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Structural and functional brain alterations revealed by neuroimaging in CNV carriers

Clara A. Moreau[1,2,3], **Christopher R. K. Ching**[4], **Kuldeep Kumar**[1], **Sebastien Jacquemont**[1,2], **Carrie E. Bearden**[5]

[1]Sainte-Justine Hospital Research Center, Montreal, Canada

[2]Department of Pediatrics, University of Montreal, Montreal, Canada

[3]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Canada

[4]Imaging Genetics Center, USC Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of the University of Southern California

[5]Semel Institute for Neuroscience and Human Behavior, Departments of Psychiatry and Biobehavioral Sciences and Psychology, University of California, Los Angeles. Semel Institute/ NPI, 760 Westwood Plaza, Los Angeles, CA 90024, USA

Abstract

Copy Number Variants (CNVs) are associated with elevated rates of neuropsychiatric disorders. A 'genetics-first' approach, involving the CNV effects on the brain, irrespective of clinical symptomatology, allows investigation of mechanisms underlying neuropsychiatric disorders in the general population. Recent years have seen an increasing number of larger multisite neuroimaging studies investigating the effect of CNVs on structural and functional brain endophenotypes. Alterations overlap with those found in idiopathic psychiatric conditions but effect sizes are 2 to 5-fold larger. Here we review new CNV-associated structural and functional brain alterations and outline the future of neuroimaging genomics research, with particular emphasis on developing new resources for the study of high-risk CNVs and rare genomic variants.

Keywords

structural MRI; functional connectivity; copy number variation; 22q11.2; 16p11.2; neuropsychiatric disorders

Corresponding authors: Carrie E. Bearden and Sebastien Jacquemont, clara.moreau@umontreal.ca, sebastien.jacquemont@umontreal.ca.

Introduction: A brief history

Over the past two decades, the study of brain alterations associated with specific genetic conditions has offered a powerful tool for investigating gene–brain-behavior relationships in humans. Earlier structural and functional neuroimaging studies revealed insights into the impact of genetic conditions such as Fragile X [3], Turner Syndrome and Williams Syndrome on brain development and downstream behavior [4]. This 'behavioral neurogenetics' approach has shed light on potential mechanisms underlying developmental neuropsychiatric disorders in the general population. These initial studies were performed before the widespread availability of genome-wide chromosomal array techniques and thus were limited to a small set of clinically recognizable conditions diagnosed with locus-specific genetic tests. In recent years, both case-control and population-based neuroimaging studies of ever-increasing sample sizes, in which DNA was also collected (Figure 1), have provided an opportunity to investigate the effects of a broader range of genetic mutations on brain structure and function. In particular, recurrent copy number variants (CNVs) associated with elevated rates of neuropsychiatric disorders, including autism spectrum disorder (ASD) and schizophrenia, have advanced knowledge of genetic drivers of structural and functional brain alterations.

Several developments in recent years have greatly accelerated progress (Figure 1). In particular, significant technical advances in both acquisition and analysis of neuroimaging data, have facilitated harmonization across sites and scanners [5], both prospectively [6] and retrospectively [7], and have substantially increased resolution of imaging acquisition protocols, thus providing greater insights into neurobiology. Secondly, increasing collection of large multi-site and population-based cohorts using common protocols, as well as increased public availability of imaging-genomic data resources [8,9], has led to important cross-CNV discoveries, described below.

Structural brain alterations in CNV carriers

Recent structural neuroimaging studies have included vastly larger samples of CNV carriers due to new efforts in data collection, development of international consortia, and, to some extent, large-scale population-based studies. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA), Variation in individual's project (VIP) and European 16p11.2 Consortia have published multi-site studies of brain structure alterations in 22q11.2, 16p11.2 [10,11], and 15q11.2 CNVs [12], applying standardized processing and analysis techniques to improve replication and generalizability of findings, while empowering comparisons with large-scale studies of idiopathic psychiatric illness. Semi-automated methods to measure MRI-derived thickness and surface area of the cerebral cortex (Text Box 1) are widely used in neuroimaging studies and have been used to model developmental and disease processes. One of the most notable observations across studies is that the effect sizes of CNV-associated brain alterations are generally 2 to 5-fold larger than those found in large-scale studies of idiopathic psychiatric disorders (Figure 2).

Insights from the 22q11.2 Microdeletion and Williams Syndrome

The 22q11.2 deletion syndrome (22q11DS; also known as Velocardiofacial Syndrome) has been more widely studied using neuroimaging techniques due to its relative frequency (at ~1/4000 live births), large effects on neurodevelopment, and well-established link with schizophrenia. One in four individuals with 22q11DS develops psychotic illness, thus providing a powerful genetics-first framework to study brain markers for psychosis. A recent meta-analysis finds that 22q11DS is associated with widespread reductions of brain volume that converge with findings from idiopathic schizophrenia [13]. Recent ENIGMA studies, which have pooled 22q11DS neuroimaging cohorts from around the world, have mapped large-scale cortical [14], subcortical [15], and white matter [16] alterations in 22q11DS using both conventional and vertex-wise methods to reveal the spatial complexity of these alterations. Individuals with 22q11DS showed a widespread and highly consistent pattern of thicker cortex and lower cortical surface area [14], as well as robust subcortical alterations including smaller overall hippocampal, putamen, amygdala, and left thalamus volumes, and larger bilateral ventricle, caudate and accumbens volumes [15]. Subcortical shape analysis revealed a complex spatial pattern of these morphometric differences between 22q11DS and typically developing individuals [15]. In the first evidence of an effect of 22q11.2 deletion size on structural anatomy, smaller deletions (1.5Mb LCRA-LCRB) were associated with significantly greater cortical surface area [14] and less extreme subcortical alterations compared to the larger, more typical deletion (~2.6Mb LCRA-LCRD) [15].

Structural brain alterations have also been investigated in Williams Syndrome (WS), a condition resulting from a deletion of 26 genes at chromosome 7q11.23, associated with marked visuospatial deficits and hypersocial personality [17]. Using an alternative approach to identify intermediate phenotypes for broader genetic association studies, researchers created a multivariate neuroanatomical score from structural brain differences found between individuals with WS and controls. These neuroanatomical scores were then associated with SNPs within the 7q11.23 WS region from neurotypical cohorts and used to identify potential loci involved in normal brain development [18].

Gene Dosage Effects on the Brain

Studies have revealed that reciprocal CNVs, (i.e., deletions and duplications at the same locus) have opposing effects on brain phenotypes. Given the correlation between the number of genomic copies (deletions or duplications) and transcriptional levels of genes encompassed in CNVs [19], one may conclude that transcription levels quantitatively modulate structural and functional neuroimaging phenotypes. Intriguingly, the direction of such dosage effects differs across CNVs [Figure 2]: while 1q21.1 and 22q11.2 show positive dosage effects on brain volume and surface area (Del<Control<Dup), 16p11.2 BP4–5 and BP1–3 show negative dosage effects on grey and white matter volumes and cortical surface area (Dup<Control<Del). Similarly, head circumference, intracranial volume (ICV), and insula volumes were negatively correlated with the number of genomic copies at the 16p11.2 BP4–5 locus [10]. These brain alterations were present at age 4 and remained stable across childhood, adolescence and early adulthood [20]. 16p11.2 BP1–3 deletion carriers were also found to have higher ICV, putamen, pallidum, and caudate brain volumes, whereas individuals with reciprocal duplications had lower brain volumes [11]. In contrast, 22q11.2

reciprocal CNVs show positive gene dosage effects for ICV, gray/white matter volume, cortical surface area, and hippocampal volumes, with a negative gene dosage effect for mean cortical thickness, caudate, and corpus callosum volume [21]. Similar principles of gene dosage apply to sex chromosome aneuploidies, where there are large-effect negative associations between the number of additional X chromosomes and total cortical surface area, as well as total brain volume [22]. 15q11.2 deletion carriers show a similar pattern to 22q11.2 deletions, albeit with much smaller effects, involving lower surface area and thicker cortex across frontal, cingulate, and pre-and post-central regions compared to duplication and non-carriers [12], as well as reciprocal alterations in white matter, with duplications showing higher fractional anisotropy compared to controls and duplications (Del>Control>Dup) [23]. However, the very small effect size observed for 15q11.2 duplications means that much larger studies will be needed to confirm these preliminary findings. Notably, 15q11.2 CNVs have consistently small effects on both brain and neurobehavioral traits, including psychiatric disease risk and cognition [24,25]. Taken together, the observed dose-response on brain traits observed across multiple CNVs suggests that neuroanatomical variation may be sensitive to gene dosage across multiple genomic regions. This is in line with the highly polygenic architecture of cortical surface area, observed in GWAS of common variants [26]. Furthermore, pervasive effects of gene dosage across cortical and subcortical structures suggests these effects may be driven by genes important in early neurodevelopment.

Shared vs. Distinct Neuroanatomic Effects across CNVs

The polygenic nature of psychiatric conditions and the pleiotropic effects of genomic-risk variants could potentially be explained by the shared effects of genomic variants on brain alteration. The proportion of shared and specific effects associated with CNVs remains unknown. A recent examination of subcortical variation across CNVs found significantly smaller volumes (hippocampus, thalamus, putamen, pallidum, and accumbens) in 49 unaffected individuals carrying at least one of 12 CNVs known to increase risk for schizophrenia [27]. These subcortical volume decreases mediated a proportion of the negative association between CNVs and fluid intelligence. Another cross-CNV study found that CNV-associated penetrance scores for psychiatric illness were associated with medial (cingulum and corpus callosum) white-matter microstructure and morphological features [28]. However, larger samples, including a broader list of genomic variants, are required to draw robust conclusions on the putative convergence of CNVs on shared brain alterations.

Effects of CNVs versus effects of idiopathic Schizophrenia and ASD on Brain Structure

One of the key goals of neuroimaging studies of ‘neuropsychiatric’ CNVs is to determine whether there is convergence with underlying neuroanatomic alterations observed in complex polygenic idiopathic (i.e., behaviorally defined) developmental psychiatric disorders. To date, observations suggest that 1) CNVs with opposing effects on brain structure and function may be associated with the same neuropsychiatric condition; e.g., 16p11.2 deletions and duplications are both associated with high ASD risk); and 2) The effect sizes of rare variants on neuroimaging endophenotypes are concordant with their effects on cognitive and behavioural traits [10,29] observed for neuroimaging phenotypes in idiopathic schizophrenia, ASD, and ADHD (Figure 2) [30,31]; 3) Additional factors present

in CNV carriers who develop a psychiatric condition demonstrate neuroimaging similarities with that particular condition, as suggested by findings from the multisite 22q-ENIGMA study where large demographically well-matched subgroups of 22q11.2 deletion carriers with and without a psychotic disorder were investigated. Notably, those with 22q11DS and a history of psychosis showed significantly thinner frontal-temporal cortex [14], as well as smaller thalamic, hippocampal and amygdala volumes compared to 22q11DS cases without a history of psychosis [15]; these findings converge with those from the largest studies of cortical and subcortical structure in idiopathic schizophrenia [32,33]. In contrast, analysis of white matter revealed a sharply diverging pattern from idiopathic schizophrenia [34], characterized by higher fractional anisotropy and lower diffusivity [16] (Text Box 1), suggesting distinct connectivity profiles may drive similar clinical outcomes. If indeed CNVs increase risk for neuropsychiatric disorders through distinct brain mechanisms, this would suggest that there may be mechanistically distinct subgroups with divergent brain alterations within behaviorally defined (idiopathic) cohorts, with this heterogeneity resulting in much smaller average effect sizes and diluting signal (Figure 2).

Functional connectivity across CNVs

Functional connectivity (FC) studies have provided critical insight into the architecture of brain networks involved in neuropsychiatric disorders. FC represents the intrinsic low-frequency synchronization between different neuroanatomical regions. It is measured via resting-state functional magnetic resonance imaging (rs-fMRI) which captures fluctuations of blood oxygenation as an indirect measure of neural activity across brain areas when no explicit task is performed (Text Box 1). The field has gained traction, characterizing increasingly reproducible results [35] and demonstrating FC dimensions shared across diagnostic categories, suggesting that correlations observed at the molecular level are also present at the brain network level [36].

Few studies to date have investigated the effect of neuropsychiatric CNVs on FC patterns. Recently a ‘mirror’ effect of gene dosage on mean (global) connectivity was identified at the 16p11.2 proximal locus. This opposing effect was not observed for FC at the regional level. Regional FC alterations associated with 16p11.2 deletion included a thalamic-sensorimotor over-synchronization, weaker long-range functional coupling of frontal and temporoparietal regions, and disrupted connectivity of the posterior insula, pre-supplementary motor cortex, and basal ganglia (beta values > 1 [Figure 2]) [37,38]. Duplications at the 16p11.2 proximal locus, in contrast, had a smaller effect on connectivity and mostly involved the amygdala-hippocampus complex, cerebellum, and the basal ganglia.

Functional imaging studies at the 22q11.2 locus have shown evidence for large-scale network dysconnectivity, with underconnectivity in default mode, visual, and frontoparietal networks consistently observed in deletion carriers compared to controls [38–40]. Several studies also reported thalamocortical overconnectivity involving somatomotor regions and underconnectivity in frontoparietal associative networks, indicating that this effect maps onto large-scale resting-state networks with a dissociation along a sensory-associative hierarchy. The opposite effect was observed for the hippocampus in regards to somatomotor

and associative network connectivity, suggesting disruption of thalamic-hippocampal circuitry in 22q11 deletion carriers [38,41].

FC has also been investigated in WS using an *a priori* approach [17]. Given that the intraparietal sulcus has been previously found to be structurally and functionally abnormal in WS, the authors investigated whole-brain connectivity with this seed region. Compared to typically developing children, those with WS showed opposite FC patterns of the intraparietal sulcus with visual processing regions (underconnectivity) and with social processing regions (overconnectivity) [17]. Other CNVs have not yet been investigated with functional MRI; as such, the generalizability of these patterns to other CNVs is unknown.

There is evidence that FC alterations in CNVs such as 16p11.2 and 22q11.2 deletions delineate dimensions that generalize to idiopathic ASD and schizophrenia. The connectivity signatures of both 16p11.2 and 22q11.2 deletions showed similarities with dysconnectivity patterns of individuals with either idiopathic schizophrenia or autism, but not ADHD. Notably, individuals with FC patterns that more closely resembled FC signatures of deletion carriers showed more severe cognitive and behavioral symptoms. Regions showing the greatest FC similarities across both deletions and idiopathic psychiatric conditions included the thalamus, temporal pole, putamen, posterior insula, and above all the thalamus and somatomotor regions [38]. This pattern of findings is consistent with an emerging body of evidence for common neurobiological substrates of psychopathology (e.g., [42]).

Linking CNV-associated neuroimaging alterations to temporal and cytoarchitectural patterns of gene expression

Studies investigating the effects of CNVs on brain structure and function have provided a complex catalog of brain alteration patterns linked to different genomic loci. However, mechanisms linking CNVs to brain architecture remain largely unknown. Recent advances in large-scale, high-throughput transcriptomics, highlighted by the availability of brain-wide gene expression atlases such as the Allen Human Brain Atlas [43], have opened opportunities to study the relationship between temporal and spatial distribution of gene expression and macroscopic neuroimaging phenotypes. Studies have investigated how gene expression relates to independently measured functional connectivity [44], neuroanatomical hierarchy [45], and patterns of cortical alteration in idiopathic ASD [46] and schizophrenia [47]. However, to date, only two studies have investigated associations between human brain gene expression and CNV-associated neuroimaging alterations [38,48].

Seidlitz and colleagues linked structural MRI-derived cortical changes with spatial patterns of CNV gene expression. By studying multiple neurogenetic disorders known to increase the risk for one or more neurodevelopmental disorders, researchers revealed significant correlations between the spatial variation in cortical anatomy with the spatial expression of cell-type-specific patterns of CNV gene expression in neurotypical adults. This noninvasive, transcriptional vulnerability model provides a potential link between MRI-derived brain phenotypes and the underlying cell types and genomic mechanisms influencing neurogenetic disorders [48].

Moreau and colleagues showed a significant association between the functional connectivity signatures of two neuropsychiatric CNVs, deletions at 22q11.2 and 16p11.2, and the spatial expression patterns of genes encompassed in the respective genomic loci [38,48]. However, many genes outside these 2 loci also exhibited similar levels of association. This redundancy has been hypothesized to represent a factor underlying similarities between the two CNV FC signatures and may explain why many CNVs affect a similar range of neuropsychiatric symptoms.

While these studies show the potential of combined analysis of brain imaging and transcriptome data, further studies covering a broader landscape of CNVs, concomitant with spatio-temporal patterns of gene expression, are required to unveil the underlying mechanisms that regulate the mapping of genetic risks onto brain alterations and potential organizing principles of neurodevelopment.

The future of neuroimaging genomic research

Datasets currently available for the analysis of CNVs.—Studies on CNVs to date have been conducted either by recruiting clinically ascertained CNV carriers or by calling CNVs in unselected populations or (to a lesser extent) disease cohorts that were previously genotyped with the initial aim of conducting GWAS. While the latter strategy has enabled access to large sample sizes with a 0.5 to 3% rate of moderately to mildly deleterious CNVs, the former approach is the only way to obtain neuroimaging data in individuals with large and extreme effect-size variants. As an example, the low frequency of CNVs in the general population, such as in UK-Biobank [27,49,50], will provide limited power to individually study neuroimaging effects of large effect size CNVs because this healthy cohort of relatively high-functioning individuals includes very few participants with significant cognitive and behavioral deficits. The Adolescent Brain Cognitive Development Study (ABCD) [51] is a long-term prospective study of brain development, with around 10,000 children recruited between ages 9–10 and followed into early adulthood. ABCD is currently among the largest neuroimaging cohorts, and ongoing CNV identification will provide additional observations of CNV effects on neuroimaging traits in unselected populations. It also constitutes a more sociodemographically diverse cohort than those currently available, another urgent need in the field. Beyond unselected populations, however, large neuroimaging genomic datasets are almost non-existent in psychiatric cohorts. Currently, there are no autism cohorts and only a few small (n<100) schizophrenia cohorts with such data. The European Autism Interventions - A Multicenter Study for Developing New Medications (EU-Aims) will be the first dataset with neuroimaging genomic data, including approximately 250 individuals with ASD. We are not aware of any ongoing large-scale neuroimaging genomic data collection in psychiatric cohorts; such cohorts would provide valuable insights into genetic effects on brain structural and functional architecture across the allelic frequency, as detailed below.

Developing new resources for the study of CNVs and rare genomic variants with large effect sizes

To increase our understanding of the effects of deleterious variants on brain architecture, efforts must be made to recruit individuals presenting with a broad spectrum of cognitive

deficits and neuropsychiatric symptoms. Based on previous studies [52–54], this ascertainment strategy would provide a 10 to 30-fold enrichment in large effect size variants, including CNVs and single nucleotide variants. Further enrichment would also include individuals selected on the basis of having a deleterious genomic variant. A genetics-first genome-wide cohort would provide a yield of developmental psychiatric CNVs approximately 100-fold higher compared to an unselected population [50]. As such, the burden of large effect-size CNVs in a cohort of 10000 individuals recruited through psychiatric, developmental pediatrics and genetic clinics would be equivalent to the mutational burden in 500,000 to 1,000,000 individuals from the general population. Genomics, neuroimaging, as well as dimensional neurobehavioral assessments in such a cross-disorder cohort would provide multiscale information unmatched by any current resources. It would provide a valuable resource for the fields of neuroimaging, genomics, and neurodevelopmental disorders. To achieve a multiscale and multimodal dataset while limiting cost, assessments could be aligned with those conducted in an unselected population to provide a larger group of unaffected individuals for comparison, thus ascertaining a broad spectrum of genomic and clinical variation.

Conclusion

Identifying gene functions that may mediate the effect of CNVs on neuroimaging traits and risk for psychiatric conditions will require genome-wide analyses of a large number of genomic variants that alter genes with a broad variety of functions. Neuroimaging studies in animal models of CNVs are also beginning to shed light on the pathophysiology underlying brain alterations detected in human CNV carriers, although very few studies to date have directly compared neuroimaging findings between CNV mouse models and humans [37,55,56]. Transitioning from the current candidate studies to genome-wide analyses of rare variants will require large-scale efforts ascertaining individuals enriched for high-risk variants across a broad spectrum of neuropsychiatric symptoms. While in the near future, datasets will likely remain underpowered for gene-based association studies, other strategies collapsing variants across molecular pathways and developmental processes (weighted burden) would provide significant insight into mechanisms underlying the effects of rare variants on the structure and function of the brain.

Collectively, the research presented here summarizes insights that CNVs can offer into fundamental principles of brain development, in the context of health and disease. Such genetics-first neuroimaging approaches, combined with top-down data-driven neuroimaging subtyping performed in idiopathic psychiatric conditions[1] will advance understanding of neural mechanisms of psychopathology.

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Competing interests

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Text Box 1.

Why study neuroimaging in CNVs?

There is a consensus that substantial heterogeneity underlies the neurobiology of developmental psychiatric conditions such as autism and schizophrenia [1,2].

Neuroimaging has been used to characterize atypical brain patterns in idiopathic psychiatric conditions and findings have highlighted small effect sizes and variability across studies, likely due to neurobiological heterogeneity. As such, it has become increasingly clear that stratification at the molecular, and brain network level is a prerequisite for identifying mechanisms in behaviorally defined conditions.

The study of brain alterations associated with specific genomic disorders (large effect size variants) offer a powerful tool for investigating gene–brain-behavior relationships in humans. Specifically, neuroimaging studies of CNVs: 1) provide intermediate phenotypes on the causal pathways between variants and cognition 2) offer a window into potential shared biological mechanisms between these highly penetrant large-effect mutations, where the molecular basis is known, and idiopathic (behaviorally defined) neuropsychiatric disorders; 3) can shed light on fundamental principles of brain development and help dissect the heterogeneity of neuropsychiatric disorders.

Definitions

Pathogenic CNV:

A CNV of large effect size on neurodevelopment which contributes substantially to the neurodevelopmental symptoms of a patient. Such variants are also referred to as “clinically significant”.

Gene dosage effect:

Effects related to a change in the number of genomic copies (deletions or duplications).

Surface area:

As with cortical thickness, semi-automated MRI processing techniques can be used to estimate the surface area of the cortical mantle and have been widely used to study brain development in healthy and clinical populations. MRI-derived measures of surface area are thought to be driven by the number of cortical columns and are likely under differential genetic control than cortical thickness.

Cortical thickness:

Measures of local thickness of the cerebral cortex can be obtained from widely used (and histologically validated) MRI processing techniques that measure the distance between the pial surface and gray/white matter boundary beneath the cortical ribbon. Local thickness measures are thought to vary with the number of cells within the cortical column, where thickness decreases from childhood onward.

Diffusion tensor imaging (DTI):

A widely used method to infer the underlying microstructural organization of brain tissue by quantifying the local direction and magnitude of water diffusion, especially in white matter.

Fractional anisotropy (FA):

A scalar measure derived from the DTI model that provides the degree of anisotropy in a given region and has been related to degree of axonal packing.

Mean Diffusivity (MD):

Another scalar measure from DTI that quantifies the total velocity of diffusion, a signal that has been tied to tissue cellularity, edema and necrosis.

Resting-state functional connectivity:

Resting-state functional magnetic resonance imaging (rs-fMRI) captures fluctuations of blood oxygenation as an indirect measure of neural activity across brain areas when no explicit task is performed. Functional connectivity represents the synchronization of oxygenation fluctuation between different neuroanatomical regions. Each connection value is measured by the correlation of low-frequency activities between 2 regions. Robust functional brain networks measured by rs-fMRI are also recapitulated by spatial patterns of gene expression in the adult brain.

Global and regional functional connectivity (FC):

Global FC represents the mean value of connectivity strength across all regions in the brain. Regional FC is the connectivity between a given region and the rest of the brain.

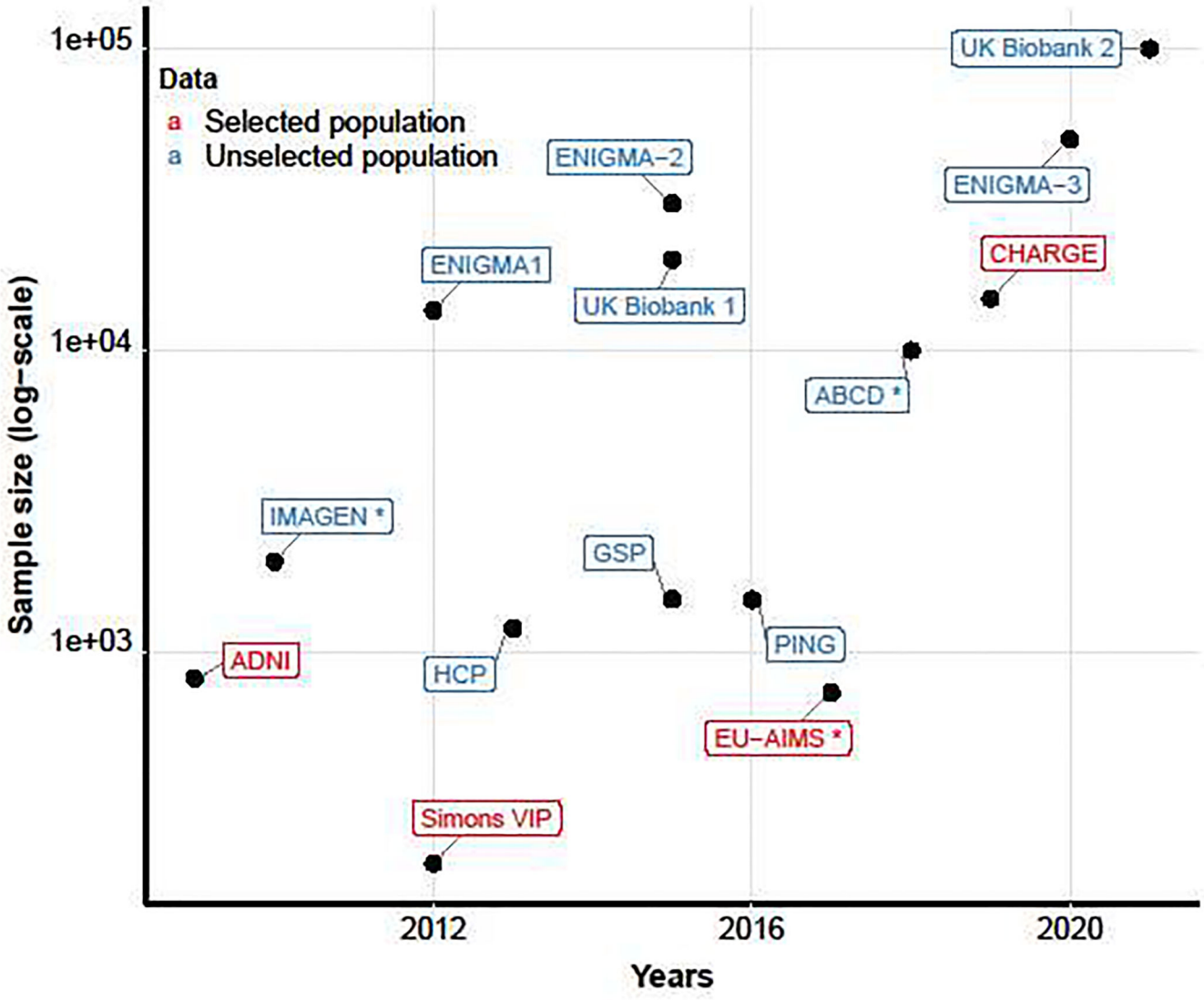

Figure 1.

Collection of genomic and brain imaging data has been exponential in the past 5 years. Cohorts for Heart and Aging Research in Genomic Epidemiology: CHARGE [57,58]; Alzheimer's Disease Neuroimaging Initiative: ADNI [59]; IMAGEN [60]; Simons Variation in Individuals Project: Simons VIP [61]; Enhancing Neuro Imaging Genetics through Meta-Analysis: ENIGMA 1 [5]; Human Connectome Project (HCP [62]; Brain Genomics Superstruct Project: GSP [63]; ENIGMA 2: [64]; SchizConnect [65]; UK-Biobank [9]; The Pediatric Imaging, Neurocognition, and Genetics: PING [66]; European Autism Interventions A Multicentre Study for Developing New Medications: EU-AIMS [67]; The Adolescent Brain Cognitive Development: ABCD [68]; ENIGMA-3 [26]; UK-Biobank release [69,70].

Red: Selected population (disease-first or genetic-first cohort), Blue: unselected population; "*" Longitudinal study.

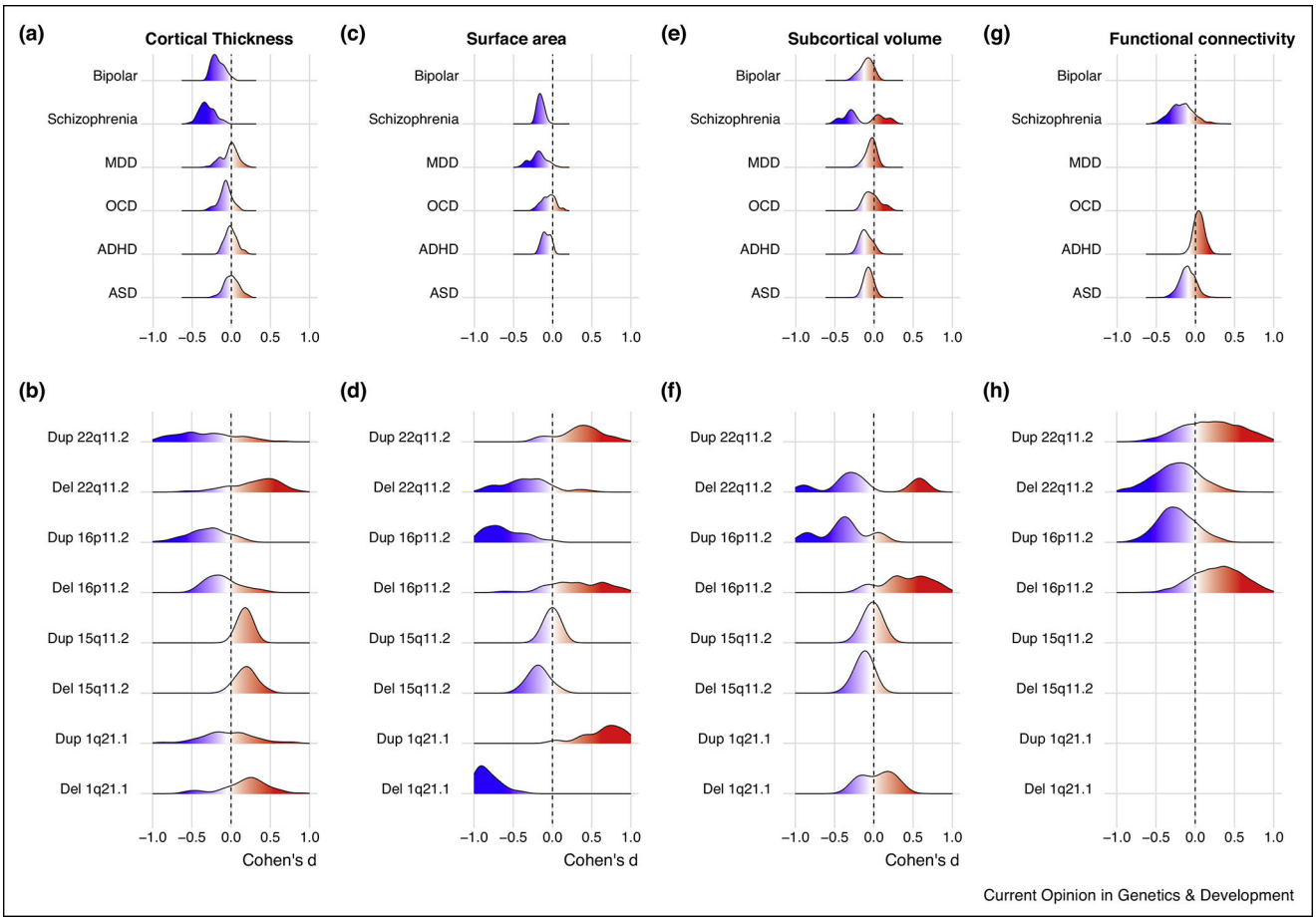

Figure 2.

Cortical thickness (A-B) and Surface area (C-D): Effect sizes are shown for Schizophrenia: n=4,474 patients with schizophrenia vs. 5,098 HC [32]; ASD: n=1,571 patients with ASD vs. 1,651 HC [31]; Major Depressive Disorder (MDD): n=2,148 patients with MDD vs. 7,957 HC [71]; Obsessive Compulsive Disorder (OCD): n=1,905 patients with OCD vs. 1,760 HC [72]; Bipolar Disorder: n=6,503 patients with Bipolar Disorder vs. 1,837 HC [73]; ADHD: n=2,246 patients with ADHD vs. 1,934 HC [74].

22q11.2 deletion: n=474 carriers vs. 315 HC [14]; 22q11.2 duplication: n=19 carriers vs. 312 HC; 16p11.2 BP4–5: n=80 deletion carriers, n=69 duplication carriers, and 312 HC; 1q21.1: n=25 deletion carriers, n=16 duplication carriers, and 312 HC [75]; 15q11.2: n=203 deletion carriers, n= 306 duplication carriers, and 45247 HC [12]

Subcortical volume (E-F): ADHD: n=1,713 patients with ADHD, and 1,529 HC [76];; Bipolar Disorder: n=1,710 patients with BIP, and 2594 HC [77]; MDD: n=1,728 patients with MDD, and 7,199 HC [78]; OCD: n=1,830 patients with OCD, and 1,759 HC [79]; Schizophrenia: n=2,028 patients with SZ, and 2,540 HC [33]. 22q11.2 deletion: n=533 subjects with 22q11DS, and 330 HC [15].

Functional MRI (G-H): Schizophrenia: n=241 patients with SZ, and 242 HC; ASD: n=225 patients with ASD, and 234 HC; ADHD: n=289 patients with ADHD, and 474 HC; 16p11.2 proximal (BP4–5) locus: n=20 subjects with 16p11.2 deletion, n=23 subjects with 16p11.2

duplications and 79 HC; 22q11.2: n=46 subjects with 22q11.2 deletion, n=12 subjects with 22q11.2 duplication and 43 HC [38].