brain architecture. Emerging properties of the genome (e.g. evolutionary constraint score) and of the brain (e.g. gradient of the functional organization) may be used to leverage further predictive models in psychiatry. Such models will help to understand the mechanisms at play, and could therefore guide potential care at the first stages of the psychiatric condition.

V. References

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VI. Supplementary Material, Methods, and Results: Paper 1

Supplemental Material and Methods

Objectives and methods overview

Aims	Objectives	Methods
AIM1. Characterize the impact of gene dosage on connectivity for CNVs at the 16p11.2 and 22q11.2 genomic loci	1.1. Describe the effect of gene dosage at the 16p11.2 and 22q11.2 genomic loci on global FC.	Connectome Wide Association Study (CWAS): Linear model contrasting CNV carriers with respective controls.
	1.2 Test if deletions and duplications have mirror effects at the connection level.	
AIM2. Test if FC-signatures of deletions represent dimensions observed in idiopathic ASD, SZ, or ADHD.	2.1 Characterize the effect size of idiopathic Autism, Schizophrenia, and ADHD on FC.	Same as 1.1. CWAS: Linear model contrasting cases of each psychiatric groups with respective controls.
	2.2 Test similarities between whole-brain connectomes of CNVs and idiopathic psychiatric conditions.	Pearson correlation between beta maps obtained from each CWAS and individual connectomes of either cases or controls of each group.
	2.3 Investigate regions that contribute to similarities observed in 2.2	The same method used in 2.2 applied to each of the 64 regional FC patterns.
	2.4 Identify the relationship between regions identified in 2.3 and cognition	Pearson R computed in 2.3 was correlated to the cognitive measure of each individual
	2.5 Associate the deletion FC-signatures with spatial patterns of genes expression within both loci	PLSR and correlation analyses between spatial patterns of gene expression and FC-signatures

Table VI-1 Aims, objectives and methods overview

Samples

16p11.2 cohort

Imaging data of 16p11.2 CNV carriers and typically developing controls were acquired by the Simons variation in individuals project (VIP) consortium (202) across 2 sites. We excluded 44 individuals from the analysis due to insufficient quality of the imaging data (cf. Supplementary Methods, quality control). The final 16p11.2 sample includes 122 individuals. Over 90% of the deletion carriers and 69% of the duplication carriers met criteria for at least one clinical psychiatric diagnosis (Table 1**)**. Control subjects were recruited from the general population (extra-familial subjects), and had no major DSM-V diagnosis. The duplication group includes 2 individuals with a triplication.

22q11.2 cohort

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. We excluded 16 individuals from the analysis due to insufficient quality of the imaging data (cf. Supplementary Methods, quality control). The final 22q11.2 sample includes 101 individuals. 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 tesla 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 (178).

Idiopathic ASD

The ABIDE dataset(12) is an aggregate sample of different studies including imaging and behavioural 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 in 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 459 male individuals, 225 individuals with ASD and 234 healthy controls, from 10 recording sites.

Idiopathic schizophrenia

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(361);https://openfmri.org(362)) or local scanning at the University of Montréal. All patients were diagnosed with SZ according to DSM-IV or DSM-V criteria, as a function of the time of 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 controls 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 with the Positive and negative syndrome scale (PANSS,(217)) or the Scales for the assessment of positive/negative symptoms (SAPS/SANS,(363)). In order to allow for group analyses, SAPS/SANS scores were converted into PANSS scores using published regression-based equations(364).

Idiopathic ADHD

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/ (203)). Data from seven sites were retained after exclusion of 184 individuals. We included in our study a total of 763 subjects, 289 patients diagnosed with ADHD and 474 healthy controls.

This database provided child and adolescent data. Scores related to ADHD symptoms were measured using Conner's Parent Rating Scale-Revised, Long Version (CPRS-LV (365)).

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 (205). 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 timepoint was mapped to the MNI space (366) 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 timepoints (367). 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 data were visually controlled for quality of the co-registration, head motion, and related artifacts by one rater. Not all six datasets were examined by the same raters, yet all raters followed the same standardized quality-control procedure (368). If there was co-registration failure of either the functional image to individual T1 or individual T1 to MNI template registration, we attempted a manual fix by changing the parameters of the preprocessing pipeline. 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 (Supplementary Materials and Methods).

Aligning the gene expression maps from AHBA to the MIST64 functional parcellation

To investigate the transcriptomic relationship of altered FC in each deletion, we aligned publicly-available atlas of gene expression in the adult human cortex from the Allen Human Brain Atlas (AHBA) dataset (196) to the MIST64 brain parcellation following previously published guidelines for probe-to-gene mappings and intensity-based filtering (210) and adapting the abagen toolbox (211). We normalized expression values within each brain sample across genes for each of the 6 donors and then for each gene across samples for each donor using a scaled robust sigmoid normalization. We computed the mean of the normalized values of all samples encompassed within each functional region of the MIST64. This was performed for each donor and then averaged across donors. A leave-one-donor out sensitivity analysis generated 6 expression maps. The principal components of these 6 expression maps were highly correlated (average Pearson correlation of 0.993). The same high correlation was observed for the differential Stability score (average Pearson correlation of 0.987).

Normalized gene expression value was available for each of the 15663 genes and for each of the 64 functional brain regions.

Supplemental Results

Sensitivity analyses on psychiatric diagnoses in 22q11.2 deletion

We compared the FC signatures of 22q11.2 deletion carriers with and without ASD. Both FC signatures showed the same global underconnectivity and were strongly correlated with the one presented in the manuscript despite the smaller sample size (r=0.83 to 0.90). The same sensitivity analysis also showed that ADHD diagnosis had no detectable influence on the 22q11.2 deletion FC signature. We performed the similarity analyses between 22q11.2 deletion profiles and idiopathic conditions after exclusion of 22q11.2 subjects with either ASD or ADHD. The same regions were driving similarities with 22q11.2 FC profiles irrespective of diagnoses.

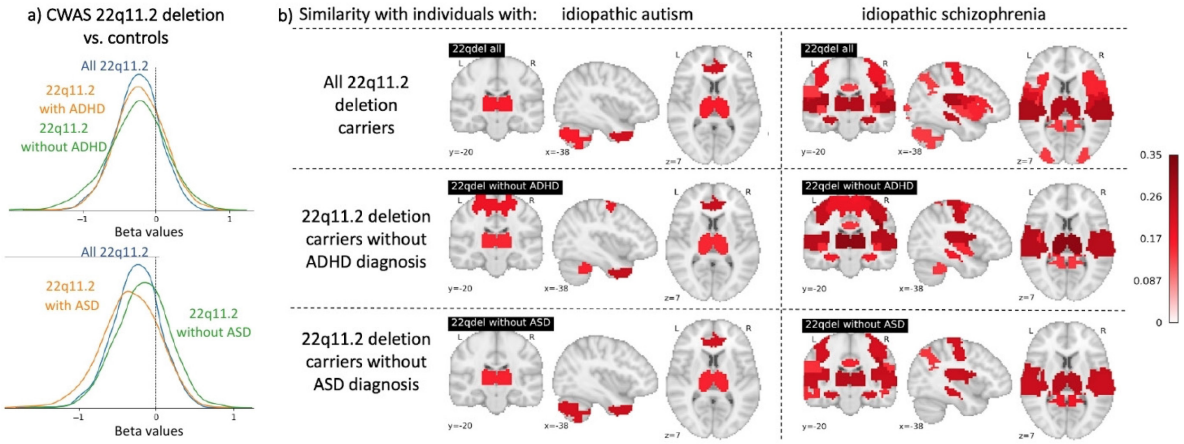

Figure VI-1 Sensitivity analyses on psychiatric diagnoses in 22q11.2 deletion

Legend: a) Density plots show the distribution of beta coefficients of CWAS contrasting controls and subgroups of 22q11.2 deletion (with and without diagnoses, in orange and green respectively). The full 22q11.2 sample is in blue. Under-connectivity is present in all 22q11.2 subgroups irrespective of diagnosis. b) Similarities between 22q11.2 regional FC-signature and individuals with ASD and SZ. The same regions showed similarities in all 22q11.2 subgroups irrespective of psychiatric diagnosis, despite the 2-fold decrease in sample size. Maps are thresholded maps (FDR). Color scale represents the similarity effect size (Mann Whitney, rank biserial correlation).

Sensitivity analyses on age

We performed a sensitivity analysis after excluding older controls to obtain identical age distributions (mean 12.7 and 13.0 years respectively) in the 16p11.2 deletions and control groups. The CWAS performed before and after excluding adults provides the same results albeit with decreased power: The 2 beta maps are highly correlated (r=0.967) and their distribution (b) overlaps perfectly.

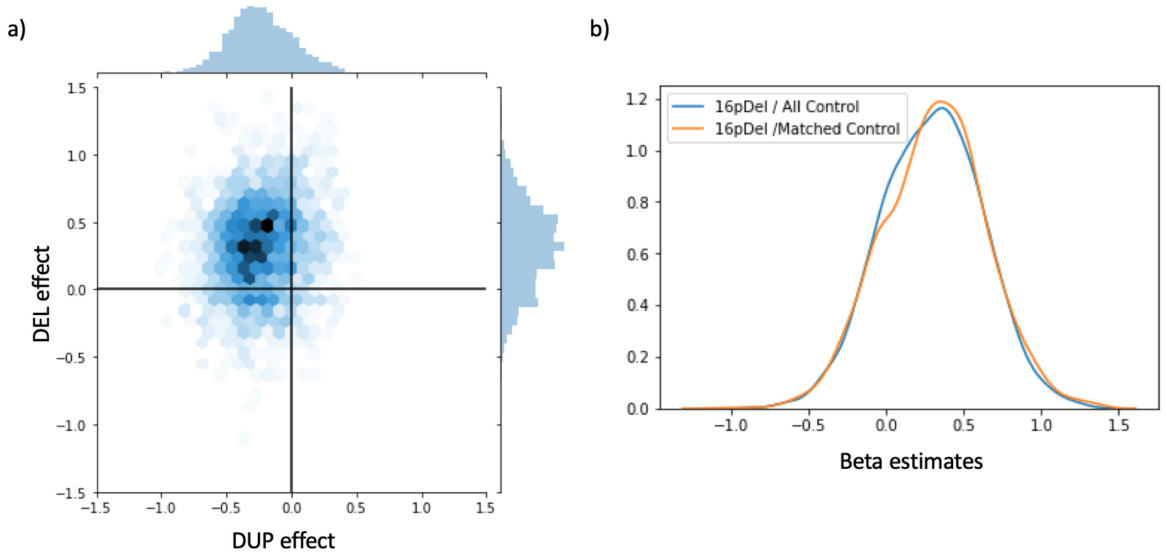

Figure VI-2 Sensitivity analyses on age distribution in 16p11.2 deletion carriers

Legend: (a): Scatterplot (*hexagonal plot*), showing estimates (beta values) from connectome-wide association studies (CWAS) performed between 16p11.2 CNVs and their respective controls excluding adults to obtain a matched age distribution. The scatterplot is identical to figure 1.a demonstrating that age distribution does not affect our results.

Sensitivity analysis on the number of remaining frames in 16p11.2 deletion carriers

We performed a sensitivity analysis by excluding all individuals with less than 60 frames (n=4 deletion carriers, 4 duplication carriers, 10 controls). The CWAS results were very close to those obtained with all participants. FC-signatures before and after exclusion showed an r=0.94 and r=0.89 for 16p11.2 deletions and duplications respectively.

Mirror effects of gene dosage in 16p11.2 CNV are present at the network level

We investigated how mirror effects of gene dosage at the individual network level follow the organization of the brain into canonical resting-state networks.

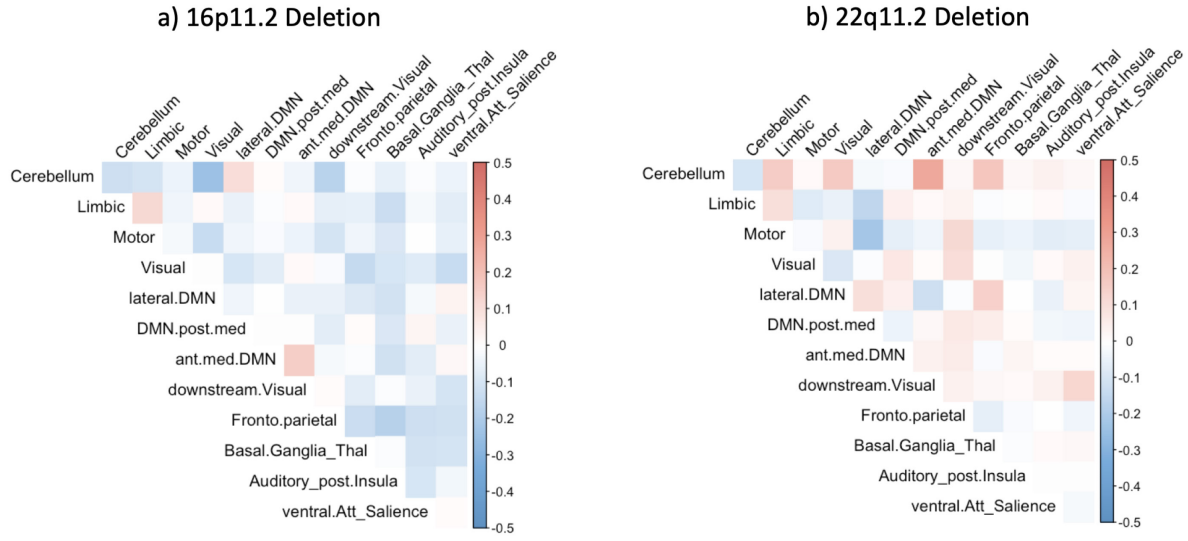

Figure VI-3 Mirror effects of gene dosage at the network level

Legend: Gene dosage effects at the connection level are shown broken down into the 12 corresponding functional brain networks (Supplementary Table S1.10) for the 16p11.2 (a) and 22q11.2 (b) genomic loci. Red colors reflect effects in the same direction for deletions and duplications. Blue colors reflect mirror effects for deletions and duplications (i.e. an increase in FC is associated with one, but a decrease is associated with the other). For the 16p11.2 CNVs, networks exhibited more mirror connectivity alterations than would be expected by chance (p = 0.006, two-sided). By contrast, 22q11.2 CNVs showed an equal number of connections with mirror and uni-directional alterations across networks.

Effect of Schizophrenia on FC

Idiopathic SZ showed overall underconnectivity affecting 835 connections, with the strongest alterations affecting the frontoparietal, auditory, ventral attention and limbic networks (dorsal anterior cingulate cortex, dorsal anterior and posterior insula, ventral posterior insula, and inferior marginal sulcus sulcus) (Figures 3a-b, Supplementary Tables S1.7 and S1.9, Supplementary Figure 4). Over-connectivity was restricted to 24 connections (cerebello-motor and thalamo-auditory, Figure 3c-d), in line with previous reports (116,119,369) (859 connections survived FDR correction in total, $q < 0.05$, p ranging from 0.02 to 1e-12).

Effect of ASD on FC

Underconnectivity in ASD was driven by seed regions in the limbic, lateral DMN, and cerebellar networks and over-connectivity was restricted to the thalamus connectivity profile, with the medial somatomotor network (MOTnet_m), in accordance with previous reports (12,240,370) (temporal pole, anterior middle temporal gyri, lateral fusiform gyrus, anterior middle frontal gyrus, and cerebellum VIII-ab) (Figures 3, Supplementary Tables S1.5 and S1.9, Supplementary Figure 4). Seventy-five connections (73 under and 2 overconnected) survived FDR correction ($q < 0.05$), with p ranging from 0.01 to 1e-5.

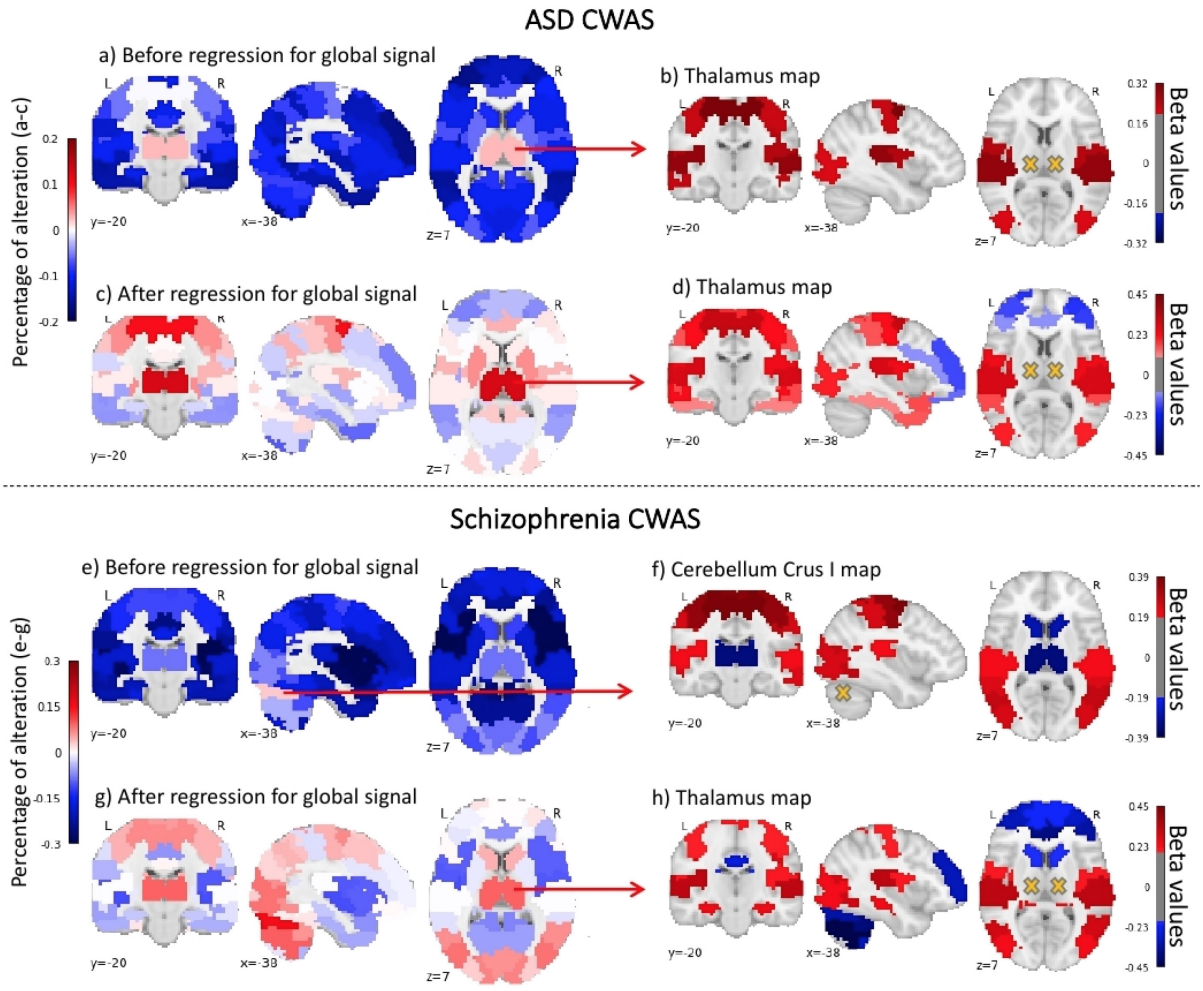

Figure VI-4 Effects of ASD and SZ on FC before and after adjustment for global signal

Legend: The adjustment removes the mean shift (global underconnectivity observed in ASD and SZ). The alterations of each region and network relative to one another remain similar before and after adjustment and both FC-signatures (beta maps) are highly correlated (r=0.98). This also demonstrates that ASD and SZ are associated with a mean shift in connectivity as well as a reorganisation of networks relative to one another.

Effect of medication on FC alterations in autism

A sensitivity analysis testing the effect of medication was performed with excluding 55 individuals with autism and one control from the analysis. Connectome-wide analysis on the non-medicated subgroup showed overall underconnectivity. Underconnectivity was significant (FDR) in 28 connections. The beta map of this analysis was highly correlated (r= 0.96) with the initial CWAS performed on the full sample including ASD subjects with medication.

Effect of ADHD on FC

For ADHD, none of the individual connections survived FDR correction (nominally significant alterations were observed in the posterior middle temporal and lateral occipitotemporal gyri, posterior medial visual network, the cerebellum-VI and the left intraparietal sulcus) (Supplementary Tables S1.8 and S1.9).

Effect of sex on FC alterations in SZ and ADHD

A sensitivity analysis was performed on 179 male participants with schizophrenia and 189 male controls. Males with idiopathic SZ also show overall underconnectivity with 472 connections surviving FDR. The beta map of this analysis excluding females was highly correlated (r= 0.95) with the initial CWAS performed on the full sample.

The same analysis was performed in the ADHD sample. The beta map of the analysis excluding females was highly correlated (r= 0.93) with the initial CWAS performed on the full ADHD sample.

Figure VI-5 Seed regions showing similarities between 16p11.2 and 22q11.2 deletions and Autism and Schizophrenia

(see below)

Seed regions showing similarities between 16p11.2 deletion and Schizophrenia

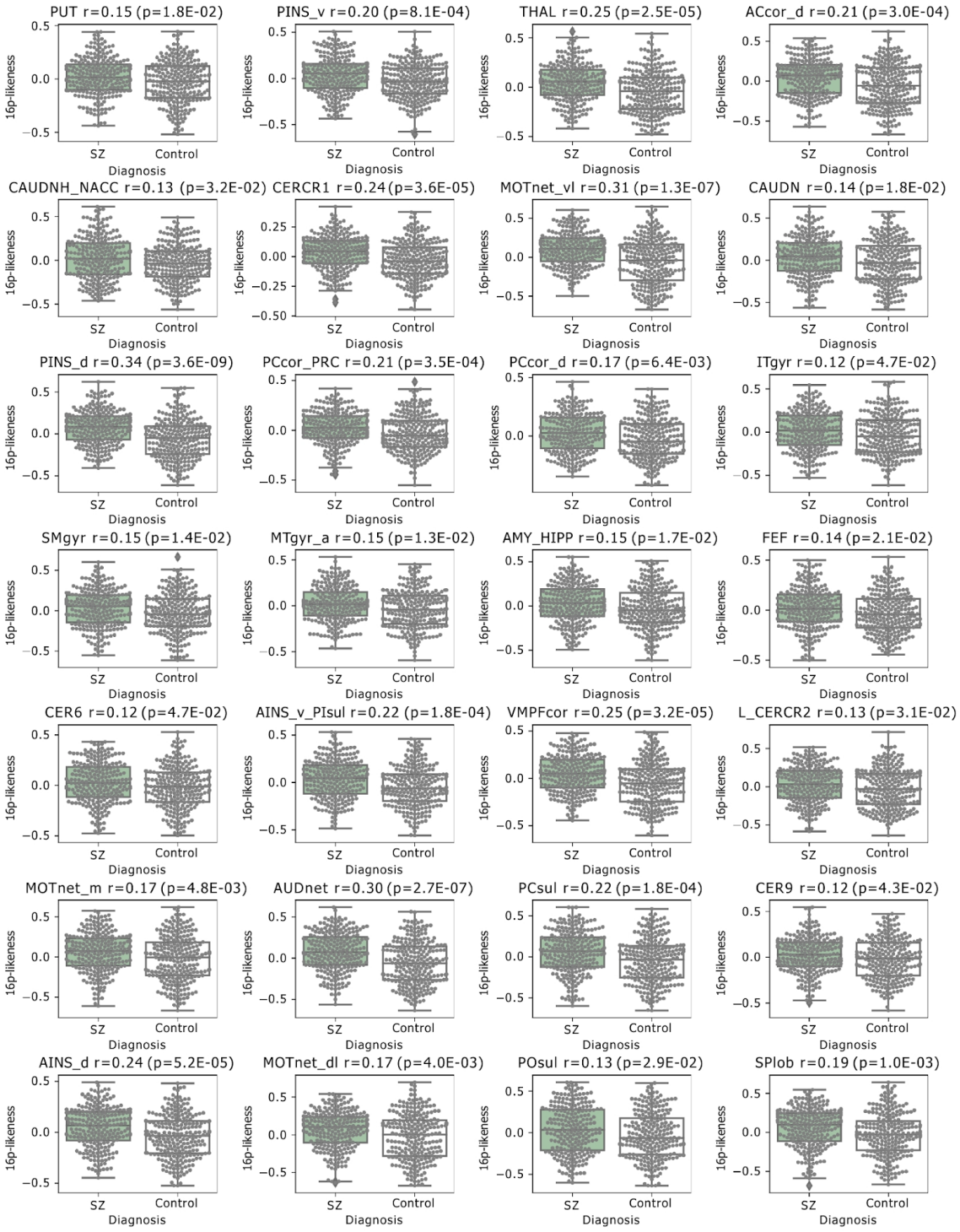

Figure 5a: Legend: Similarities between regional FC of 16p11.2 deletions and individuals with idiopathic SZ compared to their respective controls. Grey dots correspond to individuals in either the SZ or control group. Boxplots for individuals with SZ (green) and their respective controls (white) illustrate the observed group differences in similarity values. Similarity values (Pearson's R, Grey dots) were derived by computing Pearson's correlations between the regional FC-signatures. Differences between SZ or controls are tested using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 64 regions ($q < 0.05$).

Seed regions showing similarities between 22q11.2 deletion and Schizophrenia

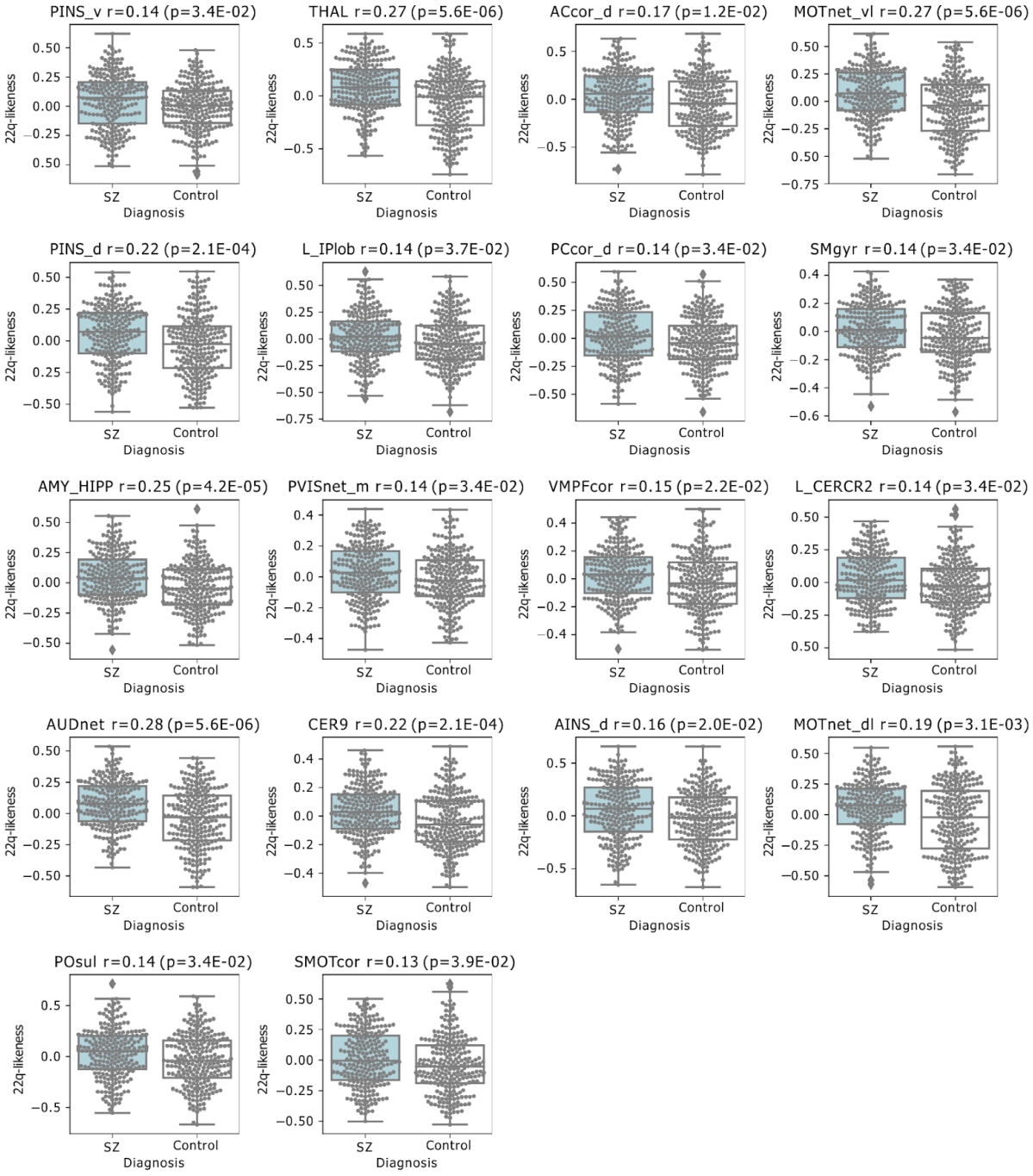

Figure 5b: Legend: Similarities between regional FC of 22q11.2 deletions and individuals with SZ compared to controls. Grey dots correspond to individuals in either the SZ or control group. Box plots for individuals

with SZ (blue) and their respective controls (white) illustrate the observed group differences in similarity values.

Similarity values (Pearson's R, Grey dots) were derived by computing Pearson's correlations between the regional FC-signatures. Differences between SZ or controls are tested using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 64 regions ($q < 0.05$).

Seed regions showing similarities between 16p11.2 deletion and Autism

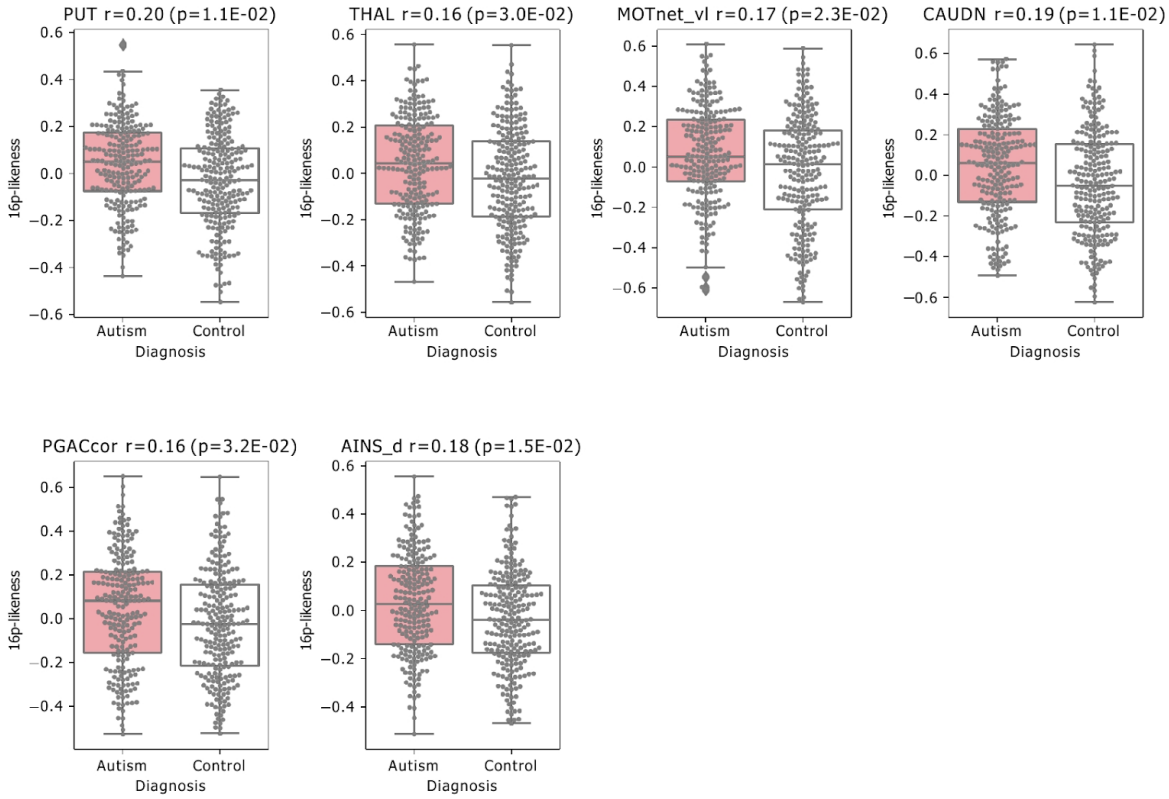

Figure 5.c Legend: Similarities between regional FC of 16p11.2 deletions and individuals with ASD compared to controls are shown. Grey dots correspond to individuals in either the ASD or control group. Box plots for individuals with ASD (red) and their respective controls (white) illustrate the observed group differences in similarity values. Similarity values (Pearson's R, Grey dots) were derived by computing Pearson's correlations between the regional FC-signatures. Differences between SZ or controls are tested using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 64 regions ($q < 0.05$).

Seed regions showing significant similarity between 22q11.2 deletion and Autism

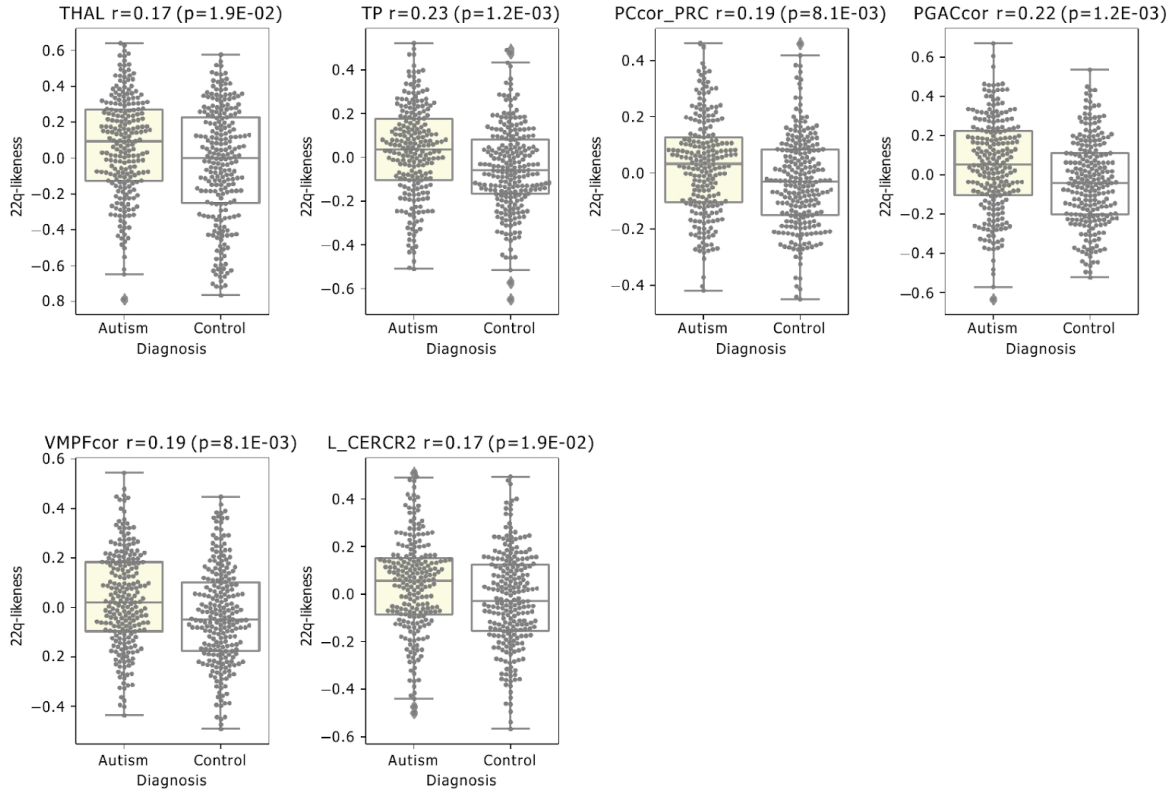

Figure 5.d Legend: Similarities between regional FC of 22q11.2 deletions and individuals with ASD compared to controls are shown. Grey dots correspond to individuals in either the ASD or control group. Box plots for individuals with ASD (yellow) and their respective controls (white) illustrate the observed group differences in similarity values. Similarity values (Pearson's R, Grey dots) were derived by computing Pearson's correlations between the regional FC-signatures. Differences between SZ or controls are tested using a Mann-Whitney U test. We reported significant group differences after FDR correction accounting for the 64 regions ($q < 0.05$).

Do the same seed regions contribute to the similarity between either 16p11.2 or 22q11.2 deletions and individuals with SZ and ASD?

Many of the same seed regions contribute to the similarity between either 16p11.2 or 22q11.2 deletions and individuals with SZ (a). This is less the case for autism.

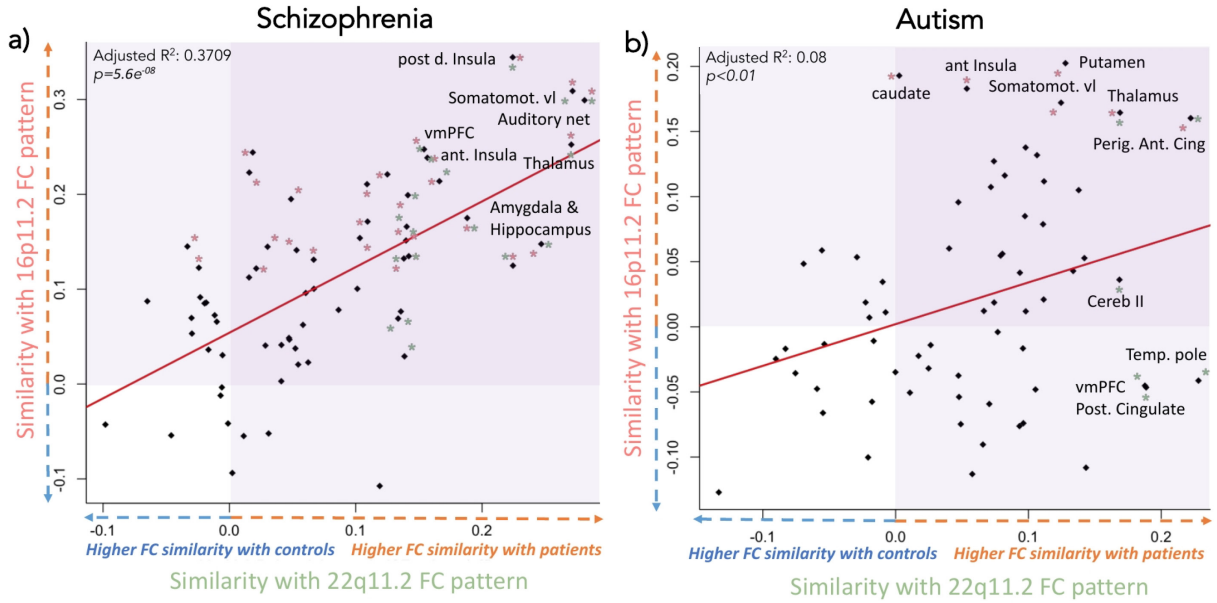

Figure VI-6 Do the same seed regions contribute to the similarity between either 16p11.2 or 22q11.2 deletions and individuals with SZ and ASD?

Legend: The horizontal axes show the Mann Whitney effect size (rank biserial correlation) representing the connectivity similarity between the 22q11.2 deletion FC-signature and individuals with idiopathic SZ (a) or ASD (b) compared to controls. The vertical axes show values (biserial correlation) representing the connectivity similarity with the 16p11.2 deletion FC-signature and individuals with idiopathic ASD (a) or SZ (b) compared to controls. Positive values (orange arrows) on the horizontal and vertical axes represent higher connectivity similarity between the deletion FC-signatures and individuals with SZ (a) or ASD (b) compared to their respective controls. Negative values (blue arrows) represent a higher similarity with control individuals. Seed-based connectivity signatures that show significant (FDR corrected) connectivity similarity with deletions are coloured (pink stars for 16p11.2 and green stars for 22q11.2).

Regional similarities between the individual FC profiles of subjects with a psychiatric diagnosis and FC-signatures of 16p11.2 and 22q11.2 duplications

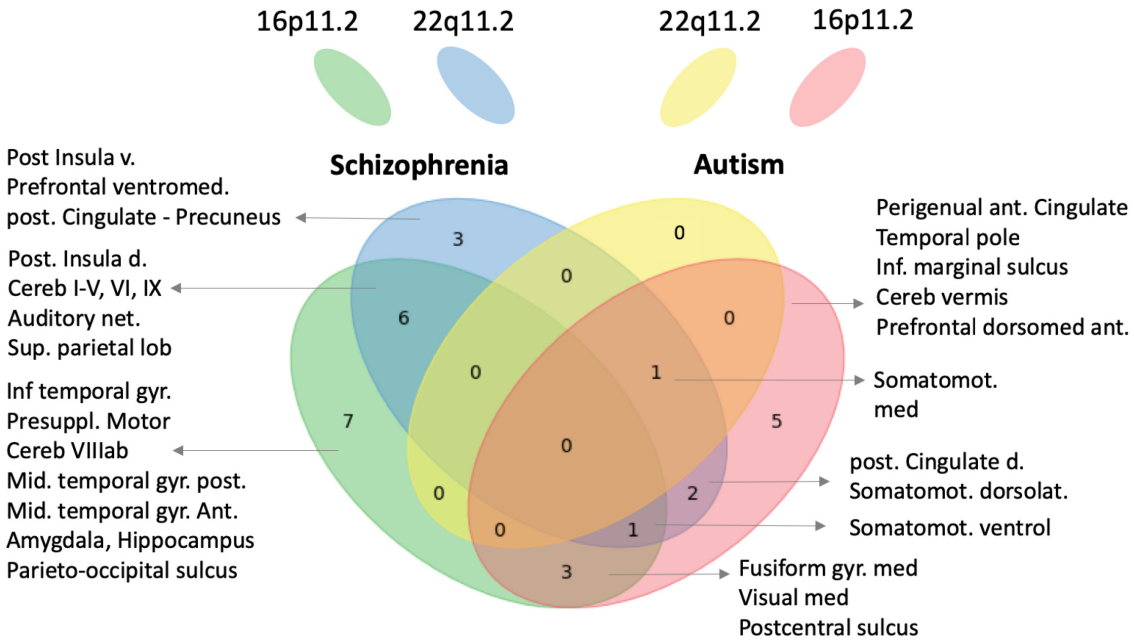

Figure VI-7 Regional similarities between the individual FC profiles of subjects with a psychiatric diagnosis and FC-signatures of 16p11.2 and 22q11.2 duplications

Legend: The FC-signatures of both duplications (group level) were decomposed into 64 seed-regions. Deletion FC-signatures are correlated to the individual connectomes of subjects with either ASD, SZ or control subjects. Of note, the correlation results in the mean centring of all region-based FC-signatures. Significantly increased similarities with either ASD and SZ are presented on the right and the left side of the diagram, respectively.

Some of these regions overlap with those identified in the same analysis using FC-signatures of both deletions: SZ individuals show similarities with both 16p11.2 deletion and duplication for 2 regions (Inferior and middle temporal gyrus)

SZ individuals show similarities with both 22q11.2 duplication and deletion for 6 regions (ventral/dorsal posterior insula, ventromedial prefrontal cortex, dorsolateral somatomotor cortex, cerebellum IX, auditory network) and with 16p11.2 duplication and deletions for 9 regions (parieto occipital sulcus, amygdala/ hippocampus, inf & middle gyrus anterior and posterior temporal gyrus, superior parietal lobule, cerebellum VI, posterior insula, dorsal prefrontal ventromedial cortex). ASD individuals show similarities with both

16p11.2 deletion and duplication for 2 regions perigenual anterior cingulate cortex, ventrolateral somatomotor cortex.

For 11 regions, controls rather than individuals with ASD or SZ showed increased similarities with duplications. This increased similarity with controls was never observed for deletion FC-signatures.

Similarity between the individual FC profiles of subjects with a psychiatric diagnosis and the FC-signatures of the 16p11.2 and 22q11.2 deletions and duplications

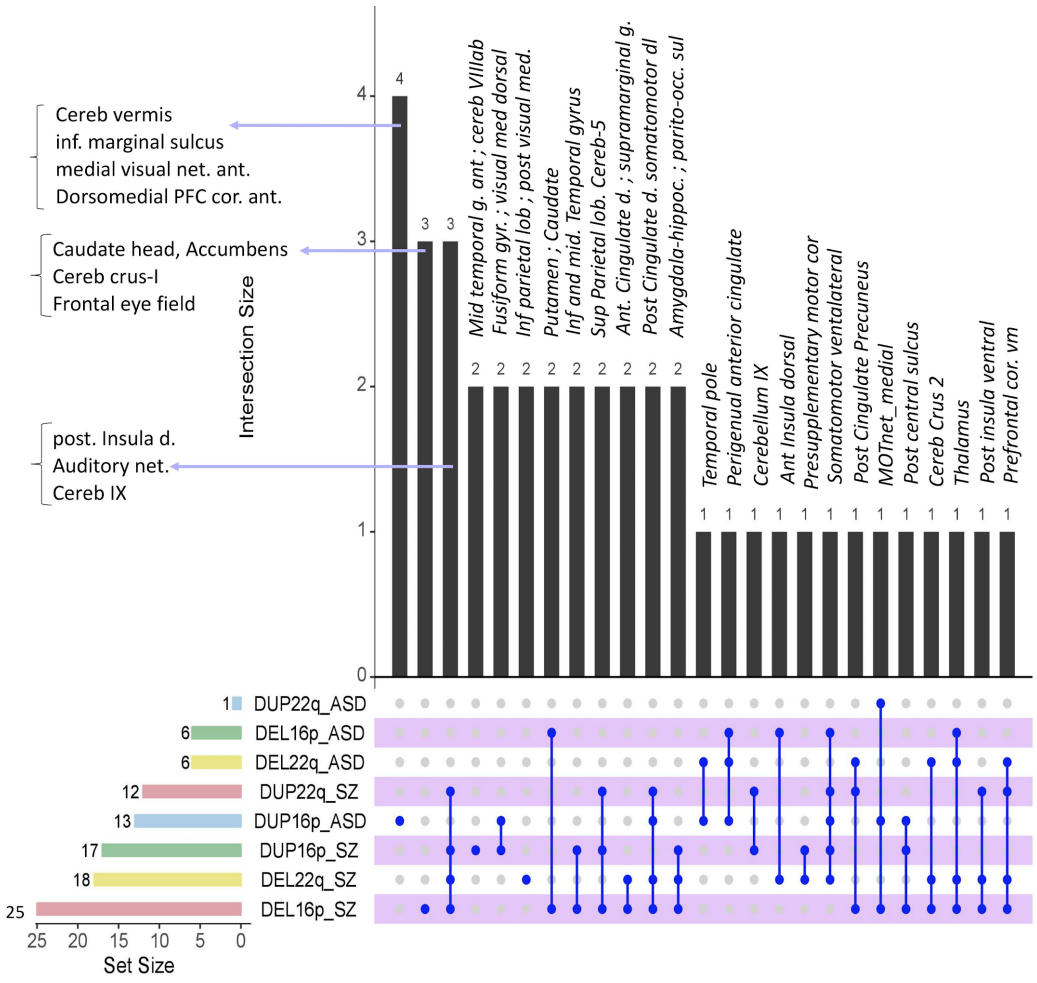

Figure VI-8 Similarity between the individual FC profiles of subjects with a psychiatric diagnosis and the FC-signatures of the 16p11.2 and 22q11.2 deletions and duplications

Legend: Because a Venn diagram showing overlapping brain regions across 8 comparisons (conditions, dels and dups) is impractical, we used the UpSet R package (371) to combine results from both Venn-Diagram (presented in Figure 4 (deletion) and in Supplementary Figure 6 (duplication)).

The dark blue lines and points show regions contributing to several similarities.

The 8 rows represent the 8 comparisons between the 4 CNVs and idiopathic ASD or SZ.

For example, the 23rd vertical black bar represents the thalamus which contributes to similarities across 4 comparisons (the 4 connected dark blue dots, representing the 16p11.2 and 22q11.2 deletion-FC-similarity with either ASD or SZ).

Horizontal bars on the bottom left represent the number of seed regions showing significant similarities for each comparison (eg. 6 regions showed similarity between 16p11.2 deletion-FC-signatures and ASD-FC-profiles). Y-axis: number of regions showing similarities between CNV carriers and idiopathic SZ or ASD.

Additional information on motion for each cohort after preprocessing

	ADHD	CON	SZ	CON	ASD	CON	16PDEL	16PDUP	16PCON	22QDEL	22QDUP	22QCON
Mean (frames)	160	159	152	166	139	153	83	83	85	110	121	126
Sd (frames)	53	59	50	49	52	49	18	23	20	42	34	30
Mean (% scrubbed)	0.13	0.25	*	*	0.24	0.16	0.26	0.25	0.23	0.25	0.18	0.14
Sd (% scrubbed)	0.15	0.26	*	*	0.23	0.18	0.15	0.2	0.16	0.28	0.22	0.2

Figure VI-9 Additional information on motion for each cohort after preprocessing

Legend: Mean (frames): mean number of frames remaining after scrubbing per individual; Mean (% scrubbed): Mean percentage of frames excluded per individual; SD: Standard Deviation; 16PDEL: 16p11.2 deletion; 16PCON: 16p11.2 control; 16PDUP: 16p11.2 duplication; 22QDEL: 22QCON: 22q11.2 control; 22q11.2 deletion; 22QDUP: 22q11.2 duplication. Sensitivity analysis on the number of remaining frames in 16p11.2 deletion carriers.

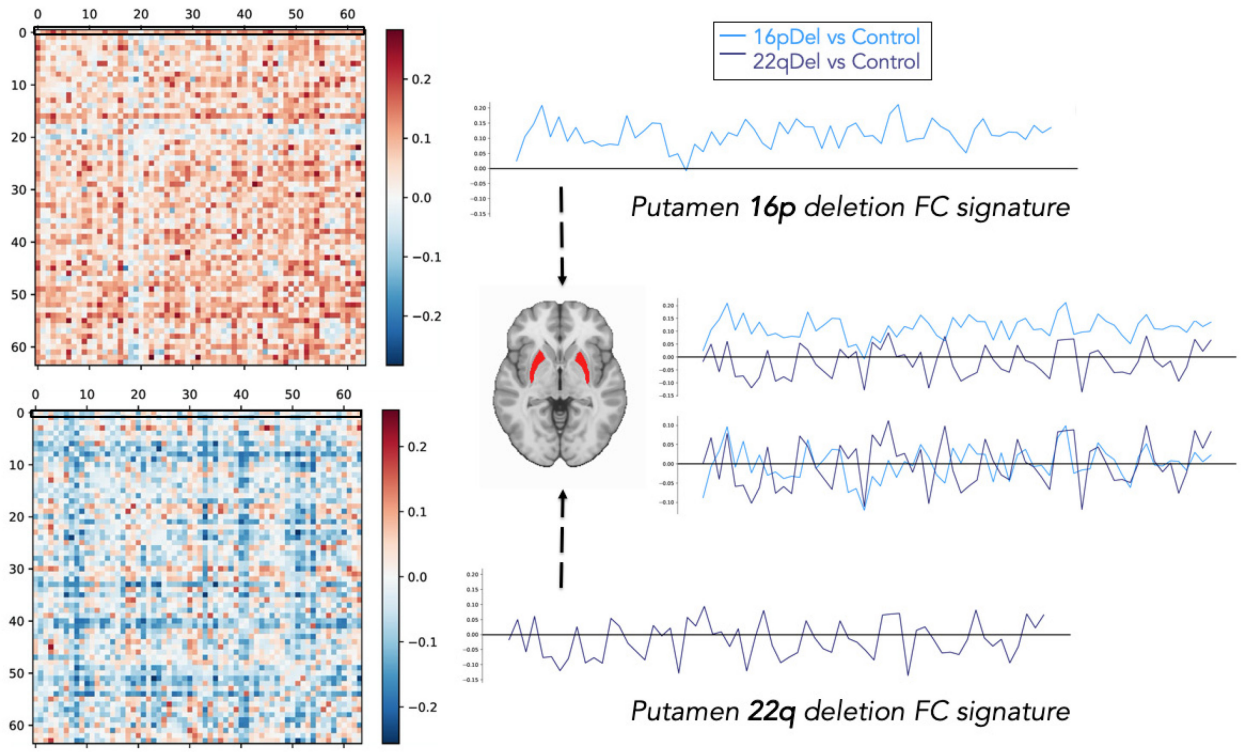

Figure VI-10 Method figure to illustrate the differences between whole-brain and regional analyses

Legend: Left side: beta-map (16p11.2 vs. controls and 22q11.2 vs. controls CWAS results). Right side: vectors of alterations of the putamen.

Table VI-2 CWAS beta estimates, ranking, region and networks labels

(see external excel Supplementary_Table_paper1_S1.xlsx)

Table VI-3 . Similarity of individuals with idiopathic psychiatric disorders with deletion FC-signatures

(see external excel Supplementary_Table_paper1_S2.xlsx)

Table VI-4 Association between similarity with deletion FC-signatures and symptom severities

(see external excel Supplementary_Table_paper1_S3.xlsx)

Table VI-5 Association between FC-signatures and spatial patterns of gene expression

(see external excel Supplementary_Table_paper1_S4.xlsx)

VII. Supplementary Material, Methods, and Results: Paper 2

Objectives and methods overview

Aims	Objectives	Methods
AIM1. Characterize the impact of gene dosage on connectivity for CNVs at eight genomic loci	1.1. Describe the effect of gene dosage at loci on global FC	*CWAS: Linear model contrasting CNV carriers with controls*
	1.2. Describe the relative effect of gene dosage at genomic loci on FC at the regional level.	*CWAS: Linear model contrasting CNV carriers with controls, adjusting models for mean connectivity*
AIM2. Test if FC-profiles of CNVs represent dimensions observed in idiopathic ASD, SZ, or ADHD.	2.1 Test similarities between whole-brain connectomes of CNVs and idiopathic psychiatric conditions	*Pearson correlation between beta maps obtained from each CWAS and individual connectomes of either IPCs cases or IPCs controls*
	2.2 Investigate regions that contribute to similarities with psychiatric conditions	*The same method used in 2.1 applied to each of the 64 regional FC patterns*
AIM3. General effect of haploinsufficiency on FC and latent component shared across CNVs and IPCs	3.1 Investigate the linear effect of scores of intolerance to LoF on FC for DEL and DUP	*Linear model testing the effect of pLI scores on FC in the CNVs carriers and non-carriers population*
	3.2 Identify the relationship between regions identified in 2.3 and clinical severity scores	*Correlation between similarity to pLI-FC-profile and IQ, ADOS, SRS measures of each individual*
	3.3 Identify latent components shared across CNVs and IPC	*Exploratory factor analysis across 15 FC-profiles (identified in 1.2)*

Table VII-1 Aims, objectives and methods overview

List of abbreviations

Copy number variants (**CNVs**) ; Single nucleotide variants (**SNVs**) ; Deletions (**DEL**); Duplications (**DUP**) ; Autism spectrum disorder (**ASD**) ; Schizophrenia (**SZ**) ; Attention deficit hyperactivity disorder (**ADHD**); Neuropsychiatric disorders (**NPs**); Idiopathic psychiatric conditions (**IPC**);

Functional Connectivity (**FC**) ; Diffusion-weighted imaging (**DWI**); Chromosomal microarray (**CMA**); Connectome Wide Association Study (**CWAS**).

Probability of being loss-of-function intolerant (**pLI**); Gene's intolerance to protein loss of function (**pLoF**); Variation of uncertain significance (**VUS**).

Full-scale intelligence quotient (**FSIQ**), Autism Diagnostic Observation Schedule (**ADOS**), Social Responsiveness Scale (**SRS**)

Cohorts

Montreal Brain Canada-dataset

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. 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 in 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, 5 other NP-CNVs carriers and intra familial 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 (189)). 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, 2 other CNVs carriers (NRXN1 deletion and 15q13.3 deletion) and extrafamilial controls (n=8) were included after the exclusion of 4 individuals due to quality control criteria.

Lausanne CHUV-dataset

CNV carriers were clinically ascertained. All the MRI scans have been performed at the CHUV using the same scanner (Prisma 3T) as the one used for Montreal cohort. The full scanning protocol is the same as the one used at Montreal: http://www.bic.mni.mcgill.ca/users/jlewis/BrainCanada/MCIN/

Three participants had a diagnosis for ASD. We excluded 6 subjects after quality controls. The final data include 16p11.2 deletion (n=4) carriers, 1q21.1 duplication (n=3) carriers (PI: A. Maillard, Project SNF, PMPDP3 171331).

SFARI SimonsVIP-dataset

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 (202) across 2 sites. We excluded 50 individuals from the analysis due to 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 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 (178). We excluded 25 individuals from the analysis due

to 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, 22q11.2 BPB-BPD (2 deletion and 3 duplication carriers) and extrafamilial controls (n=43).

UK BioBANK dataset

CNVs calling procedure

The UK Biobank genomics data were available for 21,820 individuals with MRI. The individuals DNA (blood samples) were genotyped using the Affymetrix Axiom Array with 805,426 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, that were 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 a parallel. The pipeline is compatible for Unix architectures and optimized for low resource computers. We implemented CNV calling procedures for PennCNV(372) and QuantiSNP (373). 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 (6). 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) (192). We annotated CNV within the 4 loci (1q21.1, 15q11.2, 16p11.2, 22q11.2 see table 1). 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 (180).

Final sample description

After standard quality control procedure and exclusion of 432 subjects, we were able to add to our sample: 2q13 deletion (n=36) and duplication (n=7) carriers, 16p11.2 deletion (n=4) and duplication (n=2) carriers, 1q21.1 deletion (n=9) and duplication (n=7) carriers, 1q21.1 TAR duplication carriers (n=18), 15q11.2 deletion (n=65), and duplication (n=70) carriers, 15q13.3 duplication (n=40) carriers, 22q11.2 BPB-BPD (n=7) duplication carriers, as well as other NP-CNVs for additional pLI analysis (n=54 carriers) and non-carriers (n=4245) from UK Biobank.

Idiopathic ASD dataset - ABIDE1

The ABIDE dataset (12) is an aggregate sample of different studies including imaging and behavioural data for individuals with an Autism Spectrum Disorder (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 in 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 459 male individuals, 225 individuals with ASD and 234 healthy controls, from 10 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 (361); https://openfmri.org (362)) 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,(217)) or the Scales for the assessment of positive/negative symptoms (SAPS/SANS,(363)). In order to allow for group analyses, SAPS/SANS scores were converted into PANSS scores using published regression-based equations(364).

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/ (203)). Data from seven sites were retained after the exclusion of 184 individuals. We included in our study a total of 763 subjects, 289 patients diagnosed with ADHD and 474 healthy controls.

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 (205). 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 (366) using the combined spatial transformations. Slow frequency drifts were modelled 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 (367). 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).

Details are provided here: https://github.com/claramoreau9/NeuropsychiatricCNVs_Connectivity

Quality Control

Preprocessed data were visually controlled for the quality of co-registration, head motion, and related artefacts by one rater. Not all datasets were examined by the same raters, yet all raters followed the same standardized quality-control procedure (368). If there was co-registration failure of either the functional image to individual T1 or individual T1 to MNI template registration, we attempted a manual fix by changing the parameters of the preprocessing pipeline. 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.

Psychiatric diagnoses and FSIQ

CNV	Status	n clin	FSIQ	ASD	ADHD	SZ
15q11.2	DEL	1	-	0	0	0
	DUP	1	89	0	0	0
1q21.1	DEL	9	97 (17)	2	2	0
	DUP	7	88 (29)	2	2	0
22q11.2	DEL	43	77 (14)	23	19	3
	DUP	11	96 (20)	4	5	0
16p11.2	DEL	37	87 (15)	7	7	0
	DUP	29	90 (21)	3	3	0
Additional CNVs		12	88 (19)	0	3	0
Idiopathic Psychiatric Conditions	**SZ**	242	-	-	-	242
	ASD	225	104 (17)	225	-	-
	ADHD	289	107 (14)	-	289	-

Table VII-2 Psychiatric diagnoses and FSIQ

Legend 2.1: 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; IPCs: Idiopathic Psychiatric Conditions; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity-Disorder.

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
15q13.3	DUP	0	0	1	1	0	0	0	0	0	0
2q13	DEL	1	0	0	0	3	0	0	0	0	0
	DUP	1	0	0	0	1	0	0	0	0	0
Controls	CON	69	6	1	97	44	2	0	1	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

Legend 2.2: Diagnosis information for the CNV carriers identified in the UK Biobank. More information about diagnostic code are available in UK Biobank website.

CNV	Status	n tot /clin	N Frames	Frames scrubbed	Motion
15q11.2	DEL	66 / 1	387	95.7	0.18 (0.06)
	DUP	71 / 1	383.7	103.1	0.18 (0.06)
15q13.3	DUP	40 / 0	414	72	0.18 (0.05)
2q13	DEL	36 / 0	390.2	96.9	0.18 (0.06)
	DUP	30 / 0	374.7	112.2	0.17 (0.05)
1q21.1	DEL	25 / 9	226.9	173.9	0.18 (0.06)
	DUP	16 / 7	241.2	129.3	0.2 (0.06)
	DUP-TAR	18 / 0	387.6	100.2	0.17 (0.05)
22q11.2	DEL	43 / 43	120	28.2	0.18 (0.07)
	DUP	19 / 11	208.2	83	0.18 (0.09)
16p11.2	DEL	41 / 37	162.6	85.8	0.22 (0.08)
	DUP	31 / 29	114.22	57.9	0.21 (0.09)
Additional CNVs		66 / 12	348.1	112.9	0.18 (0.06)
CNVs Controls		4427 / 0	355.6	123	0.19 (0.06)
Idiopathic Psychiatric Conditions	**SZ**	242 / 242	152.5	-	0.16 (0.06)
	ASD	225 / 225	139.3	45.7	0.18 (0.05)
	ADHD	289 / 289	160	-	0.15 (0.04)
IPCs Controls		950 / 0	159.5	29.6	0.15 (0.04)

Table VII-3 Motion after preprocessing

Legend: N Frames: mean number of frames remaining after scrubbing. Frames scrubbed: Mean number of frames excluded per individual; DEL: deletion; DUP: duplication; Chr: chromosome number; IPCs: Idiopathic Psychiatric Conditions; SZ: schizophrenia, ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity-Disorder n = tot /clin: total number of participants /number of participants clinically ascertained.

Supplementary Results

AIM 1

CNVs FC-profiles without adjusting for mean connectivity and sensitivity analyses

16p11.2 CNVs

The deletion was associated with a global increase in connectivity (z-scores = +0.16, p=0.03, Supplementary Tables 4-5), with 99 connections (94 positives, 5 negatives) surviving FDR correction (beta values ranging from -0.71 to 1.48 z-scores, Figure 1.d). Over-connectivity predominantly involved the putamen, the caudate and accumbens nuclei, the orbitofrontal cortex, the thalamus, and the left inferior parietal lobule. The duplication showed that a decrease in only 3 connections survived FDR involving the amygdala-hippocampus complex, and the caudate and accumbens nuclei (z-scores = -0.13, p=0.05, Supplementary Tables 4-5).

FC profiles obtained before adjustment for mC were correlated with our previous study (r=0.70, for 16p11.2 deletion, r=0.83, CI=[0.82; 0.84] for 16p11.2 duplication) (231). We performed a sensitivity analysis only including clinically ascertained 16p11.2 carriers (Montreal Brain Canada, Define Cardiff, Lausanne, and SVIP cohorts, supplementary Figure 1). FC-profiles were strongly correlated to our previously published findings (r=0.79, CI=[0.77; 0.8] for 16p11.2 deletion, r=0.87, CI=[0.86; 0.88] for 16p11.2 duplication) (231).

22q11.2 CNVs

The deletion was associated with a decrease in connectivity with 3 connections surviving FDR correction (Table 2, and Supplementary Tables 2-5), involving the perigenual anterior cingulate cortex, the caudate nucleus, the amygdala and hippocampus, and the accumbens nucleus. The FC profile obtained before mC was correlated with previously published results (231) r=0.86 (CI=[0.85; 0.87]). As all the deletion were provided by UCLA centre, we ran the CWAS analysis without any other control sites and found that 38 connections survived FDR (underconnectivity). This FC profile was highly correlated with our first paper (r=0.99).

The 22q11.2 duplication showed a global increase in FC of 0.27 z-scores (p=0.02, Supplementary table 5, Figure 1). We observed over-connectivity in 12 connections (FDR, $q < 0.05$), with beta values ranging from

-0.52 to 1.10 z-scores. Regions showing the strongest mean connectivity alterations included the lateral frontal pole, the posterior medial visual network, the orbitofrontal cortex, the vermis, and the right middle frontal gyrus (Supplementary Tables 4-5).

We performed a sensitivity analysis showing that FC-profiles using the full dataset and the FC-profiles excluding the non-clinically ascertained participants (UK Biobank scanning sites). This new FC-profile performed using UCLA, Brain Canada, and Define data, was highly correlated to previous findings (r=0.87, Supplementary Figure 1 (231)).

We performed an additional sensitivity analysis matching controls for scanning site, age, sex, and motion (n=246) 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]).

We investigated the effect of the 22q11.2 duplication [B-D]. As expected, we showed that FC profiles ([A-D], [B-D]) were not correlated (r=0.15). Regarding this weak correlation, we did not include the 22q11.2 CNVs with breakpoints starting by B to run the 22q11.2 CWAS and to obtain the 22q11.2 duplication FC-profile.

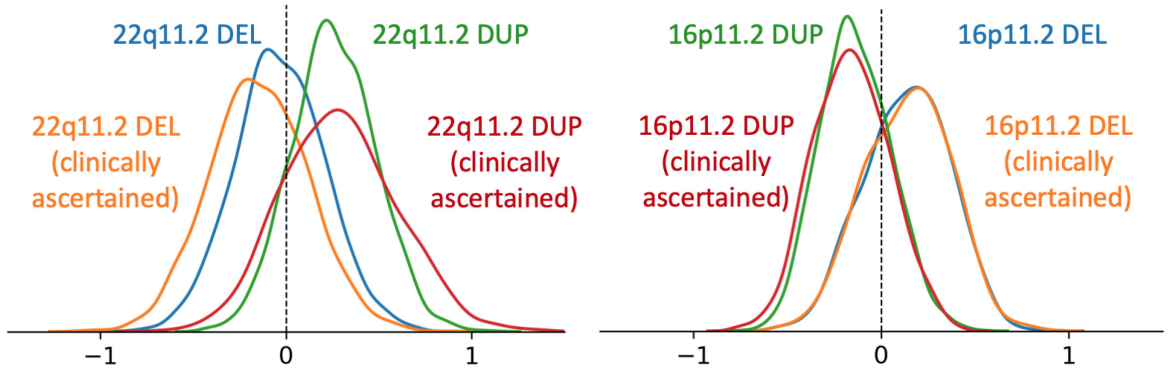

Figure VII-1 Clinically ascertained 16p11.2 and 22q11.2 CNVs carriers

Legend: Density plots represent the distribution of 2080 beta estimates for the CWAS (whole brain contrast of cases versus controls) for the 22q11.2 CNVs (left) and 16p11.2 CNVs (right) groups, using all the available subjects (blue and green, for deletion and duplication respectively) or only the clinically ascertained CNVs carriers (orange and red).

1q21.1 CNVs

The 1q21.1 deletion carriers showed a mean reduction in connectivity with 1 connection surviving FDR correction between the dorsal precuneus and dorsal visual stream regions (Supplementary Table 5). The 1q21.1 duplication showed a global increase in FC of 0.51 z-scores ($p=3x10^{-4}$) with 804 connections surviving FDR correction (beta values ranging from -0.7 to 1.5 z-scores, Supplementary Table 5). Only 2 connections exhibited underconnectivity. Overconnectivity predominantly involved the caudate nucleus, the putamen, the thalamus, and the medial somatomotor network, as well as the left inferior frontal sulcus.

Sensitivity analyses showed that FC-profiles obtained using all sites and only those including clinically ascertained carriers were correlated (r=0.75 for deletion, and r=0,78 for duplication, supplementary Figure 2).

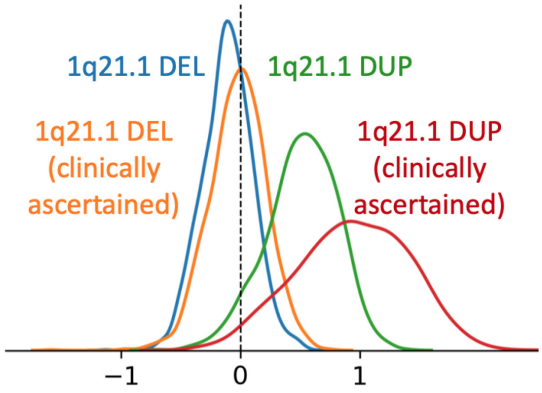

Figure VII-2 Clinically ascertained 1q21.1 CNVs carriers

Legend. Density plots represent the distribution of 2080 beta estimates for the CWAS (whole brain contrast of cases versus controls) for 1q21.1 CNVs, using all the available subjects (blue and green, for deletion and duplication respectively) or only the clinically ascertained CNVs carriers (orange and red).

2q13 CNVs

The 2q13 duplication showed a decrease in FC of 0.25 z-scores (p=0.003, beta values ranging from -0.8, 0.23) when compared with control subjects (Figure 1b). We observed under-connectivity in 12 connections (FDR, $q < 0.05$) involving the medial somatomotor network, the left inferior parietal lobule, the anterior middle frontal gyrus, and the orbitofrontal cortex (Supplementary Table 5). 2q13 deletions did not significantly affect the connectivity.

15q11.2 CNVs

The 15q11.2 deletion was associated with a decrease in mean connectivity (z-scores = -0.13, p=0.03), with 51 connections surviving FDR correction (beta values ranging from -0.52 to 0.36 z-scores, Figure 1c). Underconnectivity predominantly involved the lateral DMN, the visual, and frontoparietal networks. Regions showing the strongest mean connectivity alterations included orbitofrontal cortex, the anterior middle temporal gyrus and dorsomedial prefrontal cortex (Supplementary Table 5).

The 15q11.2 duplication showed a global decrease in FC of 0.16 z-scores (p=0.006) when compared with control subjects. We observed under-connectivity in 235 connections (FDR, $q < 0.05$), with beta values ranging from -0.6 to 0.21 z-scores. Under-connectivity predominantly involved the orbitofrontal cortex, the inferior temporal gyrus, the frontal eye field, the postcentral sulcus, and the temporal pole (Supplementary Table 5).

Summary of CWAS results

Loci / ∑ pLI	CNV	n pos	n neg	min-max	var	n pos	n neg	min-max	var
		not mean connectivity adjusted				*mean connectivity adjusted*			
1q21.1 *1.7*	DEL	0	1	[-1.1; 0.6]	0.04	0	3	[-1; 0.7]	0.04
	DUP	804	2	[-0.7; 1.5]	0.09	9	4	[-1; 1]	0.08
TAR (*3.4*)	DUP	0	0	/	0.04	0	0	/	0.04
2q13 *0*	DEL	0	0	/	0.02	0	0	/	0.02
	DUP	0	12	[-0.8; 0.2]	0.02	0	0	/	0.02
15q11.2 *1.7*	DEL	0	51	[-0.5; 0.4]	0.02	1	0	[-0.4; 0.5]	0.02
	DUP	0	235	[-0.6; 0.2]	0.02	11	16	[-0.5; 0.4]	0.02
15q13.3 *(1.6)*	DUP	0	0	/	0.02	0	0	/	0.02
16p11.2 *7.06*	DEL	94	5	[-0.7; 1.5]]	0.06	76	84	[-0.9; 1.4]	0.06
	DUP	0	3	[-1.0; 0.6]	0.04	1	3	[-0.9; 0,7]	0.04
22q11.2 *10.5*	DEL	0	3	[-1; 0.7]	0.06	25	21	[-0.9; 0.8]	0.06
	DUP	12	0	[-0.5; 1.1]	0.05	0	0	[-0.7;0.8]	0.05
ADHD		0	0	[-0.2; 0.3]	0.0	0	0	/	0.01
ASD		2	79	[-0.4; 0.3]	0.01	21	9	[-0.3; 0.4]	0.01
Schizophrenia		17	1181	[-0.7; 0.4]	0.03	203	233	[-0.4; 0.6]	0.02

Table VII-4 Summary table of Connectome Wide Association Studies results

Legend: The number of connections surviving FDR for each connectome wide association study with and without adjusting for mean connectivity (right and left side respectively). ∑ pLI: sum of pLI of all genes encompassed in CNVs. pLI: the probability of being loss of function intolerant. DEL: deletion; DUP: duplication; ASD: autism spectrum disorder; SZ: schizophrenia; ADHD: attention deficit hyperactivity disorder.

Table VII-5 CWAS results without adjusting for mean connectivit

See external excel file Supplementary_Table_paper2_S5.xlsx.

Legend: Number of connections surviving FDR for each of the 13 connectome wide association studies (one per spreadsheet) without adjusting for mean connectivity (aim1.1) (*n_connections_affected*), and percentage of altered connections (FDR corrected) per region (*percent_discovery*).

Table VII-6 CWAS results after mean connectivity adjustment

See external excel file Supplementary_Table_paper2_S6.xlsx.

Legend: Number of connections surviving FDR for each of the 11 connectome wide association studies (one per spreadsheet) adjusting for mean connectivity (aim1.2) (*n_connections_affected*), and percentage of altered connections (FDR corrected) per region (*percent_discovery*)

AIM 2

Spatial regional similarities between CNVs connectivity-profiles and individuals with IPC compared to controls

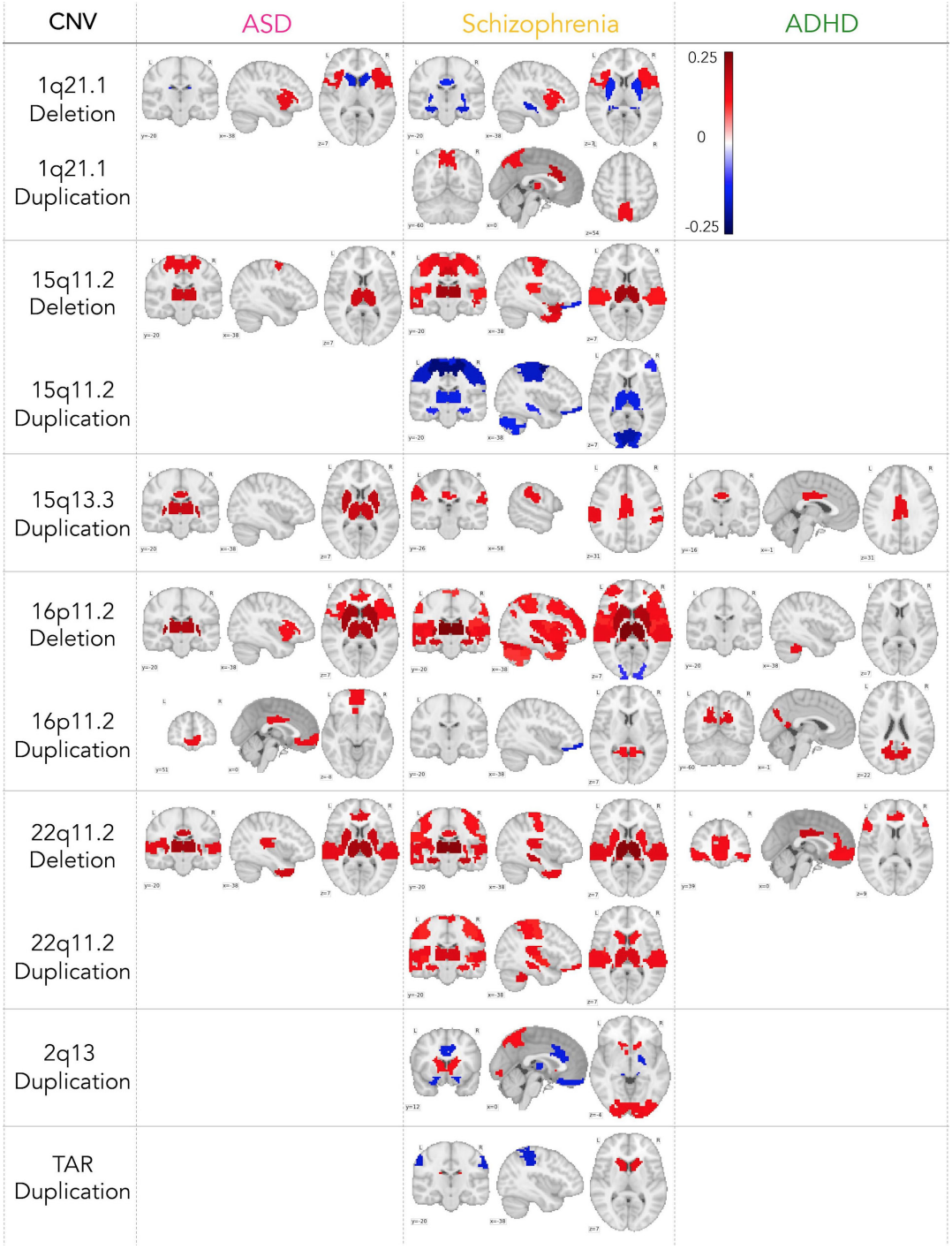

Figure VII-3 Spatial regional similarities between CNVs connectivity-profiles and individuals with IPC compared to controls

Legend: The whole-brain connectivity-profiles of CNVs were decomposed into 64 seed-based regions and compared to the individual connectivity-profiles of subjects with a psychiatric diagnosis, and their respective controls.

We compared (Mann-Whitney) 1] the spatial similarity between CNV connectivity-profiles and individuals with IPCs, and 2] the spatial similarity between CNV connectivity-profile and controls.

The color scale is the effect size (rank biserial correlation provided by Mann-Whitney test) of the spatial similarity for each region.

Positive (red) reflects higher similarity between CNV connectivity-profiles and individuals with IPC, while negative (blue) reflects higher similarity with controls. All the values (rank biserial correlation, qval, pval) are available in the Supplementary Table 7 (21 spreadsheets for the 21 brain maps with significant similarities between CNVs and idiopathic psychiatric conditions).

Table VII-7 CNV regional similarity to IPC and controls

See external excel file Supplementary_Table_paper2_S7.xlsx

Legend: The effect size (rank biserial correlation provided by a Mann-Whitney test) of the spatial similarity between the regional CNV-connectivity-profiles and individuals with IPC are detailed for all CNVs and idiopathic conditions (aim 2.b and Figure 3b). Positive value reflects higher similarity between CNV connectivity-profiles and individuals with IPC, while negative value reflects higher similarity with controls. q-values are FDR adjusted and p-values are non-adjusted. (21 spreadsheets for the 21 brain maps displayed in Supplementary Figure 3, with significant similarities between CNVs and idiopathic psychiatric conditions).

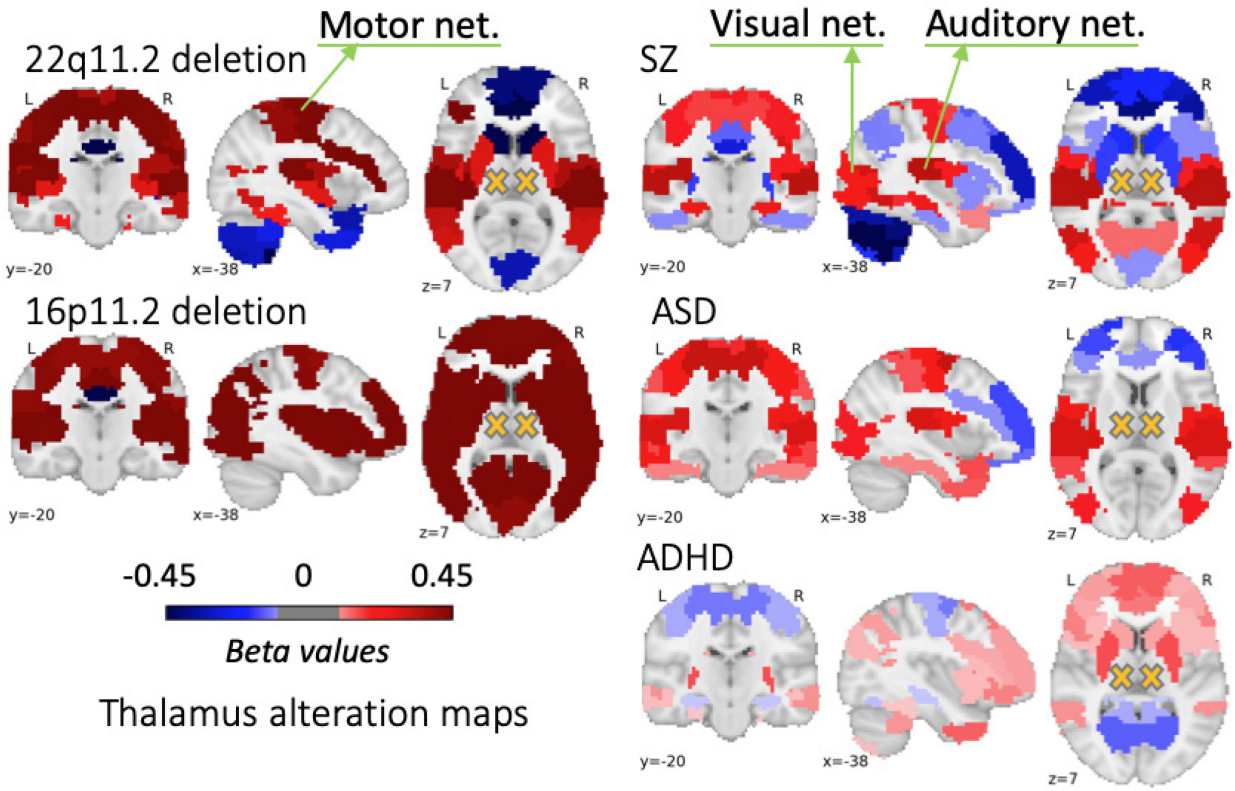

Figure VII-4 Brain maps from the seven CWAS performed in paper#1 representing beta values of the thalamus seed region.

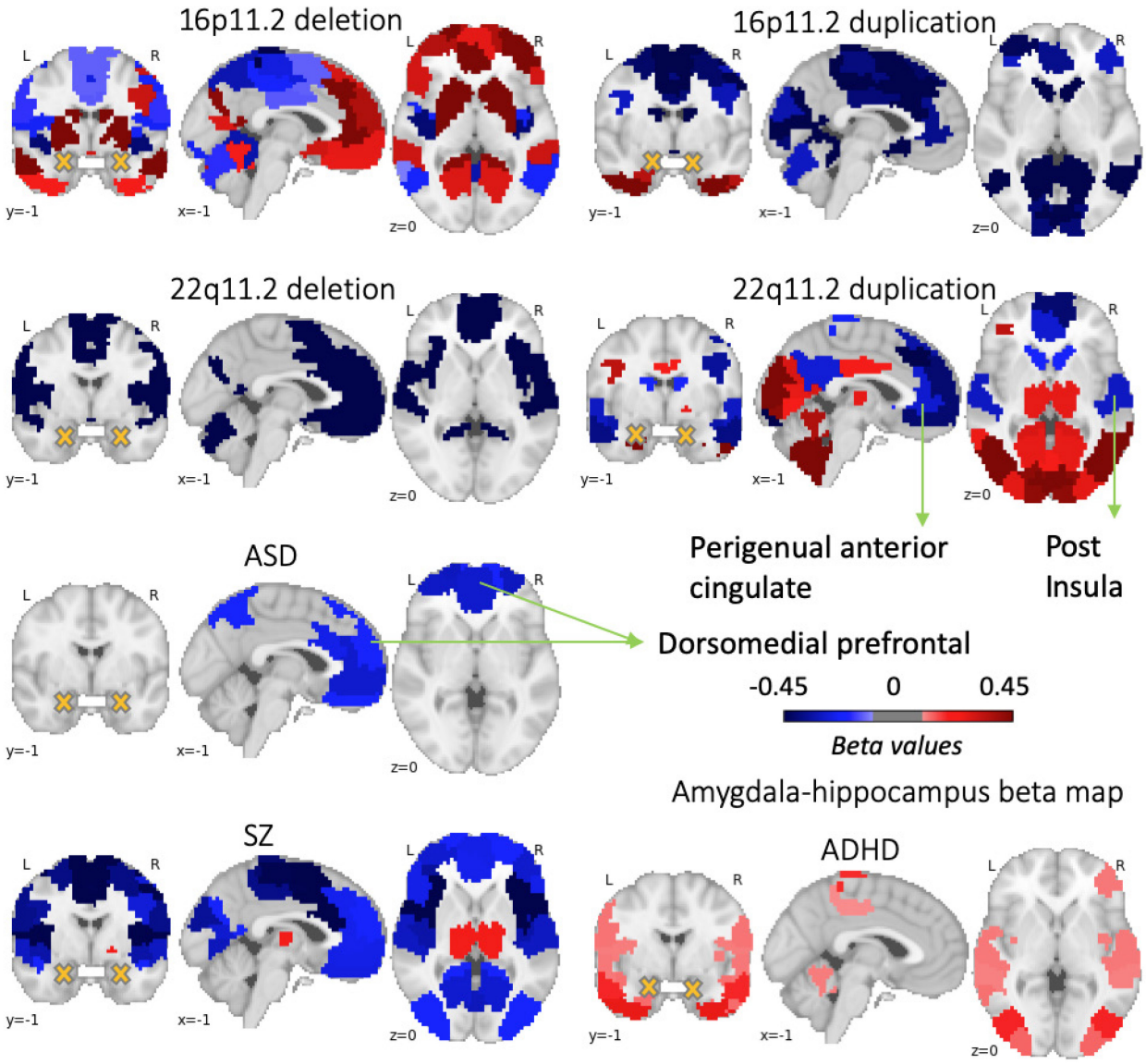

Figure VII-5 Brain maps from the seven CWAS performed in paper#1 representing beta values of the amygdala-hippocampus seed region

AIM 3

Relative regional connectivity in idiopathic psychiatric conditions

Autism spectrum disorder CWAS showed 30 altered connections after mC-adjustment (21 positives, 9 negatives, FDR, $q < 0.05$) with beta values ranging from -0.34 to 0.44 z-scores (Supplementary Table 6, Figure 1.p) mostly driven by the thalamus, the temporal pole, the posterior cingulate cortex, the precuneus, the anterior middle temporal gyrus, and the medial somatomotor network.

SZ CWAS showed 203 and 233 altered connections after mC-adjustment (positives and negatives respectively, FDR, $q < 0.05$) with beta values ranging from -0.44 to 0.057 z-scores (Supplementary Table 6, Figure 1.p) mostly driven by the somatomotor network, the dorsal anterior cingulate, the ventral posterior insula, and the thalamus.

No connection survived in ADHD CWAS after mC-adjustment (Supplementary Table 6, Figure 1.p).

Sensitivity analyses excluding female participants in IPC and controls

A sensitivity analysis was performed on 179 male participants with SZ and 665 male controls. The beta map of this new CWAS analysis excluding females was highly correlated ($r= 0.95$) with the initial CWAS performed on the full sample. The same analysis was performed in the ADHD sample (n=226 male participants with ADHD, n=665 IPC controls without female). The beta map of the analysis excluding females was as well correlated ($r= 0.80$) with the initial CWAS performed on the full ADHD sample.

Sensitivity analyses excluding ASD and ADHD participants with medication

A sensitivity analysis was performed on 122 participants with ASD and the respective 180 controls excluding subject with medication at the MRI scan time and subject without information about pharmacological treatment. The beta map of this new CWAS analysis was correlated ($r= 0.81$) with the initial CWAS performed on the full sample including subjects with medication. The same analysis was performed for ADHD using “Medication naive versus Not medication naive” information provided by the ADHD-200 consortium the same result (no connection survived FDR). We did not have individual medication information for the SZ cohorts.

Haploinsufficiency regional similarity to severity scores

Table VII-8 Haploinsufficiency regional similarity to severity scores

See external excel file Supplementary_Table_paper2_S8.xlsx.

Legend: Pearson r computed between the 64 regions of the haploinsufficiency connectivity-profile and the regional profiles of individuals based on their cognitive and behavioural measures (aim 3.2). Corresponding p values and q values are provided per region for Full-Scale Intelligence Quotient (FSIQ) in the first spreadsheet, Autism Diagnostic Observation Schedule (ADOS) in the second spreadsheet, and Social Responsiveness Scale (SRS) in the third one.

Exploratory Factor Analysis

The first LC grouped mild effect size CNVs and ASD. Top contributing regions were the inferior temporal gyrus, the temporal pole, the cerebellum crus-1, the thalamus and the ventromedial prefrontal cortex. The second LC grouped SZ and 16p11.2 CNV. Contributing regions included the medial and dorsolateral motor network, the thalamus, the dorsal anterior cingulate cortex, the cerebellum crus-1, the superior parietal lobule and the dorsal posterior insula.

The third LC showed high factor loadings for the 22q11.2 deletion. Contributing regions included the anterior cingulate cortex, the thalamus, the lateral and medial posterior visual network, the ventromedial prefrontal cortex, the temporal pole, and the caudate nucleus. LC3 also showed a high spatial similarity with the connectivity-profile of pLI across deletions (r=0.57).

Exploratory Factor Analysis regional loading scores

Table VII-9 Exploratory Factor Analysis regional loading scores

See external excel file Supplementary_Table_paper2_S9.xlsx.

Legend: Exploratory Factor Analysis across 15 connectivity profiles (12 CNVs and 3 idiopathic psychiatric conditions). We reported regional loading scores (n=64 regions) for each of the 3 latent components.

MIST functional parcellation labels

Table VII-10 MIST functional parcellation labels

See external excel file Supplementary_Table_paper2_S10.xlsx.

Legend: Multi-resolution parcellation of functional networks (28). We report the full names of the 64 functional regions ('ROI_full_name_64') encompassed in twelve functional networks ('Networks_12'). Visualisation and more details about parcellations are available through this interactive dashboard https://simexp.github.io/multiscale_dashboard/index.html