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Dissecting autism and schizophrenia through neuroimaging genomics

Clara A. Moreau,1,2,3 Armin Raznahan,4 Pierre Bellec,2 Mallar Chakravarty,5 Paul M. Thompson6,† and Sebastien Jacquemont1,†

These authors contributed equally to this work.

Neuroimaging genomic studies of autism spectrum disorder and schizophrenia have mainly adopted a ‘top-down’ approach, beginning with the behavioural diagnosis, and moving down to intermediate brain phenotypes and underlying genetic factors. Advances in imaging and genomics have been successfully applied to increasingly large case-control studies. As opposed to diagnostic-first approaches, the bottom-up strategy begins at the level of molecular factors enabling the study of mechanisms related to biological risk, irrespective of diagnoses or clinical manifestations. The latter strategy has emerged from questions raised by top-down studies: why are mutations and brain phenotypes over-represented in individuals with a psychiatric diagnosis? Are they related to core symptoms of the disease or to comorbidities? Why are mutations and brain phenotypes associated with several psychiatric diagnoses? Do they impact a single dimension contributing to all diagnoses?

In this review, we aimed at summarizing imaging genomic findings in autism and schizophrenia as well as neuropsychiatric variants associated with these conditions.

Top-down studies of autism and schizophrenia identified patterns of neuroimaging alterations with small effect sizes and an extreme polygenic architecture. Genomic variants and neuroimaging patterns are shared across diagnostic categories suggesting pleiotropic mechanisms at the molecular and brain network levels. Although the field is gaining traction; characterizing increasingly reproducible results, it is unlikely that top-down approaches alone will be able to disentangle mechanisms involved in autism or schizophrenia.

In stark contrast with top-down approaches, bottom-up studies showed that the effect-sizes of high-risk neuropsychiatric mutations are equally large for neuroimaging and behavioural traits. Low specificity has been perplexing with studies showing that broad classes of genomic variants affect a similar range of behavioural and cognitive dimensions, which may be consistent with the highly polygenic architecture of psychiatric conditions.

The surprisingly discordant effect sizes observed between genetic and diagnostic first approaches underscore the necessity to decompose the heterogeneity hindering case-control studies in idiopathic conditions. We propose a systematic investigation across a broad spectrum of neuropsychiatric variants to identify putative latent dimensions underlying idiopathic conditions. Gene expression data on temporal, spatial and cell type organization in the brain have considerable potential for parsing the mechanisms contributing to these dimensions’ phenotypes. While large neuroimaging genomic datasets are now available in unselected populations, there is an urgent need for data on individuals with a range of psychiatric symptoms and high-risk genomic variants. Such efforts together with more standardized methods will improve mechanistically informed predictive modelling for diagnosis and clinical outcomes.

1 Sainte Justine Research Center, University of Montréal, Montréal, Québec H3T 1C5, Canada
2 Centre de Recherche de l’Institut Universitaire de Gériatrie de Montréal, Montreal, Québec H3W 1W5, Canada
3 Human Genetics and Cognitive Functions, CNRS UMR 3571, Université de Paris, Institut Pasteur, Paris, France
4 Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health Intramural Research Program, Bethesda, MD 20892, USA

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Introduction: clinical diversity in autism and schizophrenia

Evolving boundaries

The nature and definition of autism spectrum disorder (ASD) and schizophrenia have been highly debated for decades. Classifications evolved over time, merging and splitting clinical manifestations. The broadening of diagnostic criteria together with improved clinical awareness has resulted in an increase of ASD prevalence in the past decades, reaching estimates of 1 in 59.1 In contrast, the schizophrenia population prevalence of ~1% has remained relatively stable.2 Clinical diversity in schizophrenia was already reported by Bleuler, who described schizophrenia as a ‘group of schizophrenias(s)’ suggesting that this was a disorder with many possible clinical manifestations. Autism was introduced as a term in 1911 as one of four ‘types of impairment in SZ with affectivity, association, and ambivalence’.3 Autism was later described by Kanner4 and Asperger,5 to refer to a dimension of schizoid disorders. By the 1970s, researchers had clearly defined autism and childhood schizophrenia as separate conditions.6

The introduction of positive and negative symptoms in the 1980s helped to delineate subgroups of schizophrenia-like manifestations and therefore subgroups of patients. Negative symptoms in schizophrenia (such as social avoidance and emotional flatness) are also partially found in autism where they may be referred to as impairments in communication and motivation.7 Patients with either ASD or schizophrenia present difficulties in interpreting social cues associated with eye gaze, as well as deficits in theory of mind tasks.8 Schizophrenia is now defined as a severe mental illness involving disordered thought and perception, with a characteristic onset in late adolescence or early adulthood.9

To help distinguish both conditions, a ‘trumping rule’ accompanied autism in the DSM-III: autism should not be diagnosed in the presence of delusions, hallucinations, and incoherence. Today (DSM-V), spectrum terminology in ASD unifies three previously separate (DSM-IV) diagnoses: autistic’s disorder, Asperger’s disorder, and pervasive developmental disorder—not otherwise specified (PDD-NOS). Childhood-onset schizophrenia is now a recognized subtype of schizophrenia, defined by an onset before the age of 13 years. Approximately 30% of children and adolescents with childhood-onset schizophrenia also have ASD.10,11

It has been suggested that ASD and schizophrenia are extreme representations of symptomatic dimensions that extend into the normal range.13,14 but these putative dimensions have not yet been identified. Measures of autistic-like traits have been developed (e.g. the Social Responsiveness Scale) to examine subthreshold autistic features in other psychiatric conditions (such as schizophrenia) and non-psychiatric populations.15 Measures of social communication performed in the general population are genetically correlated with both ASD (during middle childhood) and schizophrenia (later adolescence).16 These approaches are in line with dimensional models such as the National Institute of Mental Health’s Research Domain Criteria Project (RDoC).17

Comorbidities are major pitfalls in top-down studies

Psychiatric comorbidities, which are common in neuropsychiatric disorders, present major caveats for any diagnosis-first studies. When a major diagnosis is assigned to an individual, it will guide treatment and enrolment in future research projects, often ignoring comorbidities. Neuroimaging and genetics findings may relate to core features of the diagnosis of interest or the spectrum of accompanying comorbidities.

Indeed, over a third of patients with ASD meet criteria for other conditions such as obsessive-compulsive disorder (OCD), anxiety, mood disorders, intellectual disability, attention deficit hyperactivity disorder (ADHD), or epilepsy.17,18 Although 15–25% of youth with ADHD meet the criteria for ASD, and 50–70% of those with ASD present comorbid ADHD,19 diagnostic criteria for ADHD and ASD did not allow their simultaneous diagnosis until the latest revision of the DSM-V.20 Intellectual disability, classified as an ASD specifier in the DSM-V, is likewise observed in ~35% of individuals with ASD and can confound diagnostic instruments.21,22 A study of comorbidity within mental disorders in 5.9 million Danish individuals showed that a prior diagnosis of schizophrenia increased the risk of additional developmental disorders (including autism and intellectual disability, hazard ratio > 15), substance use, as well as personality and behavioural disorders (hazard ratio > 10).23 A prior diagnosis of developmental disorders increased the risk for intellectual disability (hazard ratio = 50), organic and behavioural disorders (hazard ratio > 15), and schizophrenia (hazard ratio = 8).

Comorbidities are also sex-dependent.24 For example, adult females with ASD are more likely to be diagnosed with comorbid OCD, mood, or eating disorders, rather than ASD, thereby underestimating the rate of ASD in young females.

Lessons learned from top-down studies

Reproducible neuroimaging findings in autism spectrum disorder and schizophrenia are limited

The most consistent structural MRI finding in ASD is, on average, a higher total brain volume (Fig. 1). This is mainly reported before 24 months.33,38,46,47 but is also observed in older individuals with autism (+ 0.25 Cohen’s d).39 Although debated,48 lower volumes of the cerebellum and corpus callosum and increased CSF volume were also recurrently reported in ASD compared to controls.38,49
Inconsistent findings have been reported for the hippocampus, amygdala, thalamus and basal ganglia. Such heterogeneity and small effect sizes (Cohen’s d < 0.3; Fig. 2) underscore the necessity for large samples allowing subtyping strategies.

To improve reproducibility, the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium increased sample size by aggregating data from 49 scanning sites. This effort identified smaller volumes of the pallidum, putamen, amygdala, and nucleus accumbens with small effect sizes (0.13 Cohen’s d). Cortical thickness was higher in the frontal cortex and smaller in the temporal cortex (0.21 Cohen’s d). Subsequent studies of cortical morphometry in ASD reported higher mean cortical thickness (Cohen’s d = 0.22) compared to controls, in particular in the inferior frontal and prefrontal cortex, in the superior temporal, postcentral and posterior cingulate gyri, and the precuneus (Cohen’s d < 0.32). Superior temporal gyrus and inferior frontal sulcus cortical thickness were negatively correlated with age and full-scale intelligence quotient (FSIQ) in the ASD group. These two large studies provided convergent results, but authors also noted inconsistencies (cortical thickness decreases in the ENIGMA study), which in part have been reconciled by adjusting the stringency of quality checking (e.g. motion) across both studies.

Asymmetry in ASD has also been under scrutiny. An ENIGMA study of 54 datasets reported cortical asymmetry involving mainly the superior frontal gyrus (Cohen’s d = 0.13), the medial frontal, orbitofrontal, inferior temporal, and cingulate regions, that were reduced in ASD compared to controls.

Likewise, functional connectivity has been investigated in ASD. Resting-state functional MRI is particularly appropriate to study psychiatric paediatric population because it enables data acquisition on functional connectivity without patient participation (contrary to task-based functional MRI) and limits excessive motion during scanning. Several analytical methods applied to a large aggregate dataset showed a widespread decrease of connectivity in ASD compared to controls across all datasets. Underconnectivity was predominantly observed in the default mode network (DMN; Fig. 3 and Table 1), the salience, the visual, and the auditory networks. Thalamocortical overconnectivity (in particular, between the thalamus and the sensorimotor network) is also a finding replicated in most studies. Many other findings are inconsistent across sites and may reflect differences in ascertainment and mechanistic heterogeneity in ASD. These include reduced long-range connectivity, increased short-range connectivity, and decreased homotopic connectivity. Furthermore, functional connectivity is a field that lacks standardization and many analytical strategies are used by different groups (e.g. whether to perform global signal regression is an ongoing debate in the field and creates discrepancies across publications).

As an example, the largest resting-state functional MRI study in ASD identified four datasets reproducible patterns of underconnectivity within sensorimotor networks and overconnectivity within the frontoparietal networks (Fig. 3 and Table 1) across datasets (0.2–0.6 Cohen’s d). However, these results were not found by previous studies, likely due to different analytical strategies. The ‘gradient’ analysis of human functional networks provides an additional coordinate system. It has been studied in the general population, and more recently in ASD. In normative/typically developing studies, this framework identifies a smooth transition along a gradient from unimodal areas of function (sensory, auditory, motor, visual) to higher-order transmodal areas (e.g. DMN). Studies showed that both extremes of the rostrocaudal gradient were decreased in ASD. Further analyses revealed cortical surface area decreases in ASD specifically within transmodal medial prefrontal and posterior cingulate regions. Results have been less conflicted in schizophrenia. Although both conditions are associated with small effects, those detected in...
schizophrenia are typically 2–3-fold larger than in ASD (Fig. 2). This difference, which is puzzling as ASD and schizophrenia have similar severities and prevalence, may suggest a lower level of neuroanatomical heterogeneity in schizophrenia compared to autism. A large meta-analysis reported a global grey matter reduction that was mainly driven by the dorsomedial and orbitofrontal cortex, as well as the medial temporal, insula, thalamic, and striatal area.31 The ENIGMA consortium (2028 schizophrenia and 2540 controls) reported smaller hippocampus (Cohen’s $d = –0.46$), amygdala (Cohen’s $d = –0.31$), thalamus (Cohen’s $d = –0.31$), nucleus accumbens (Cohen’s $d = –0.25$), and larger pallidum (Cohen’s $d = 0.21$) and lateral ventricle volumes (Cohen’s $d = 0.37$).34 A follow-up study (4474 schizophrenia and 5098 controls) examined cortical thickness and surface area35 showing a decrease in the total surface area driven by frontal and temporal lobe regions (Cohen’s $d = –0.25$). A widespread decrease in cortical thickness (Cohen’s $d = –0.52$) was also reported. Adjusting for mean cortical thickness showed thinner cortex in fusiform, parahippocampal, and inferior temporal gyri, and thicker cortex in the precuneus, and superior parietal cortex (Cohen’s $d = 0.25$). CT differences were greater in the group of individuals treated with antipsychotic medication and were correlated with illness duration.35 Of note, treatment may play a larger role in neuroimaging studies in schizophrenia compared to ASD due to the lower frequency of medication in the latter group.

Functional imaging studies in schizophrenia show reduced mean connectivity but in the absence of large functional MRI datasets in schizophrenia, results should be interpreted with caution.32,67 This is predominantly observed within the DMN, ventral attention, frontoparietal, and somatomotor networks (Fig. 3 and Table 1).68 In contrast, the thalamus has been reported as overconnected with the somatomotor network and the middle temporal gyrus (correlated with positive symptoms) and underconnected with cerebellar regions (correlated with delusions and bizarre behaviour).37,69 Cerebellar (Crus-I, lobule IX and lobule X) overconnectivity has been also reported with the salience and sensorimotor networks.42 An ongoing debate is whether to consider resting-state as a collection of individual states that may be captured using dynamic connectivity. Studies showed that functional networks are dominated by contributions from common organizational principles and conjunction of individual features.70 Therefore, disease-related effects that are state-dependent might appear as highly heterogeneous because of limited temporal sampling.

Earlier top-down studies were vastly underpowered to report effects in ASD and schizophrenia (e.g. analyses of the corpus callosum volume in ASD48), but larger studies are now yielding more reproducible findings. Small effect sizes reported in both schizophrenia and ASD might be an indicator of significant heterogeneity (Fig. 2). Several factors such as medication exposure (e.g. antipsychotic medications might modulate the functional MRI signal31,32) and the stage of the disease could confound these findings. There are likely subgroups associated with different patterns of brain alterations, possibly cancelling each other out in idiopathic cohorts. Examples of such effects are 16p11.2 deletions and duplications that equally increase autism risk but are associated with mirror effects on neuroimaging traits such as the insula volume.73 The subgroups and dimensions nested within conditions have however remained elusive. Furthermore, many of the alterations described above have been observed across several psychiatric conditions and CNVs. Distributions of Cohen’s $d$ are represented for case-control studies in ASD, schizophrenia (SZ), ADHD and CNVs using three modalities: cortical thickness (A, D and G, from Park et al.50 and Modenato et al.51); surface area (B, E and H, from Moreau et al.44 and Modenato et al.51) and Functional connectivity (C, F and I, from Moreau et al.44,52). The same Cohen’s $d$ distributions are presented for two large (22q11.2 and 16p11.2), one moderate (1q21.1) and one small effect size (15q11.2) deletion and duplication (D–I) from Modenato et al.31 and Moreau et al.52 For cortical thickness, surface area, and functional connectivity, CNVs show a much larger effect size at the global (mean shift) and regional level (spread of the Cohen’s $d$ distribution) compared with psychiatric conditions.
Neuroimaging and genomic dimensions across diagnostic boundaries

Neuroimaging traits and genetic factors specific to a psychiatric diagnosis have yet to be identified. The field has, however, progressed in characterizing neural substrates and genomic variants common across disorders.

In one of the first large transdiagnostic efforts, anterior cingulate area and anterior insula were among the top regions to demonstrate shared anatomical alterations across schizophrenia, bipolar disorder, major depression, addiction, OCD, and anxiety.16,45 Shared alterations were the highest between psychotic disorders and minimum with anxiety and OCD. A neuroanatomical investigation of ASD, schizophrenia identified five single nucleotide polymorphisms (SNPs)25 and 145 SNPs, respectively. However, predictive models suggest that as sample sizes increase, the rate of future common variant discoveries for ASD will be between those for schizophrenia and major depression.93

Figure 3 Correspondence between brain regions and functional networks. What constitutes a core functional network is not clear, and no universal taxonomy has been adopted yet.57 Networks have been defined at several levels of resolution including the commonly used 7-network parcellation (top right) compared to the 12-network MIST parcellation (bottom right) (https://simexp.github.io/multiscale_dash board/index.html). See also Table 1.

The polygenic architecture of autism spectrum disorder and schizophrenia

Twin studies estimate the genetic contribution to ASD and schizophrenia around 73–93% and 79%, respectively.74–76 Heritability estimates are, however, based on models [phenotype (P) = G(genetic) + E(environment)] that do not take into account the interaction between G and E. These estimated values may, therefore, be inflated by mechanisms such as assortative mating or dynamic effects.77

Most of the genetic contribution is due to common variants. Although the contribution of rare mutations to the total population liability is modest (5%), they contribute substantially to individual risk78 and occur mostly de novo. They are identified in 20% of individuals with ASD,79,80 and have important implications for carriers. Among these rare variants, copy number variants (CNVs) are routinely screened in the clinic using chromosomal microarray analysis. Sixteen recurrent CNVs have been associated with ASD (Fig. 1).30,81 However, studies of non-recurrent CNVs estimate that any 1 megabase deletion or duplication including coding elements increases autism risk (albeit mildly) with a mean odds ratio (OR) of 1.6 and 1.2, respectively.82

Large effect size CNVs, such as the 16p11.2 deletion, are identified in 7–14% of patients with ASD.21,83 Rare large effect-size SNVs are identified in 13–15% of individuals with ASD.83 Exome sequencing studies have identified 102 genes conferring high risk for ASD, intellectual disability, and related neurodevelopmental conditions.84,85 These large risk ASD genes were enriched in the genome-wide association study (GWAS) signal of schizophrenia and educational attainment, as well as gene ontology terms including gene neuronal regulation and neuronal communication.85

For schizophrenia, large risk variants have been harder to identify in comparison with ASD.86 Early candidate gene studies identified rare putative large risk schizophrenia genes (e.g. COMT, DISC1, D7NB1, and NRG1), but they were not subsequently replicated.87 Burden analyses show that de novo variants distributed across many coding genes are over-represented in schizophrenia.88 However, few genes have been robustly identified as large effect-size risk factors for schizophrenia (i.e. SETD1A, NRXN1).89,90 Eight CNVs have been formally associated with schizophrenia with OR ranging from 2 to 309,91 and eight additional CNVs met criteria for suggestive association (Fig. 1).27,92 However, burden analyses have demonstrated that many more CNVs increase risk for schizophrenia.77

The common-allele model posits that the psychiatric condition results from the cumulative effect of multiple common alleles with small effects. The yield of GWAS studies has significantly increased with sample size. The latest studies in ASD and schizophrenia identified five single nucleotide polymorphisms (SNPs)25 and 145 SNPs, respectively. However, predictive models suggest that as sample sizes increase, the rate of future common variant discoveries for ASD will be between those for schizophrenia and major depression.93

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observed for neurological conditions. A recent study along general dimensions.

ning diagnoses. Genes expressed in the brain from the second trimester. Modelling association with two or more conditions and 23 with four or more anorexia nervosa, OCD, and Tourette syndrome, 109 (75%) showed ASD, ADHD, schizophrenia, bipolar disorder, major depression, shared alterations in network connectivity predominantly in the ventral salience and the frontoparietal networks, and the DMN. An underconnectivity pattern was identified between the DMN and the ventral salience network and between the frontoparietal and the salience networks. An overconnectivity pattern was found between the DMN and frontoparietal network and between the DMN and salience network.

Overall, these studies suggest that neuropsychiatric disorders may be related to similar hubs of vulnerability including the anterior cingulate cortex, the DMN, the frontoparietal network (especially prefrontal regions), and the insular cortex. Although these findings should be interpreted with caution, recurrent involvement of these brain areas could be due to their complex functions such as social cognition and executive functions, in line with the RDoC and p-factor. Neuroimaging dimensional reduction such as the gradient approach may help position psychiatric conditions along general dimensions.

Genetic correlations between psychiatric conditions are well-replicated findings and are much higher than what has been observed for neurological conditions. A recent study showed that among 146 genome-wide significant SNPs reported in ASD, ADHD, schizophrenia, bipolar disorder, major depression, anorexia nervosa, OCD, and Tourette syndrome, 109 (75%) showed association with two or more conditions and 23 with four or more neuropsychiatric disorders. These 23 SNPs were located within genes expressed in the brain from the second trimester. Modelling the joint genetic architecture of these eight conditions identified three groups of neuropsychiatric disorders: compulsive, mood, and psychotic, as well as early-onset conditions. These results suggest pleiotropic mechanisms as well as genetic dimensions spanning diagnoses.

Similar observations have been reported for rare variants. Twenty nine pathogenic CNVs were shared across ASD and schizophrenia, including recurrent CNVs at 12 loci (such as 1q21.1, 3q29, 15q11.2, 16p11.2, 16p13.11, 17p12, 22q11.2). Gene set analyses pointed towards a substantial overlap of biological pathways involved in both disorders. Identified mechanisms included synaptic/neuron projection, cell adhesion/junction, MAPK signalling, transcription/gene expression regulation, and the actin cytoskeleton. Shared mechanisms have been also investigated using gene expression data. Analyses of post-mortem cortex samples revealed shared gene-expression profiles between ASD and schizophrenia, as well as bipolar disorder and schizophrenia. Shared differential expression profiles involved downregulation of neuronal and synaptic signalling pathways with a gradient of transcriptomic severity showing the largest changes in ASD compared with schizophrenia or bipolar disorder.

Overall, genetic factors appear to converge early on at the transcriptional level, which may in part explain phenotypic and neuroimaging traits shared across psychiatric conditions.

**Bottom-up approach: large effect genetic variants to dissect mechanisms in psychiatry**

The relevance of conducting bottom-up studies emerged from the questions raised by genetic discoveries of top-down studies. First, why are mutations overrepresented in individuals with a psychiatric diagnosis, and are they related to core symptoms of the disease or to comorbidities? Second, why are mutations associated with several diagnoses (pleiotropy), and do they impact a single dimension contributing to all diagnoses?

By contrast to the top-down approach, the bottom-up recruitment based on the presence of a genetic risk factor for neuropsychiatric disorders (Fig. 4), allows for the investigation of pathways related to a particular biological risk for psychiatry irrespective of any clinical phenotype. The statistical power required to conduct bottom-up studies limits this approach to genetic variants with large enough effect size and population frequency. Clinical routine investigation using whole-genome chromosomal microarrays revealed that CNVs are present in 10–15% of children with neuropsychiatric disorders. Many recurrent neuropsychiatric CNVs have large effect sizes (~1 Cohen’s d; Fig. 2) on cognitive and neuroimaging traits and are natural candidates to conduct genetic first studies.

**Deep phenotyping one mutation at a time**

Recurrent CNVs at the 16p11.2 and 22q11.2 loci are among the most frequent high-risk mutations associated with ASD and schizophrenia. Deletions and duplications between breakpoints 4 and 5 on chromosome 16p11.2 were first linked to ASD in 2008. Carriers of the duplication have a higher risk of developing schizophrenia (OR = 9.4). Both 16p11.2 deletions and duplications have been enriched in a broad spectrum of other conditions including ADHD and intellectual disability.

Genetic first studies have estimated effect sizes of ~1.5 Cohen’s d on IQ, and ~1.4 Cohen’s d on phonological memory for deletions. A smaller decrease in IQ is associated with duplications (~0.8 Cohen’s d). Both CNVs do also affect social responsiveness (~3 Cohen’s d), as well as gross and fine motor skills.

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Table 1 Regions involved in the main functional networks

<table>
<thead>
<tr>
<th>Networks</th>
<th>Seed regions included</th>
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<tbody>
<tr>
<td>Salience network</td>
<td>Anterior insula, anterior cingulate</td>
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<tr>
<td>Frontoparietal = central executive network</td>
<td>Dorsolateral prefrontal cortex, posterior parietal cortex</td>
</tr>
<tr>
<td>Auditory network</td>
<td>Superior temporal gyrus, posterior insula dorsal, auditory region</td>
</tr>
<tr>
<td>Somatomotor network</td>
<td>Ventrolateral, dorsolateral, medial motor regions (precentral gyrus)</td>
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<tr>
<td>Sensorimotor network</td>
<td>Amygdala, hippocampus, fusiform gyrus, posterior insula sulcus, temporal pole, inferior temporal gyrus and orbitofrontal cortex</td>
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<tr>
<td>Limbic network</td>
<td>Caudate nucleus, putamen, thalamus</td>
</tr>
<tr>
<td>Basal ganglia and thalamus</td>
<td>Ventromedian prefrontal, posterior cingulate cortices, precuneus, temporal medial lobe</td>
</tr>
<tr>
<td>DMN</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Cerebellar network</td>
<td>Right temporal-parietal junction and right ventral frontal cortex</td>
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<tr>
<td>Ventral attention network</td>
<td>Intraparietal sulci and frontal eye fields</td>
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<tr>
<td>Dorsal attention network</td>
<td>Visual regions</td>
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<td>Visual network</td>
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See also Fig. 3.
### Box 1 What have top-down and bottom-up neuroimaging genetic studies taught us?

<table>
<thead>
<tr>
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<th>Top-down studies</th>
<th>Bottom-up: Genetic-first studies</th>
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<tbody>
<tr>
<td><strong>Effect-size on neuroimaging traits</strong></td>
<td>On average, the effect sizes observed in schizophrenia, ASD, and ADHD were lower than 0.5 and 0.2 Cohen’s d (Fig. 2A–C), while behavioural adaptive symptoms lie beyond–2 Cohen’s d.</td>
<td>Moderate to large effect-sizes (&gt; 0.8) observed in neuropsychiatric mutations were observed across cognition, behaviour and neuroimaging (Fig. 2D–F) phenotypes. Mirror gene-dosage effects on neuroimaging phenotypes highlight continuous dimensions that correlate with levels of gene expression.</td>
</tr>
<tr>
<td><strong>Polygenicity</strong></td>
<td>Common variants in more than 1000 genes have been associated with risk for ASD and schizophrenia. Studies have estimated that every mega base of the genome encompasses common variation associated with schizophrenia. 16 and 21 CNVs, as well as 145 and 5 SNPs, have been associated with ASD and schizophrenia, respectively (Fig. 1). Models suggest that (i) any 1 megabase CNV (including coding genes) in the genome increases the risk of ASD; and (ii) 10,000 genes negatively impact cognitive ability when deleted.</td>
<td>Multiple genes with small individual effects appear to contribute to the overall neurodevelopmental symptoms of most neuropsychiatric CNVs. Many CNVs appear to impact similar traits such as cognitive abilities. Neuroimaging studies suggest that single genes and CNVs may potentially converge on shared patterns of anatomical and functional alterations.</td>
</tr>
<tr>
<td><strong>Genetic and neuroimaging correlations</strong></td>
<td>Genetic correlation is widespread across psychiatric conditions and is much higher than what is observed across neurological disorders. Among 146 genomewide significant SNPs reported in at least one of eight psychiatric conditions, 109 showed association with two or more disorders including ASD and schizophrenia.</td>
<td>Large effect size rare variants including CNVs and SNVs are associated with a broad spectrum of phenotypes, and multiple diagnoses including ASD, schizophrenia, ADHD.</td>
</tr>
<tr>
<td><strong>Pleiotropy</strong></td>
<td>Rare and common variants in the genome show redundant associations with cognitive traits, psychiatric conditions and potentially neuroimaging traits.</td>
<td>Pleiotropic effects of rare and common genomic variants likely underlie the high rate of clinical comorbidities in psychiatry as well as the plurality of brain endophenotypes associated with a particular set of symptoms.</td>
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The contrast between effect-size observed in bottom-up and top-down studies provides indirect evidence of mechanistic heterogeneity in behaviourally defined psychiatric conditions.

The opposing effects of deletions and duplication (often associated with the same condition) offer an example of brain imaging signals cancelling each-other out. The latter may lead to small effect neuroimaging sizes in top-down case-control studies.

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**anthropometric phenotype has been reported with deletions mainly associated with obesity and macrocephaly and duplications associated with underweight, and microcephaly. Again, effects are large ranging from 0.8 to 1 Cohen’s d.**

**Neuroimaging analyses reported negative gene-dosage effects on total brain volume, total grey and white matter with again similar large effect sizes.** Once effects on global volumes are taken into account, a mirror negative gene dosage effect was observed for the insula volume. Other altered regions were only observed in deletions: transverse temporal gyrus, the calcine cortex (Cohen’s d > 1), superior and middle temporal gyrus (Cohen’s d < −1) or in duplications: caudate and hippocampus (control> duplication, −0.5 > Cohen’s d > −1). At the functional level, a negative gene dosage effect on global connectivity was identified. After accounting for global signal, regional alterations in deletion included a thalamic-sensorial overconnectivity, impairment of frontoparietal network with temporoparietal regions, and strong disturbance of the posterior insula, the presupplementary motor cortex, and the basal ganglia (beta values from −0.8 to 1.4 z-scores). Duplications had a smaller effect on connectivity and mostly involved the amygdala-hippocampus complex, the cerebellum, and the basal ganglia.

**Deletion at the 22q11.2 locus is the largest risk factor for schizophrenia (OR = 68) and up to 30% of adolescents and adults will develop psychosis.** Children with 22q11.2 deletion have also a high risk of developing ASD (OR = 32), ADHD, and anxiety disorders. Duplications are less severe and are inherited in 70% of the cases (compared to deletions which are de novo in over 90% of individuals). While studies suggested a protective effect for schizophrenia the duplication has been associated with a wide range of phenotypes, including ASD, psychomotor development, speech delay, and cognitive deficits. Ascertainment bias remains an issue in the study of genomic disorders which are often recruited in the clinic. Although this is particularly true for smaller effect size variants but may also apply to a lesser degree to 22q11.2.

**ENIGMA 22q11.2 deletion T-weighted studies reported a global decrease in surface area and an increase in mean cortical**
thickness (Cohen’s d: surface area = 1, cortical thickness = 0.6), particularly in temporal and cingulate cortices. Subcortical analyses showed decreased volumes and abnormal shape of the thalamus, putamen, hippocampus, and amygdala volumes (Cohen’s d = –0.9), as well as a greater lateral ventricle volume. The duplication shows an opposing pattern for mean cortical thickness, intracranial volume, and the hippocampus volume. Functional MRI studies have shown mirror effects at the global connectivity level. Underconnectivity between DMN, limbic, and frontoparietal networks is observed in deletions compared to control. Studies replicated a thalamocortical overconnectivity involving somatomotor regions and underconnectivity involving default mode network. The opposite effect was observed for the hippocampus in regard to somatomotor and frontoparietal network connectivity. 

However, it remains unclear if rare variants such as 16p11.2 and 22q11.2 represent mechanistic exceptions or if they may delineate dimensions that are generalized to idiopathic ASD and schizophrenia. This has been investigated at the functional connectivity level. The 16p11.2 deletion connectivity signature showed similarities with individuals diagnosed as either idiopathic schizophrenia or ASD and was associated with higher cognitive and behavioural impairments. Connectivity similarities were driven by the thalamus, the basal ganglia, and the cingulate areas. The 22q11.2 deletion connectivity profile showed similarities with individuals with idiopathic schizophrenia, ASD, and to a lesser extent with ADHD in particular through the thalamus, temporal pole, putamen, and the posterior insula. The thalamus and somatomotor regions played a critical role in dysconnectivity observed across both deletions and idiopathic psychiatric conditions. 

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. The 16p11.2 chromosomal region contains 29 unique genes and none of them has been formally linked to the 16p11.2 clinical phenotype. However, a smaller critical region of five genes, which includes TAOK2 and KCTD13, has been identified. Animal studies on TAOK2 reported dosage-dependent effects including changes in brain size and neural connectivity. 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. The overexpression of the human KCTD13 gene in zebrafish embryos induces a decrease in head size whereas deletion of the zebrafish orthologue yields a macrocephalic phenotype, but follow-up studies did not replicate KCTD13 findings.

Among the 50 genes within the 22q11.2 locus, COMT, TBX1, SEPT5, and DGCR8 were studied as putative critical drivers of the phenotype but results remain inconsistent. Importantly, an excess of de novo loss of function mutations has not been reported in any of the genes within the 16p11.2 and 22q11.2 regions. Overall, these studies show that association evidence for a CNV does not automatically imply that a single or even few genes are driving the effects.

Common and specific effects of genomic variants on intermediate brain phenotypes

Single variant approaches reported in the previous chapter can only be applied to a few recurrent pathogenic variants frequent enough to establish a case-control study design. Thus, the effects of most rare deleterious variants remain undocumented. Single variant studies are therefore at odds with the extreme polygenicity of schizophrenia and ASD highlighted by GWAS discussed in the top-down approach. Several studies have suggested that every megabase of the genome contains common variation associated with increased risk for schizophrenia. This infinitesimal model also referred to as omnigenic applies to ASD and evidence shows that any megabase deletion including coding genes increases the risk for this condition. In this context, two non-exclusive hypotheses could be pursued: (i) an infinite number of disease-associated variants map onto an infinite number of neuroimaging patterns; and (ii) variants converge on a parsimonious set of large scale network alterations. The first hypothesis alone appears improbable because ASD and schizophrenia case-control neuroimaging studies would have otherwise obtained no result.

In the effort to characterize specific and shared effects of CNVs on neuroimaging outcomes, a first cross-genetic study clustered neuroanatomical alterations across 26 different genetic mouse models of autism (including 16p11.2 CNVs, MECP2, NRXN1, and FMR1). Regional differences (relative to total brain volume) were heterogeneous but some regions were recurrently affected across models including the temporoparietal area, the cerebellar cortex, the frontal lobe, the hypothalamus, and the striatum. The authors clustered anatomical alterations and identified three distinct subgroups driven respectively by the limbic system, white matter structures/basal ganglia/thalamus, and cerebellar regions. Knockout mouse models from this study seemed to recapitulate the heterogeneity seen with the imaging findings in autism patients.

Similar studies in humans have been extremely difficult to implement because of the lack of data on individuals with genotypic variants. Recent access to neuroimaging genetic data in the UK Biobank enabled the study of 12 schizophrenia-associated CNVs in the general population (n = 49 unaffected CNV carriers with schizophrenia, including 16p11.2, 22q11.2, NRXN1, 15q11.2, and 1q21.1 CNVs). The thalamus, the hippocampus, and the nucleus accumbens showed decreased volumes in CNV schizophrenia carriers. Thalamic and hippocampal volumes appeared to mediate effects on cognitive performances. A functional resting-state study of 502 carriers of eight neuropsychiatric CNVs (22q11.2, 16p11.2, 15q11.2, and 1q21.1 CNVs) showed that deletions and duplications had strong effects on connectivity. The level of brain dysfunction was also associated with the known levels of risk conferred by mutations. Connectivity signatures of 16p11.2 and 22q11.2 deletions showed similarities across several networks involving the frontoparietal, DMN, ventral attentional, and somatomotor networks. Disconnectivity profiles across eight CNVs and idiopathic ASD, schizophrenia, and ADHD were summarized by three latent components involving the thalamus, the temporal pole, the anterior cingulate, and the ventromedial prefrontal cortex. The level of similarity between CNVs and idiopathic conditions was associated with mutation severity and was driven by the thalamus, and the posterior cingulate cortex, previously identified as hubs in transdiagnostic psychiatric studies (cf. ‘Lessons learned from top-down studies’ section). Beyond categorical diagnoses, CNV connectivity signatures were correlated with measures of autism severity and IQ. 

The extreme polygenicity of ASD and schizophrenia suggests that broad groups of rare and common variants share cognitive effects and neuroimaging patterns. A weighted linear model was developed to estimate the effect of CNVs on IQ using scores of intolerance to protein loss-of-function in a dataset of 24,000 individuals from unselected and psychiatric cohorts with cognitive assessments. These models could predict the effect size of any CNV with 80% accuracy. Deletions of >50% of the coding genome negatively impacted IQ, and this is consistent with infinitesimal/omnigenic models. The same linear weighted model using scores of intolerance to protein loss-of-function was used to explain functional connectivity across CNVs at 18 genomic loci in 502 carriers and 4427 non-carrier individuals. Deletions measured with scores of intolerance to probability of being loss-of-function intolerant (pLI) were associated with a general connectivity signature involving the thalamus, the anterior cingulate cortex, and the somatomotor network. This general deletion signature
Future directions: linking microscale and macroscale observations

Gene expression data from the brain at the developmental, spatial and cell type levels provides highly granular information to annotate the brain function genetic variants at the micro- and macroscale levels (Fig. 5). A major hypothesis is that patterns of gene expression will allow us to understand the relationship between mutations and their effects on brain architecture and behaviour. Work from the Allen Institute suggests that a set of genes constitutes the core transcriptional machinery of the human brain. Thirty-two modules of co-expressed genes were identified—based on their spatial patterns of expression—highlighting a genome-wide redundancy. They were enriched for specific cell types, intracellular components, and associated with neurodevelopmental and degenerative conditions. This canonical transcriptional organization of the genome (the default gene network) is also highly correlated with the brain’s functional network architecture, such as with the default mode network and the principal gradient of macroscale cortical organization.

Genomic variants in genes with a similar cortical organization or temporal pattern may lead to a shared set of brain alterations at the structural and functional levels. In other words, patterns of gene expression may predict patterns of neuroimaging alterations in carriers of CNVs and other genomic variants. Recently spatial patterns of cortical anatomy changes in individuals with 22q11.2 deletions, as well as aneuploidies (sex chromosomes and Down syndrome), were found to be correlated with cortical spatial expression of genes within the 22q11.2, X and Y chromosomes. The same observations have been reported at the functional connectivity level, by testing the association between connectivity-signatures of 22q11.2 and 16p11.2 deletion profiles and the brain expression patterns of genes encompassed in this genomic loci. However, it appears that these relationships are not specific. For example, the spatial brain expression pattern of 1834 genes (genome-wide false discovery rate) were correlated with the...
22q11.2 functional brain connectivity profile. Indeed, many genes share similar spatial and temporal expression patterns, which may potentially explain the polygenic architecture of brain organization and psychiatric condition as well as the shared variance of cortical alterations across psychiatric disorders.148

The cytoarchitecture of the human brain may also help understand the link between genomic variants, their associated brain alterations and psychiatric conditions. For example, genes preferentially expressed in oligodendrocytes show a cortical distribution in their expression that is positively correlated with intracortical myelination measured by magnetization transfer.149 Brain alterations caused by CNVs and sex chromosome aneuploidies have also been associated with gene expression distributed along gradients of cell types.147 A similar approach has also linked cell types to patterns of brain alterations associated with ASD, ADHD, bipolar disorder, schizophrenia, OCD, and major depression. This ‘virtual histology’ approach reveals that the cortical expression patterns of pyramidal, microglia, astrocyte genes were correlated with cortical thickness alteration maps of eight psychiatric conditions.148

Although temporal expression during brain development is a dimension that is likely to impact brain architecture, it has not yet been associated with MRI alteration observed in carriers of CNVs and genomic variants. These exciting attempts to bridge macro- and micro-scale observations are initiating fruitful collaborations between genomics, neurobiology, computational and evolutionary neuroscience.

Functional dimensions disturbed across psychiatric conditions may also be distributed through these modules of co-expression and functional gradients.150 Such properties might be related to emerging properties of the genome and the recent evolution of the human brain.151,152

Conclusion: what have we learned and what are the next steps?

Early neuroimaging genomic studies in psychiatry were plagued by small sample sizes and inappropriate candidate gene strategies. Studies of psychiatric disorders were performed on the assumption of relative specificity (Box 1). With access to larger datasets in the past years, both top-down and bottom-up neuroimaging-genomics studies have gained traction with increased reproducibility of nature and effect-size of the alterations. The effect sizes of rare variants on neuroimaging endophenotypes are concordant with effects previously measured for the same variants on brain structure, cognitive and behavioural traits.73,133 This is in striking contrast with the effect sizes observed for functional connectivity and brain structure in schizophrenia, ASD, and ADHD, which are 3–5-fold lower (Fig. 2).35,39

This surprising discordance of effect-sizes observed between bottom-up (rare variants) and top-down studies (idiopathic conditions) underscore the necessity to dissect results from case-control studies conducted in idiopathic conditions with results from large-effect size rare variants. We propose a genetically-informed stratification by systematically investigating a broad spectrum of neuro-psychiatric variants. This should allow for the identification of latent dimensions in idiopathic conditions.
The shared neuroimaging dimensions identified across psychiatric conditions are in line with the genetic correlation demonstrated between the same conditions as well as pleiotropic effects of genomic variants (Fig. 1). Findings also suggest a staggering diversity of brain endophenotypes across different genomic variants and idiopathic psychiatric conditions. Therefore, the time has not yet arrived to draw firm conclusions about the nature of the potential neuroimaging convergence (or lack thereof), across genetic risk and psychiatric conditions.

The neuroimaging field is increasingly moving towards harmonization using systematic analytical methods, atlas, and data structure as well as reporting standards including effect sizes and un-thresholded beta map (Poldrack Nature). Large efforts have been in building platforms to associate imaging modalities and genetic data

Only a few datasets currently allow neuroimaging genomic studies (Fig. 6): UKBB are large population cohorts with great potential to study genomic variation and neuroimaging phenotypes, but they include few individuals with mental illnesses and behavioural deficits. EU-AIMS is among the few psychiatric cohorts integrating genomics, neuroimaging and cognitive data, in ~250 individuals with autism. Given our assumptions on the mechanistic heterogeneity in ASD, one would expect that a neuroimaging genomic dataset of several thousand individuals with autism would be required to provide the power to investigate brain-molecular dimensions. Of note, there are currently no neuroimaging genomic cohorts in schizophrenia that are available to the community. The ENIGMA consortium has also been instrumental in moving the field and has provided well-powered meta-analytic studies.

Neuroimaging genetic studies investigating large effect size mutations are lagging behind those focused on common variation. Closing this gap will require investing in new large scale cohorts with exome/genome sequencing data collected in individuals with a broad spectrum of psychiatric conditions. Cohorts with such data include UKBB and EU-AIMS. Alternative strategies include gene cohorts ascertaining individuals with previously identified large effect size neuropsychiatric variants such as ENIGMA-CNV, ENIGMA 22q11.2, and Quebec 1000 families. These efforts should provide significant power to associate brain mechanisms to genomic variants, molecular mechanisms, and mental illnesses. They will likely improve predictive modelling at the individual level and guide the development of mechanistically informed predictive tests with clinical utility.

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Competing interests

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