Where the genome meets the connectome: understanding how genes shape human brain connectivity

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Abstract

The integration of modern neuroimaging methods with genetically informative designs and data can shed light on the molecular mechanisms underlying the structural and functional organisation of the human connectome. Here, we review studies that have investigated the genetic basis of human brain network structure and function through three complementary frameworks: (1) the quantification of phenotypic heritability through classical twin designs; (2) the identification of specific DNA variants linked to phenotypic variation through association and related studies; and (3) the analysis of correlations between spatial variations in imaging phenotypes and gene expression profiles through the integration of neuroimaging and transcriptional atlas data. We consider the basic foundations, strengths, limitations, and discoveries associated with each approach. We present converging evidence to indicate that anatomical connectivity is under stronger genetic influence than functional connectivity and that genetic influences are not uniformly distributed throughout the brain, with phenotypic variation in certain regions and connections being under stronger genetic control than others. We also consider how the combination of imaging and genetics can be used to understand the ways in which genes may drive brain dysfunction in different clinical disorders.

Keywords: connectome, network topology, imaging, heritability, GWAS, PGS, gene expression

Introduction

The ongoing development of neuroimaging acquisition, processing, and analysis methods is enhancing our capacity to map the long-range axonal projections and functional dynamics of the human brain at the macroscopic scale, resulting in the construction of increasingly comprehensive maps of structural brain connectivity. Studies of human connectomes (Bullmore & Bassett, 2011; Fornito et al., 2016; Sporns et al., 2005; Sporns, 2011) complement work undertaken in other species and at different resolution scales (Chiang et al., 2011; Markov et al., 2014; Sporns, 2011; Zingg et al., 2014). This work has shown that numerous organizational properties of neuronal connectivity are strongly conserved across species and scales (for a review, see van den Heuvel et al., 2016), giving rise to a complex multiscale network topology (Bullmore & Sporns, 2009). These properties include a heterogeneous distribution of connectivity across network elements, resulting in some nodes, representing putative hubs, being more highly connected than others (Fulcher & Fornito, 2016; Harriger et al., 2012; Heuvel & Sporns, 2011; Towlson et al., 2013), strong inter-connectivity between these hubs, resulting in a rich-club organization that supports efficient integration of information between distributed neural systems (Bullmore & Sporns, 2012; Harriger et al., 2012; Heuvel et al., 2012), and dense connectivity between functionally related subsets of nodes, giving rise to a hierarchical, modular architecture that supports specialization and segregation of function (Betzel et al., 2017; Meunier et al., 2009; Sporns & Betzel, 2016). Connectomes also appear to be economically configured, with their total volume of wiring being near-minimal given their topological complexity (Bassett et al., 2010; Bassett & Bullmore, 2017; Gollo et al., 2018).

The consistent observation of these properties in the connectomes of different species is thought to result from common selection pressures; in particular, those that trade-off pressures to minimize wiring costs and related metabolic demands with a need for adaptive and complex function (Bullmore & Sporns, 2012). Although the role of simple physical and geometric constraints in shaping some of these features has been studied extensively (Ercsey-Ravasz et al., 2013; Henderson & Robinson, 2014; Horvát et al., 2016; Roberts et al., 2016), it is likely that genes also play a role, given the consistency of properties observed in neuronal systems with very different geometries, such as those belonging to humans and nematodes (Heuvel & Sporns, 2011; Kim & Kaiser, 2014; Towlson et al., 2013). Indeed, it would be surprising if genes were not important, given that most aspects of brain structure and function show some level of heritability (Thompson et al., 2001, 2013), and the abundant evidence from molecular studies of model systems identifying a central role for gene-expression gradients in guiding axons to their targets as the brain develops (Dickson, 2002; Goodhill, 2016).

The capacity to robustly interrogate the genetics of neuronal connectivity across large swathes of the human brain has only emerged recently, with developments in connectomics and imaging genetics. The combination of both is providing new insights into the genetic architecture of the human connectome. Here, we review the findings of this work with a focus on three genetically informative designs that yield complementary information into how genes are related to neuronal connectivity. First, we consider classical heritability studies in which data on twins are used to quantify the degree to which genes influence individual differences in brain connectivity (Posthuma et al., 2003) (Figure 1). Second, we consider association studies, which aim to identify specific DNA variants

involved in brain connectivity by correlating allelic variability across the genome with phenotypic variation in some property of brain network structure or function (Thompson et al., 2013) (Figure 2). Finally, we consider work that leverages the recent availability of anatomically comprehensive gene-expression atlases (Hawrylycz et al., 2012; Keil et al., 2018) to study how the anatomical patterning of the brain's transcriptional landscape relates to spatial variations of different aspects of structural and functional connectivity (Figure 3).

The extant evidence obtained with these three approaches indicates that global properties of brain connectivity, such as total white matter volume and the average microstructural properties, are under strong genetic influence. However, when considering specific systems, regions, or connections, genetic effects are not uniformly distributed, with the connectivity of some neural elements, particularly the connections linking network hubs, being under stronger genetic control than others. Structural connectivity also appears to be more strongly driven by genetics than functional connectivity. Moreover, different types of network properties show apparently distinct transcriptional correlates, which are often conserved across species. Together, these results identify a central role for genes in shaping connectome architecture and suggest that connectivity of the metabolically costly and functionally valuable hubs of the brain may be subject to particularly tight genetic control.

Heritability

Imaging genetic studies rely on the idea that neuroimaging-derived phenotypes are, at least partly, influenced by genes. The extent to which inter-individual differences in a phenotype are driven by genetic or environmental factors can be evaluated through classical twin-based heritability studies. These studies rely on the assumption that monozygotic (MZ) or identical twins have identical genomes whereas non-identical dizygotic (DZ) share, on average, half of their genetic information. Assuming that environmental factors influence both types of twins to a similar extent, the variance of a given phenotype, σ_P^2 , can be partitioned into components explained by genetic and environmental influences (Neale & Cardon, 1992; Zylphur et al., 2013). Overall, the genetic influences could encompass additive, dominant, recessive, and other modes of inheritance (Horita & Kaneko, 2015). However, most studies focus on the narrow-sense heritability, h^2 , which quantifies the contributions of additive genetic factors, denoted A . Environmental contributions can be further separated into effects that are common to members of a twin pair (i.e., non-genetic influences shared between members of a twin pair), denoted C , and effects that are unique to each individual, denoted E . These parameters are commonly estimated through structural equation modelling using a classical ACE model (Figure 1b).

Heritability quantifies the proportion of total trait variance that is attributable to additive genetic effects: $h^2 = \frac{A}{A+C+E}$ (M. C. Neale, 2009). It is important to emphasize that heritability only quantifies the proportion of phenotypic *variance* that can be explained by genes. It is therefore focused on understanding individual differences within a specific population and does not quantify the importance of genes in determining a given trait (Griffiths et al., 2000). Heritability estimates are therefore specific to a certain population and environmental context and a low estimate does not mean that genetic factors are irrelevant. Indeed, low heritability could arise from restricted genetic variation at the relevant loci or from the environment pushing people towards similar

phenotypes despite genetic differences. For instance, the heritability of height is very high in the environments with normal nutrition (Silventoinen et al., 2003). However, extreme nutritional restrictions lead to lower variations in height between people, resulting in lower heritability estimates (Raychaudhuri et al., 2003; Roberts et al., 1978). As a result, heritability estimates from one population cannot be directly extrapolated to different circumstances. The specificity of heritability estimates to a given context is also evidenced by the fact that heritability can change over time (Bergen et al., 2007; Fulker et al., 1988; Haworth et al., 2010).

Several extensions of the classical ACE model are available. For instance, given an estimate of the reliability of a phenotypic measure (e.g., a test-retest), it is possible to parse the contribution of measurement error to the parameter E and to define heritability based only on stable inter-individual variation (e.g., Ge et al., 2017). The inclusion of non-twin siblings into the design, as in the Human Connectome Project (Van Essen et al., 2013), can be used to parse the C parameter into common environmental effects that are twin-specific or non-twin specific, under the assumption that twins experience different environments both in utero and through development compared to non-twin siblings (Arnatkevičiūtė et al., 2020; Jinks & Fulker, 1970; Mark et al., 2017). Other extensions can help understand relationships between different traits through multivariate heritability analyses by quantifying the genetic contributions shared between two or more phenotypes (Neale & Cardon, 1992; Posthuma et al., 2003; Rijdsdijk & Sham, 2002). Inverse heritability analysis involves the use of dimensionality-reduction techniques to identify new traits with maximal heritability from a set of empirical observations (Ott & Rabinowitz, 1999; Sun et al., 2015; Wang et al., 2007).

Figure 1 Heritability in imaging genetics. a) Heritability analyses use the genetic similarity between monozygotic (MZ) and dizygotic (DZ) twin pairs to quantify how genes influence phenotypic variability. Higher phenotypic correlations between MZ twins than DZ twins imply higher heritability. b) More specifically, structural equation modelling can be used to partition the phenotypic variance of a trait (σ_p^2) into genetic (denoted A), common environmental (denoted C) and unique environmental components (denoted E), where heritability (h^2) is quantified as the proportion of variance attributed to genetic factors. Path A depends on the genetic similarity between twins: MZ twins are genetically identical (path denoted $MZ=1$); DZ twins share half of their genetic information (path denoted $DZ=1/2$). c) Voxel-wise heritability estimates for the first peak in fiber orientation distribution (FOD) measurement (top) and fractional anisotropy (bottom) derived from DWI. d) Average edge-wise heritability of hub connectivity. Top panel shows the degree distribution of the cortical connectome. The distribution has an extended tail which is consistent with the existence of highly connected hubs. Bottom panel shows the average heritability estimates for rich (hub-to-hub), feeder (hub-to-nonhub) and peripheral (nonhub-to-nonhub) links as a function of the degree threshold for defining hubs. The horizontal axis corresponds to threshold for defining hubs, such that hubs are defined as nodes with $\text{degree} > k$. Higher values on the horizontal axis thus correspond to more stringent definitions of hub nodes. Rich links consistently show increased heritability compared to other link types. Dotted horizontal line shows the mean heritability across all links, shaded area corresponds to the standard error around the mean. e) Heritability estimates for inter-regional functional connectivity derived using the classical ACE model using the average of FC measures across two sessions (top-left) and the heritability estimates of the stable, nontransient component of functional connectivity derived based on repeated measurements across two sessions (top-right). Bottom: average heritability estimates within canonical functional networks obtained using the classical ACE model (red) and estimates focused on nontransient component of functional connectivity (black). Heritability based on nontransient component is consistently higher compared to standard ACE model. Panels a, b and d adapted from (Arnatkevičiūtė et al., 2020). Panel c reproduced with permission from (Shen et al., 2014), e reproduced with permission from (Ge et al., 2017).

Numerous neuroimaging phenotypes have been studied using classical twin designs. This work has shown that global anatomical properties of the brain such as total brain volume (Baaré et al., 2001; Carmelli et al., 1998; Pfefferbaum et al., 2000; Wright et al., 2002), mean cortical thickness (van Soelen et al., 2012), and total grey (Baaré et al., 2001) and white matter volumes (Baaré et al., 2001; Bohlken et al., 2014) demonstrate high heritability; typically in the range $0.6 < h^2 < 0.9$. However, these genetic influences are not uniformly distributed across the brain, with distinct aspects of brain structure showing different levels of local heritability, indicating that genes preferentially influence individual differences in certain properties and certain regions. For example, the heritability of cortical thickness across the brain varies between 0 and 0.91 (Eyler et al., 2012; van Soelen et al., 2012). Comparably wide ranges of heritability are observed for subcortical region volumes (Thompson et al., 2001; Whelan et al., 2016) and properties of cortical folding (Pizzagalli et al., 2020). Heritability of neuroanatomical properties also change over time (Jansen et al., 2015; Pizzagalli et al., 2020). Indeed, consistent with findings for cognitive and behavioural phenotypes (Bergen et al., 2007; Briley & Tucker-Drob, 2013; Haworth et al., 2010), the heritability of neuroimaging measures often increases over time, which is sometimes attributable to an increasing correlation between genotype and environment as people get older (i.e., people tend to change their environments in a way that appeals to their genetically determined preferences).

Focusing on measures of structural brain connectivity, several twin studies have examined the heritability of morphometric properties related to structural connectivity such as total white-matter volume (Baaré et al., 2001; Bohlken et al., 2014), or measures of white-matter microstructural integrity, quantified using fractional anisotropy averaged across the entire brain (Bohlken et al., 2014; Kochunov et al., 2010; Vuoksima et al., 2017) or specific tracts (Chiang et al., 2012). In line with measures of grey matter morphometry, white-matter volume has very high heritability, exceeding 0.8 in most studies, whereas global microstructural properties show slightly lower and significantly more variable heritability, ranging from 0.24 to 0.88 across studies [for an overview see (Vuoksima et al., 2017)]. In addition to being highly heritable, global measures of white-matter structure – such as fractional anisotropy and radial diffusivity – share a proportion of their genetic variance (Kochunov et al., 2010), pointing to shared genetic influences. These findings in humans are supported by work using different genetic strains of mice showing that the heritability of global properties such as fractional anisotropy, radial, and axial diffusivity, ranges between 0.28 and 0.54 (Wang et al., 2020).

The heritability of local white-matter properties is lower when compared to global measures [for an overview see (Vuoksima et al., 2017)]. Specific tracts, such as commissural fibers through genu and posterior part of corpus callosum, association fibers in the right hemisphere, and right projection fibers in cortico-spinal tracts demonstrate moderate heritability of fiber orientation distribution peaks, $h^2 > 0.45$ – a measure used to estimate the proportion of axons aligned in different orientations (Shen et al., 2014) (Figure 1c). White-matter bundles connecting ipsilateral cortical regions with the corpus callosum also demonstrate moderate heritability, across several different measures of white-matter microstructure ranging between 0.46 and 0.69 (Sudre et al., 2017).

Moving beyond the analysis of specific white-matter tracts, we recently performed a connectome-wide study of the heritability of inter-regional structural connectivity strength and obtained genetic parameter estimates for each of 12,924 links connecting 360 brain regions. We found that the genetic influences on phenotypic variance in

connectivity strength are variable, ranging between 0 and 0.8 for measures of connectivity based on streamline count and from 0 to 0.99 for measures based on mean tract FA (Arnatkevičiūtė et al., 2020). This result suggests that genetic influences are not uniformly distributed across the connectome and that some connections are under much stronger genetic control compared to others. In particular, genetic influences were preferentially concentrated on specific types of connections - namely, those between the connectome's highly connected hubs (Figure 1d). These connections, which form the basis for the brain's rich-club organization, provide a topologically central backbone for supporting integrated brain function (Bullmore & Sporns, 2012; Heuvel & Sporns, 2011). These connections are also costly, because they extend over longer distances, on average, than other types of connections (Fulcher & Fornito, 2016; Heuvel & Sporns, 2011; Towlson et al., 2013). Thus, genes strongly influence phenotypic variability in the strength of some of the most functionally valuable and costly connections in the brain, whereas variability in the strength of connections between non-hub areas is largely driven by environmental factors. This preferential genetic influence on rich-club links suggests that these connections play a crucial role in negotiating the trade-offs between wiring cost and functional value that are thought to have shaped connectome evolution (Bullmore & Sporns, 2012).

Other studies of structural connectome topology have shown that graph theoretic measures such as characteristic path length and clustering coefficient are also significantly heritable ($h^2 > 0.5$) and that some of these genetic factors partly overlap with those associated with volumetric and microstructural white matter properties (Bohlken et al., 2014). One study found that spatial variations in average regional and modal controllability, which use linear control theory to quantify the ability of a given region to drive changes in whole-brain dynamics (Gu et al., 2015), exhibit the highest heritability in thalamic, striatal, and ventral prefrontal regions (Lee et al., 2020). These measures, however, are highly correlated with node degree (Gu et al., 2015), and the specificity of these genetic influences is unclear. Gu et al. (2020) later showed that the regional coupling between structural and functional connectomes, defined as the correlation between connectivity weight vectors quantifying its connectivity to all other areas, was highly heritable and more heritable than structural or functional connectivity strength alone.

The heritability of functional connectivity (commonly quantified as the correlation of activity fluctuations between pairs of regions), has been studied using static (Colclough et al., 2017; Fornito et al., 2011; Fu et al., 2015; Glahn et al., 2010; Sinclair et al., 2015; Sudre et al., 2017) and dynamic fMRI (Barber et al., 2021), MEG (Colclough et al., 2017), and EEG (Schutte et al., 2013; Smit et al., 2008; van den Heuvel et al., 2013). Connectome-wide heritability analyses have reported mixed results. For example, functional connectivity among 39 cortical regions derived from both fMRI and MEG recordings in the Human Connectome Project (HCP) sample demonstrated relatively low levels of genetic influence, with $h^2 < 0.2$ (Colclough et al., 2017), although the samples examined were relatively small (fMRI: 103 MZ and 54 DZ pairs; MEG: 19 MZ and 13 DZ pairs). A separate study showed that the heritability of functional connectivity within canonical functional networks, on average, is highly heritable with genetic factors explaining more than 50% of variance (Ge et al., 2017). The discrepancy between these two studies may be explained by differences in the functional connectivity estimates analyzed, since Colclough et al. relied on regularized partial correlations and Ge et al. used Pearson correlations. The former may thus reduce sensitivity to genetic effects (see also Fornito et al., 2016; Zalesky et al., 2012 for discussions).

Voxel-wise analyses of network functional connectivity estimated through spatial independent component analysis (ICA) (Barber et al., 2021; Fu et al., 2015; Glahn et al., 2010; Sudre et al., 2017; Yang et al., 2016) and seed-based connectivity (Adhikari et al., 2018) have demonstrated considerable genetic influence on several resting-state networks, including sensory (Fu et al., 2015) and transmodal association networks, ranging between $0.2 < h^2 < 0.8$ (Adhikari et al., 2018; Barber et al., 2021; Glahn et al., 2010; Sudre et al., 2017; Z. Yang et al., 2016). The average heritability of resting-state functional connectivity in the visual cortex has been shown to relate to its hierarchical level in a non-monotonic manner, such that heritability increases from V1 to V3 and then decreases with increasing hierarchical level (Haak & Beckmann, 2019). Moreover, the authors used inferred functional plasticity across hierarchical levels to demonstrate an opposite relationship where plasticity first decreases from early to mid-level cortex and then increases further of the visual hierarchy (Haak & Beckmann, 2019). Using the multiple linear regression coefficients between regional time series and all other regions, Miranda-Dominguez et al. (2018) quantified functional relationships between each pair of brain regions and investigated heritability at the level of individual regions, functional networks, and the whole brain. They identified relatively low influence of genetic factors for most measures ($h^2 < 0.2$), although estimates were higher for more global measures (Miranda-Dominguez et al., 2018). Several topological properties of resting-state fMRI and EEG networks, such as global efficiency, clustering, path length, and measure of cost-efficiency exhibit heritability ranging between 0.2 and 0.9 (Fornito et al., 2011; Schutte et al., 2013; Sinclair et al., 2015; Smit et al., 2008; van den Heuvel et al., 2013). These findings are in line with studies of structural connectivity and suggest that network properties shaped by cost-value trade-offs are particularly heritable (Arnatkevičiūtė et al., 2020).

It is important to remember that heritability estimates can be influenced by numerous data-processing and analysis choices. For example, structural connectivity can be estimated using different tractography algorithms, such as those that rely on deterministic or probabilistic algorithms. Deterministic approaches typically result in lower-density connectomes that may be prone to false negatives, whereas probabilistic algorithms yield dense connectomes that have lower specificity and which potentially contain false-positive connections (Thomas et al., 2014; Zalesky et al., 2016). These choices can impact the heritability estimates of brain-network properties. Indeed, there is evidence that higher heritability estimates are obtained for graph-theoretic measures when applying probabilistic compared to deterministic algorithms (Zhan et al., 2015). In studies of functional connectivity, the validity and utility of global signal regression, which involves the regression of a mean time course from the fMRI data, has been widely debated (Aquino et al., 2020; Liu et al., 2017; Murphy & Fox, 2017; Power et al., 2017; Saad et al., 2012). This step has been shown to substantially decrease heritability for different measures of functional network topology (Sinclair et al., 2015). Both diffusion and functional MRI pipelines rely on many different processing choices which vary in their efficacy in denoising the data (Ciric et al., 2017; Oldham et al., 2020; Parkes et al., 2018), and this variable efficacy can influence resulting heritability estimates. On a related point, the apparently higher heritability of global compared to local connectivity measures seen for both structural and functional connectivity raises questions about the underlying mechanisms. Are global measures more strongly influenced by genetic factors? Or are global measures quantified more reliably, resulting in higher heritability estimates? Analyses of test-retest measures have demonstrated that heritability estimates of resting-state functional networks do indeed depend on measurement reliability and that accounting for within-subject

variation results in increased network heritability (Ge et al., 2017) (Figure 1e). This result underscores the importance of incorporating estimates of measurement error into heritability models.

Overall, classical heritability studies of macroscale brain connectivity identify strong genetic influences over global brain measures such as white-matter and total brain volume, and averaged measures of white-matter microstructure. In contrast, the heritability of individual tracts and specific inter-regional connections is somewhat lower and is not distributed uniformly through the connectome. In particular, phenotypic variability in the strength of connections that play a critical role in negotiating cost-value trade-offs, such as those between highly connected network hubs, appears to be preferentially influenced by genes.

Association analyses

Heritability quantifies genetic contributions to individual differences in a given phenotype and informs the prioritization of heritable phenotypes for more targeted investigation. Association studies can be used to identify the specific DNA variants associated with a trait by testing for relationships between trait and allelic variation at different points scattered throughout the genome (Hirschhorn & Daly, 2005). Association analyses began with a hypothesis-driven candidate gene approach by testing a small number of selected markers hypothetically linked to the trait (Patnala et al., 2013; Thompson et al., 2013). These studies identified variants related to a range of brain-connectivity phenotypes such as white-matter microstructure (Braskie et al., 2012; Chiang et al., 2009, 2011; Jahanshad et al., 2012), topological network properties (Dennis et al., 2011), and resting-state functional connectivity (Filippini et al., 2009; Trachtenberg et al., 2012; Westlye et al., 2011). However, candidate gene studies have been called into question due to a high frequency of false-positive associations (Sullivan, 2007) and low replication rates (Hart et al., 2013; Sullivan, 2007). With increasing data availability and computational power, association analyses have been expanded to genome-wide association studies (GWAS), where the relationship between allelic variation and a given trait can be tested at each of millions of markers distributed throughout the genome (Bush & Moore, 2012; Marees et al., 2018) (Figure 2a). Due to the large number of tests performed, sample sizes in the order of 10^4 – 10^6 are required for sufficient statistical power (Hong & Park, 2012). Moreover, imaging genetic studies often investigate multiple, intercorrelated phenotypes (e.g., a given measure computed over voxels), adding an additional anatomical dimension that must be considered in the inferential procedures (Huang et al., 2015; Stein et al., 2010).

Early genome-wide association studies of connectivity-related phenotypes were conducted in modest sample sizes (i.e., $N < 400$) but nevertheless identified plausible genetic associations with measures of both structural (Elsheikh et al., 2020; Jahanshad et al., 2013) and functional connectivity (Richiardi et al., 2015). The sample sizes required for rigorous inference were soon achieved through large consortia, such as ENIGMA (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019), or population-based studies such as the UK Biobank (Elliott et al., 2018; Sudlow et al., 2015). In a comprehensive GWAS of neuroimaging phenotypes in the UK Biobank, Elliot et al. (2018) tested for associations between almost 12 million variants and 3144 brain imaging phenotypes, including measures of brain structure as well as structural and functional connectivity, in more than 8000 individuals. After correcting for the number of analyses performed, the authors identified 368 significant associations, with more than half involving white-matter tracts (Figure 2e). The majority of white-matter related phenotypes were

associated with SNPs related to genes regulating the extracellular matrix and epidermal growth factor signalling, having key roles in synaptic plasticity and myelin repair. Functional-connectivity phenotypes showed associations at lower significance thresholds and no significant associations were observed for measures of task fMRI (Elliott et al., 2018). A recent follow-up analysis using a significantly expanded discovery sample of more than 22,000 subjects and a replication sample of more than 11,000 subjects, identified 692 replicating clusters of associations with a number of imaging phenotypes, including all types of measures except task fMRI. The authors also extensively focused on associations within the X chromosome, among others, identifying a cluster of five SNPs exclusively associated with 96 measures that capture different properties of white-matter tracts (Smith et al., 2020). These findings suggest that genetic influences on phenotypic variability in neuroimaging phenotypes are particularly strong for measures of anatomical connectivity.

Preliminary evidence indicates that GWAS-identified hits for connectivity measures have relevance for understanding disease. For instance, one of the 5 SNPs identified by Smith et al., 2020 in relation to 96 different white-matter tract properties influences the expression of the FAM58A gene (i.e., the SNP is an expression quantitative trait locus, or eQTL for the gene). This gene is implicated in the rare X-linked developmental disorder, STAR (syndactyly, telecanthus and anogenital and renal malformations) (Unger et al., 2008), which is associated with callosal thinning among other brain changes (Bedeschi et al., 2017). A separate GWAS of default-mode network functional connectivity in the UK Biobank data identified a set of 19 significant SNPs that mapped to 12 genes which were enriched in a schizophrenia-related functional gene set (Wei et al., 2019). This finding aligns with substantial evidence for default mode network dysconnectivity in schizophrenia (Northoff & Duncan, 2016; Pankow et al., 2015).

Figure 2 Association studies of brain connectivity. Association analyses quantify relationships between phenotypic and structural DNA variation. In particular, genome wide association studies (GWAS) test for associations with DNA variants at millions of points throughout the genome, with the results commonly represented as a Manhattan plot (a) in which variants across chromosomes are represented on the horizontal axis and the significance of each association is shown on the vertical axis [quantified as $-\log(p)$]. When multiple variants at similar locations show a significant association with a phenotype, “towers” appear in the Manhattan plot landscape. The output of the GWAS can be used to quantify the cumulative genetic load for a selected phenotype in an independent sample of subjects through the calculation of a polygenic risk score by computing the sum of risk alleles inherited by an individual, weighted by the effect size of each allele (b). A schematic representation of risk allele frequencies between cases and controls: on average cases have a higher number of risk alleles compared to controls (c). d) Estimates of SNP-heritability for diffusion and functional imaging-derived phenotypes (IDPs). Overall, diffusion IDPs demonstrate higher heritability compared to fMRI IDPs. Different measurement classes are indicated by different colours. e) Manhattan plot visualising the GWAS results for an intracellular volume fraction (ICVF) phenotype in the right inferior longitudinal fasciculus (left). Spatial mapping of rs67827860 against voxel-wise ICVF in white matter (right). The effects are widespread across white matter tracts. Manhattan plot in the panel a and panels d and e are reproduced with permission from (Elliott et al., 2018).

GWAS data can also be used to evaluate the SNP-heritability (h_{SNP}^2) of a trait, which is quantified using the similarity between individuals at the level of genetic variants. More specifically, h_{SNP}^2 quantifies the proportion of variance in a trait that is attributable to the additive effect of a given set of common genetic variants (Yang et al., 2017; Zhu & Zhou, 2020). An advantage of this approach is that it can be used with unrelated individuals and it does not rely on some of the assumptions of the classical twin design. For example, twin studies assume that environmental influences are common between MZ and DZ twins, but some have called this assumption into question, noting that both intrauterine and postnatal environments can differ as a function of zygosity (Corseello & Piro, 2010; Joseph, 2002). The extent to which this is assumption is a problem for twin studies is a topic of ongoing debate (Conley et al., 2013; Kendler et al., 1993), but it does not apply in studies of h_{SNP}^2 in unrelated individuals. A disadvantage of h_{SNP}^2 is that it only captures similarity in common genetic variants; as such, estimates of h_{SNP}^2 are lower than narrow-sense h^2 obtained in classical twin designs. Moreover, studies of h_{SNP}^2 typically >5000 samples for reliable inference (Yang et al., 2017).

The comprehensive analysis of the UK Biobank data by Elliott et al. (2018) found statistically significant h_{SNP}^2 for numerous diffusion MRI and, to a lesser extent, functional MRI measures, suggesting that genetic influences may be more pronounced for structural compared to functional connectivity (Figure 2d). Some of the structural and diffusion MRI phenotypes demonstrated relatively high h_{SNP}^2 , exceeding 0.6 for some regional volumes and estimates of intracellular volume fraction (ICVF) (Figure 2d,e). The ICVF parameter is estimated from the NODDI modelling (Zhang et al., 2012) of DWI data aiming to quantify intra-axonal water in white matter. In line with lower SNP-heritability estimates for functional connectivity (Elliott et al., 2018), two independent studies using UK Biobank data found significant but relatively low SNP-heritability for the resting-state functional connectivity of the default mode network ($h_{SNP}^2=0.09$) (Wei et al., 2019) and for a set of topological measures derived from fMRI networks (mean $h_{SNP}^2=0.12$), including global efficiency, characteristic path length and transitivity (Foo et al., 2020). These findings align with classical twin results to suggest a lower level of genetic influence on functional connectivity compared to structural connectivity.

The results of a GWAS can also be used to estimate polygenic scores (PGS) (Dudbridge, 2013). These scores quantify the aggregate impact of multiple SNPs on a given trait (Choi et al., 2020; Wray et al., 2020). More specifically, they allow the genetic liability for a trait to be computed for any individual via a weighted sum of their alleles, where the weights are obtained from a GWAS in an independent sample (Figure 2b,c). The reliability of any association between a given PGS and imaging phenotype therefore depends on the size and validity of the original GWAS and the size of the new sample for estimating the correlation. One caveat of PGS analyses is that the scores typically only explain a small fraction of variance (rarely more than 10%) in the original target trait (Lewis & Vassos, 2020), so they only capture a limited proportion of genetic liability for that trait.

Measures of structural connectivity at the global and tract level have been linked to PGS for psychiatric disorders such as autism (Khundrakpam et al., 2020) and schizophrenia (Alloza et al., 2018), as well as PGS for quantitative phenotypes like intelligence, educational attainment (Jansen et al., 2019), and anhedonia (Ward et al., 2019). However, the findings across different measures of structural connectivity are not very consistent. For instance, age-related changes in tract-based white matter properties such as mean diffusivity and FA in older adults were

related to PGS for schizophrenia, whereas longitudinal changes in measures of network topology in the same population did not show any associations, suggesting that distinct common genetic influences affect tract microstructure and network topology (Alloza et al., 2018). Similarly, PGS for anhedonia in the general population has been linked to lower FA and higher MD in several white-matter tracts, but was unrelated to global measures of white-matter integrity (Ward et al., 2019).

Several studies have used a hypothesis-driven approach, examining how the connectivity of specific regions relates to PGSs for different disorders. For instance, insular connectivity networks have been correlated with cross-disorder PGS, as well as PGSs for bipolar disorder, autism, and schizophrenia, but not major depression or ADHD (Wang et al., 2017). Stronger global and regionally specific connectivity of the nucleus accumbens, which is known to be altered in schizophrenia (Eberle et al., 2019; Lee et al., 2018), has been associated with increased PGS for this disorder in healthy subjects (Eberle et al., 2019). It is important to note, however, that the limited predictive accuracy of polygenic scores may partly reflect the fact that PGSs do not consider rare variants, which tend to have larger phenotypic effects (Bomba et al., 2017). It may also reflect a lack of specificity in identifying key SNPs, since PGSs classically aggregate the effects of many SNPs surpassing a nominal threshold in the original GWAS. Indeed, there is some evidence that restricting PGS calculations to pre-defined set of SNPs in genes or pathways that are known to be involved in a specific disorder may increase power for identifying associations between genotype and phenotype. For example, one study only found a significant association between functional connectivity and PGS for schizophrenia when the PGS was estimated using a set of SNPs residing in the CREB-BDNF family genes, which are linked to schizophrenia and neural development; no such association was found using the full set of schizophrenia GWAS SNPs (Chen et al., 2018). A separate study found that a schizophrenia PGS calculated only using SNPs in dopamine-related genes was associated with working memory and striatal connectivity in healthy individuals (Wang et al., 2018), which aligns with the known role of dopamine the pathophysiology of the condition (Dandash et al., 2017; McCutcheon et al., 2019). Despite these results, however, the identified associations were still small, with estimates of shared variance generally below 2%.

In summary, the available evidence from GWAS research aligns with the results of classical twin studies to indicate that, compared to functional connectivity, properties of structural connectivity are more strongly influenced by common DNA variation. This may reflect the inherent dynamism of functional connectivity, and the need for neuronal activity to rapidly respond to changing environmental circumstances which is in part limited by the genetic constraints. Structural connectivity, on the other hand, appears to represent a genetically sculpted anatomical backbone that shapes and constrains how context-dependent dynamics unfold (Honey et al., 2007).

Transcriptomic analyses

Heritability analyses can be used to quantify the degree to which genes influence phenotypic variability in a given trait and association analyses can be used to identify specific DNA variants that drive these effects. The assumption is that these variants impact protein form and function, thereby giving rise to phenotypic variability. However, multiple other factors can influence the transcriptional activity of a gene and the ultimate abundance of

its protein product (Choi & Kim, 2007; Cole, 2009; Fraser et al., 2005). As such, structural DNA variation may be somewhat distal to the ultimate molecular mechanisms that influence a given phenotype. Studies of gene expression can shed light on some of these more proximal mechanisms.

It has historically been difficult to relate measures of gene expression to neuroimaging phenotypes. Gene expression in the brain must be measured post-mortem and has traditionally been assayed in only a small subset of brain regions at a time. The recent development of high-throughput tissue processing and analysis pipelines has enabled the construction of brain-wide gene-expression atlases (Harris et al., 2010; Hawrylycz et al., 2012; Lein et al., 2007) (Figure 3a-c), which have opened new opportunities for understanding how the spatial patterning of gene expression relates to anatomical variations in different aspects of brain structure and function [for a review see (Fornito et al., 2019)]. The specific method used to quantify gene expression depends on the organism of interest, required resolution, tissue availability, and a range of other factors. For example, in the nematode *C. elegans*, which has had its connectome mapped completely at the level of individual neurons and synapses (Cook et al., 2019; Varshney et al., 2011; White et al., 1986), expression profiles for each neuron have been obtained through the curation of published findings in individual experiments examining specific cells (Harris et al., 2010) or cell class-specific gene-expression patterns (Taylor et al., 2019). In larger species with high tissue availability, gene expression can be measured using *in situ* hybridization approach (Lein et al., 2007) allowing the quantification of gene expression at a cellular resolution. The Allen Mouse Brain Atlas (AMBA) (Lein et al., 2007; Ng et al., 2009) comprises such measures for over 19,000 genes at a cellular resolution, acquired at 200 μ m slices through the brain volume. Bulk-tissue microarray (Schulze & Downward, 2001), on the other hand, remains the most accessible method for high-throughput spatial transcriptomics in humans (Hawrylycz et al., 2012), allowing simultaneous quantification of the expression levels of thousands of genes. The Allen Human Brain Atlas (AHBA) provides the most anatomically comprehensive gene-expression data for the human brain, quantifying expression levels of more than 20,000 genes in 3702 different regions through microarray (Hawrylycz et al., 2012). Other atlases can be used for investigating developmental (Kang et al., 2011) and human-specific spatiotemporal gene-expression patterns (Sousa et al., 2017), however their spatial coverage is sparser than the AHBA [for an overview see (Keil et al., 2018)]. Single-cell transcriptional atlases (Darmanis et al., 2015; Lake et al., 2016) can be used to further understand cell-specific patterns of gene expression and to investigate their spatial patterns (Edsgård et al., 2018) and temporal trajectories (Rashid et al., 2017), although they too suffer from limited anatomical coverage at present.

Analyses involving transcriptional atlases have typically focused on: (i) regional gene expression; (ii) correlated gene expression (CGE) between pairs of regions; or (iii) gene coexpression networks, quantified at the level of pairs of genes, as illustrated in Figure 3c. Regional gene-expression analyses aim to identify associations between spatial variations of gene expression and spatially defined neural phenotypes at the level of brain regions. CGE quantifies the transcriptional similarity between two regions across a given set of genes and can be related to different aspects of pairwise brain connectivity, such as the presence, type, and/or strength of a connection (Arnatkevičiūtė et al., 2018; Fulcher & Fornito, 2016; Richiardi et al., 2015), whereas analyses of gene coexpression consider the similarity of regional expression profiles between pairs of genes (Forest et al., 2017; Oldham et al., 2008).

Figure 3. Linking gene expression to brain connectivity. A schematic representation of workflows relating transcriptomic atlas and connectome data: a) Anatomical locations of different cortical gene expression samples taken from donor brains comprising the Allen Human brain Atlas. Tissue samples from different donor brains are mapped to regions in a brain parcellation resulting in spatial maps of expression for each gene (b). Gene-expression profiles across thousands of genes are used to construct a gene expression matrix that quantifies the expression of each gene in every region of the brain parcellation (c). These measures can then be related to spatially varying connectivity phenotypes. Gene co-expression is quantified as the correlation between regional expression profiles of pairs of genes (columns of the expression matrix) resulting in a gene-by-gene correlation matrix. The analysis of regional expression patterns requires extracting the spatial expression profile of each gene separately and relating it to regional variations in some brain property, such as node degree. In a correlated gene expression (CGE) analysis, vectors of gene expression for each region (rows of the expression matrix) are correlated to construct a region-by-region correlation matrix. CGE values can be related to pairwise measures of brain structure or function. Panel d shows CGE for rich (hub-to-hub), feeder (hub-to-nonhub) and peripheral (nonhub-to-nonhub) links as a function of the degree threshold for defining network hubs in *C. elegans*, mouse, and human connectomes. Higher values on the horizontal axis correspond to more stringent definitions of hubs. Across all species, CGE for rich links is consistently higher compared to other links types. The increase is particularly pronounced for higher hub thresholds, which is where the actual network hubs reside. Dotted horizontal lines in each plot correspond to the mean CGE across all links. e) Regional morphometric similarity change observed in Turner syndrome (characterised by the loss of the X-chromosome) and the chromosome ranking from the PLS analysis. The chromosomes are ordered according to the median rank of their genes based on the scores from the PLS analysis. The chromosomal gene set for X chromosome shows the lowest rank which is consistent with the chromosomal deletion. f) Association between the spatial expression pattern of three gene markers for somatostatin (SST) interneurons [SST, cortistatin (CORT), and neuropeptide Y (NPY)] and reduced global brain connectivity in patients with depression. The scatter plot represents the relationship for SST genes, regression lines represent relationships for all three gene markers. g) Correlation between the mean regional expression of schizophrenia risk genes (shown in blue) and the cortical pattern of reductions in macroscale regional dysconnectivity in schizophrenia (shown in red). Panels a-c adapted from (Arnatkevičiūtė et al., 2019; Fornito et al., 2019). Figures in panel d are reproduced with permission from (Arnatkevičiūtė et al., 2018) – *C. elegans*, (Fulcher & Fornito, 2016) – mouse and (Arnatkevičiūtė et al., 2020) – human. Panel e reproduced with permission from (Anderson et al., 2020). Panel f adapted with permission from (Romme et al., 2017). Panel g reproduced with permission from (Seidlitz et al., 2020).

Most of these analyses involve scoring each gene based on its association with a selected phenotype. Since the number of genes considered is very large, inference is often performed at the level of functionally related sets of genes defined either based on a prior hypotheses of systematic annotation systems, such the Gene Ontology (GO) (Ashburner et al., 2000) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa & Goto, 2000). Gene category enrichment analyses (GCEA) involve determining whether a summary score for each category (typically the mean) is higher than expected given some null expectation (Fulcher et al., 2021).

Several studies have shown that gene-expression signatures are related to the presence or absence of connections in both micro- and mesoscale connectomes. In *C. elegans*, expression signatures can be used to predict neuronal connectivity (Kaufman, 2007; Kovács et al., 2020; Varadan et al., 2006) and incorporating the spatial location of individual neurons into those models further improves prediction accuracy (Baruch et al., 2008; Kaufman et al., 2006), suggesting that a combination of both geometric and genetic constraints shapes neuronal connectivity. Extending these findings, computational models have been developed to derive genetically-informed rules that govern the formation of neuronal connectivity in the *C. elegans* connectome (Barabási & Barabási, 2020; Kovács et al., 2020). One model based on the selective operators, that take into account expression patterns in subsets of, but not all, transcriptional factors, was able to predict the emergence of complex topological properties such as

biclique motifs in the *C. elegans* connectome (Barabási & Barabási, 2020). Subsequent work developed a model in which the combination of three separate datasets – a comprehensive neuronal connectivity map, gene-expression profiles of individual neurons, and a list of neurons in direct physical contact – was used to identify a set of rules, related to interactions between innexin genes, that predicted the formation and maintenance of gap junctions in *C. elegans* (Kovács et al., 2020). These computational frameworks provide a set of falsifiable predictions that can be later tested using more direct techniques such as single gene-knockout experiments.

In mice and rats, gene-expression profiles can predict inter-regional connectivity, with genes related to axon guidance, neuronal communication, and development being among the most informative (Fakhry et al., 2015; Fakhry & Ji, 2015; French & Pavlidis, 2011; Ji et al., 2014; Roberti et al., 2019). A model that incorporates CGE, structural connectivity, and the physical distance between pairs of brain regions has been shown to account for 62% of inter-regional functional coupling in the mouse brain (Mills et al., 2018), indicating that geometry and regional gene-expression similarity are also informative of resting-state functional connectivity.

Human research has further characterised links between transcriptional patterns and the specialization of brain areas (Anderson et al., 2018; Krienen et al., 2016; Parkes et al., 2017), neurodevelopment (Kirsch & Chechik, 2016; Whitaker et al., 2016), and a wide range of structural (Forest et al., 2017; Goel et al., 2014; Romero-Garcia et al., 2018) and functional (Cioli et al., 2014; Richiardi et al., 2015; Vértés et al., 2016) connectivity phenotypes. In line with the animal evidence for enhanced transcriptional similarity between connected regions, an early analysis of canonical resting-state functional connectivity networks found that CGE was higher within than between networks, with the effect most strongly driven by a set of 136 genes related to ion channel function (Richiardi et al., 2015). Furthermore, the transcriptional similarity of mouse orthologs for these genes also demonstrated a significantly higher correlation to the axonal connectivity of the mouse brain than expected by chance. Another study found that genes with consistently varying regional expression patterns across different donor brains in the AHBA are more strongly correlated with cortical resting-state functional connectivity than other genes (Hawrylycz et al., 2015). Subsets of these genes were later shown to differentially relate to the spatial topography of functional connectivity networks that putatively support distinct temporal processing modes; more specifically, networks involved in sensory information processing were related to genes involved in rapid, evoked activity whereas networks associated with cognitive and emotional control were associated with increased expression of genes regulating slower, sustained, and rhythmic activity (Cioli et al., 2014).

Krienen et al. (2016) later focused on a subset of 19 genes that display upregulated expression in upper cortical layers of human compared to mouse brains. The CGE of these Human Supragranular Enriched (HSE) genes was generally higher within than between canonical functional networks and strongly differentiated sensorimotor from association and paralimbic systems. Moreover, networks that share similar connectional profiles, namely preferentially connecting distant or local regional pairs, tend to have similar HSE gene expression profiles, suggesting that differences in transcriptional activity may be important in the evolution of long-range cortical connectivity (Krienen et al., 2016). Subsequent work confirmed that HSE genes show significant enrichment in regions that are characterized by abundant long-range inter-module connectivity (Vértés et al., 2016) and increased expression in regions that are highly coupled within structural covariance networks (Romero-Garcia et al., 2018).

The transcriptional correlates of specific topological properties of the connectome have also been investigated, with a particular emphasis on understanding hub connectivity. In the mouse brain, regional gene-expression profiles associated with the nodal participation coefficient, which quantifies the degree to which a node's connections are distributed across different neural systems, were enriched for genes involved in cognitive function (Rubinov et al., 2015). A subsequent analysis of inter-regional transcriptional coupling in the mouse brain demonstrated that connected pairs of hubs exhibit the highest CGE, despite being separated by longer anatomical distances compared to other pairs of regions (Fulcher & Fornito, 2016). This finding is notable considering that, in both mouse and human, the strength of CGE between regions declines sharply as a function their distance (Arnatkevičiūtė et al., 2019; Fulcher & Fornito, 2016; Lau et al., 2021). Genes driving the increased CGE between hubs were related to oxidative synthesis and metabolism of ATP (Fulcher & Fornito, 2016), in line with evidence that hub regions mediate a high proportion of signal traffic and are therefore amongst the most metabolically expensive regions of the brain (Bullmore & Sporns, 2012; Collin et al., 2014; Vaishnavi et al., 2010; Várkuti et al., 2011). A similar pattern of increased CGE between hubs has also been reported in the structural connectome at the level of neurons in *C. elegans* (Arnatkevičiūtė et al., 2018) and macroscopic human brain regions (Arnatkevičiūtė et al., 2020), indicating that, despite significant differences in animals, resolution scales, and measurement techniques, highly connected and functionally important connectome hubs have a strongly conserved transcriptional signature (Figure 3d). Similar findings have been identified in analyses of human functional connectivity networks (Vértes et al., 2016). Together these results imply that connectome hubs in different species show a strong transcriptional similarity that in mouse and human is related to their high metabolic demand.

Associations between gene expression and brain connectivity have also shed some light on the pathological changes observed in clinical disorders. A general approach used in these studies involves computing a spatial map of case–control differences in a selected imaging phenotype and relating it to spatial gene-expression patterns (in either a hypothesis-driven or data-driven way). The potential of this approach was powerfully demonstrated in a recent study of single-gene neurodevelopmental conditions such as Down syndrome, Turner syndrome, Velocardiofacial syndrome and several others, where the causal genes are known (Seidlitz et al., 2020). This analysis revealed that the spatial topography of case-control differences in each disorder, particularly with respect to regional coupling in morphometric similarity networks constructed using multiple measures of regional neuroanatomy and microstructure, is related to the specific spatial expression of the causal genes for each disorder (Seidlitz et al., 2020) (Figure 3e). In other work, regional expression of the MAPT gene, which codes for tau protein, was correlated with reduced functional connectivity in patients with Parkinson's disease whereas the SNCA gene encoding α -synuclein was not, suggesting that changes in global network properties in the disorder may be primarily mediated by tau pathology (Rittman et al., 2016). Regional decreases in global functional brain connectivity in depression, quantified as the average connectivity of a region to all other areas, have been shown to correlate with gene markers for somatostatin interneurons in post-mortem tissues derived from depression patients (Anderson et al., 2020) (Figure 3f). This finding is in line with the hypothesis that the dysfunction of cortical somatostatin interneurons plays a preferential role in the onset of depression. Moreover, the spatial expression pattern of genes down-regulated in patients ex vivo correlated with in vivo spatial patterns of

depression-related changes in anatomical and functional maps. Such associations were not found for other four comparison psychiatric disorders: schizophrenia, bipolar disorder, autism spectrum disorder, and alcohol abuse disorder. A separate study found that white-matter dysconnectivity in schizophrenia patients, quantified as the group mean difference in regional node degree between patients and controls, was correlated with the average spatial expression profile of schizophrenia-related genes identified through a GWAS (Figure 3g), thus providing a transcriptional link between structural risk variants and brain changes in the disorder (Romme et al., 2017). Using partial least squares (PLS), analysis McColgan et al. (2018) found that spatial patterning of gene expression can explain more than 65% of variance in regional corticostriatal and interhemispheric white matter connectivity loss in Huntington's disease. Enrichment analyses indicated the involvement of genes related to modulation of chemical synaptic transmission and cell projection organization highlighting the importance of genes regulating synaptic connectivity (McColgan et al., 2018).

The first wave of imaging transcriptomic studies has shown promise in shedding new light on the molecular correlates of neuroimaging phenotypes, but the analyses must be conducted and interpreted with care. One challenge is that the expression data are not “plug-and-play” and require the application of several processing steps to ensure valid analysis. These steps include appropriate mapping of tissue samples to the regions of interest, selecting representative gene probes, and accounting for inter-donor variability in gene expression, among others. Each of these steps entails different choices, which can affect the final results, complicating interpretation and limiting reproducibility. Some of these choices have been investigated in detail, leading to the proposal of recommended workflows (Arnatkevičiūtė et al., 2019), some of which have been integrated into open-source software (Markello et al., 2021).

A second challenge is caused by the intrinsic spatial autocorrelation of both the gene-expression data and most connectivity measures, which results in higher connectivity and more similar transcriptional profiles for regions separated by shorter anatomical distances, as shown in human cortex (Krienen et al., 2016; Pantazatos & Li, 2017; Richiardi et al., 2015, 2017; Vértes et al., 2016), mouse brain (Fulcher & Fornito, 2016; Lau et al., 2021), and in the head of *C. elegans* worm (Arnatkevičiūtė et al., 2018). These spatial autocorrelations are important physiological properties that may be established early in development and scale with brain growth (Lau et al., 2021). However, the autocorrelation of both expression and imaging measures violates the assumptions of independence that underpin traditional inferential methods, necessitating the use of alternative null models, such as permutation-based procedures that preserve the spatial structure of the data (Alexander-Bloch et al., 2019; Váša et al., 2018; Vértes et al., 2016), regression-based measures for removing distance effects (Arnatkevičiūtė et al., 2020; Fulcher & Fornito, 2016), or model-based techniques that generate surrogate data with the same degree of spatial correlation (Burt et al., 2018, 2020). The performance of these techniques depends on the research context, and more naïve models can inflate significance levels (Markello & Misic, 2020).

A third challenge concerns statistical inference for sets of genes using GCEA. Traditional GCEA workflows have been adapted from studies of individual tissue samples or of structural DNA variation and compute the statistical significance of a given gene category with reference to a null ensemble generated by randomizing gene-to-category assignments. Fulcher et al. (2021) showed that this null model can lead to a high rate of false positives when applied to purely random phenotypic maps with an average inflation in the false-positive rate across all GO

categories exceeding 500-fold. This false-positive bias is largely driven by differences in the correlation structure of genes within a category, with categories associated with high mean gene–gene coexpression being the most susceptible to false-positive bias. Gene-specific variations in spatial autocorrelation additionally modulate this effect. Critically, GO categories with the highest false-positive rates tend to be related to brain function and are also most frequently reported as showing significant enrichment in the literature, raising concerns about the validity of many reports applying GCEA to transcriptional atlas data. These issues may be alleviated by using a GCEA null model that randomizes the phenotype (rather than gene-to-category annotations), and thus preserves within-category gene–gene correlations and can preserve spatial autocorrelation in the phenotype using an appropriate randomization scheme (Burt et al., 2020). Under these phenotype ensemble nulls, the number of significantly enriched categories observed across structural connectivity and cell density phenotypes in mouse and human dropped considerably [e.g., for regional connectivity degree in human, the traditional analysis identify 365 significant categories compared to 0 when using randomized phenotypes (Fulcher et al., 2021)] (see also Wei et al., 2021 for related work).

Taken together, spatial transcriptomic analyses across species indicate that anatomical variations in gene expression track patterns of structural and functional connectivity in the brain across different scales and levels of complexity, from the neuronal network of the *C. elegans* to the large-scale structural and functional networks of the human brain. Particular aspects of topological brain-network organization, such as rich-club connectivity, demonstrate conserved transcriptional signatures related to the high metabolic demand of hub regions, which is in line with their functional role as the integrative core of the connectome.

Conclusions

The intersection of connectomics and imaging genetics has already proven useful for understanding how genes sculpt the large-scale network organization of the brain, uncovering potential molecular mechanisms that may explain the emergence of particular connectivity patterns and individual differences in brain structure and function. Classical twin studies indicate that global properties of white-matter microstructure are strongly influenced by genes, with local properties generally showing smaller genetic influences that have a heterogeneous distribution throughout the brain. Phenotypic variability in the connectivity strength of links between brain-network hubs, which have an important role in negotiating cost-value trade-offs within the brain, are under particularly strong genetic influence. These connections may have thus played an important role in the evolution of complex connectome topologies. Measures of structural connectivity also appear to be more heritable than functional connectivity, which aligns with evidence from association studies demonstrating stronger genetic associations for the former set of phenotypes. These findings suggest that anatomical connectivity provides a stable, heritable substrate for dynamic, plastic, and adaptive neuronal dynamics. Analyses of transcriptional atlas data complement the twin and association findings, revealing a close link between specific aspects of network connectivity and transcriptional profiles, thus helping to bridge the gap between structural risk variants and observable brain changes in clinical disorders.

Further technical advances and increasing data availability will be able to reveal even more insights into how brain networks emerge, what drives differences between individuals, and the mechanisms that give rise to brain

network dysfunction in different brain disorders. Twin studies would benefit from the use of extended family designs and test-retest paradigms to yield more refined estimates of genetic and environmental influences than offered by the traditional ACE model. Association studies will become more widespread with the increasing availability of large, population-based datasets such as the UK Biobank and ABCD studies, necessitating the development of new tools for making sense of the multitude of associations between multiple SNPs and imaging phenotypes that will result. Analyses using transcriptional atlas data would benefit from an expansion of the donor sets to include larger and more diverse individuals, and a greater spatial coverage of time-resolved gene-expression atlases (Bakken et al., 2016; Colantuoni et al., 2011) which, when coupled with lifespan imaging data, will further our understanding of how transcriptional dynamics relate to brain network maturation and ageing both in health and disease. Expanding those atlases to incorporate single-cell transcriptomics will elucidate the specific expression signatures related to individual cell types and their related pathologies (Lein et al., 2017). Such developments will be important for better understanding the molecular basis of the large-scale organization of the human connectome.

Acknowledgements

AF was supported by the National Health and Medical Research Council of Australia (ID:1050504) and Sylvia and Charles Viertel Charitable Foundation. MAB was supported by a National Health and Medical Research Council of Australia Senior Research Fellowship.

References

- Adhikari, B. M., Jahanshad, N., Shukla, D., Glahn, D. C., Blangero, J., Fox, P. T., Reynolds, R. C., Cox, R. W., Fieremans, E., Veraart, J., Novikov, D. S., Nichols, T. E., Hong, L. E., Thompson, P. M., & Kochunov, P. (2018). Comparison of heritability estimates on resting state fMRI connectivity phenotypes using the ENIGMA analysis pipeline. *Human Brain Mapping, 39*(12), 4893–4902. <https://doi.org/10.1002/hbm.24331>
- Alexander-Bloch, A. F., Mathias, S. R., Fox, P. T., Olvera, R. L., Göring, H. H. H., Duggirala, R., Curran, J. E., Blangero, J., & Glahn, D. C. (2019). Human Cortical Thickness Organized into Genetically-determined Communities across Spatial Resolutions. *Cerebral Cortex (New York, NY), 29*(1), 106–118. <https://doi.org/10.1093/cercor/bhx309>
- Alloza, C., Cox, S. R., Blesa Cábez, M., Redmond, P., Whalley, H. C., Ritchie, S. J., Muñoz Maniega, S., Valdés Hernández, M. del C., Tucker-Drob, E. M., Lawrie, S. M., Wardlaw, J. M., Deary, I. J., & Bastin, M. E. (2018). Polygenic risk score for schizophrenia and structural brain connectivity in older age: A longitudinal connectome and tractography study. *NeuroImage, 183*, 884–896. <https://doi.org/10.1016/j.neuroimage.2018.08.075>
- Anderson, K. M., Collins, M. A., Kong, R., Fang, K., Li, J., He, T., Chekroud, A. M., Yeo, B. T. T., & Holmes, A. J. (2020). Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. *Proceedings of the National Academy of Sciences*. <https://doi.org/10.1073/pnas.2008004117>
- Anderson, K. M., Krienen, F. M., Choi, E. Y., Reinen, J. M., Yeo, B. T. T., & Holmes, A. J. (2018). Gene expression links functional networks across cortex and striatum. *Nature Communications, 9*(1), 1428. <https://doi.org/10.1038/s41467-018-03811-x>
- Aquino, K. M., Fulcher, B. D., Parkes, L., Sabarodin, K., & Fornito, A. (2020). Identifying and removing widespread signal deflections from fMRI data: Rethinking the global signal regression problem. *NeuroImage, 212*, 116614. <https://doi.org/10.1016/j.neuroimage.2020.116614>
- Arnatkevičiūtė, A., Fulcher, B. D., & Fornito, A. (2019). A practical guide to linking brain-wide gene expression and neuroimaging data. *NeuroImage, 189*, 353–367. <https://doi.org/10.1016/j.neuroimage.2019.01.011>
- Arnatkevičiūtė, A., Fulcher, B. D., Oldham, S., Tiego, J., Paquola, C., Gerring, Z., Aquino, K., Hawi, Z., Johnson, B., Ball, G., Klein, M., Deco, G., Franke, B., Bellgrove, M., & Fornito, A. (2020). Genetic influences on hub connectivity of the human connectome. *BioRxiv*, 2020.06.21.163915. <https://doi.org/10.1101/2020.06.21.163915>
- Arnatkevičiūtė, A., Fulcher, B. D., Pocock, R., & Fornito, A. (2018). Hub connectivity, neuronal diversity, and gene expression in the *Caenorhabditis elegans* connectome. *PLOS Computational Biology, 14*(2), e1005989. <https://doi.org/10.1371/journal.pcbi.1005989>
- Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., Davis, A. P., Dolinski, K., Dwight, S. S., Eppig, J. T., Harris, M. A., Hill, D. P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J. C., Richardson, J. E., Ringwald, M., Rubin, G. M., & Sherlock, G. (2000). Gene Ontology: Tool for the unification of biology. *Nature Genetics, 25*(1), 25–29. <https://doi.org/10.1038/75556>

- Baaré, W. F. C., Hulshoff Pol, H. E., Boomsma, D. I., Posthuma, D., de Geus, E. J. C., Schnack, H. G., van Haren, N. E. M., van Oel, C. J., & Kahn, R. S. (2001). Quantitative Genetic Modeling of Variation in Human Brain Morphology. *Cerebral Cortex*, 11(9), 816–824. <https://doi.org/10.1093/cercor/11.9.816>
- Bakken, T. E., Miller, J. A., Ding, S.-L., Sunkin, S. M., Smith, K. A., Ng, L., Szafer, A., Dalley, R. A., Royall, J. J., Lemon, T., Shapouri, S., Aiona, K., Arnold, J., Bennett, J. L., Bertagnolli, D., Bickley, K., Boe, A., Brouner, K., Butler, S., ... Lein, E. S. (2016). A comprehensive transcriptional map of primate brain development. *Nature*, 535(7612), 367–375. <https://doi.org/10.1038/nature18637>
- Barabási, D. L., & Barabási, A.-L. (2020). A Genetic Model of the Connectome. *Neuron*, 105(3), 435–445.e5. <https://doi.org/10.1016/j.neuron.2019.10.031>
- Barber, A. D., Hegarty, C. E., Lindquist, M., & Karlsgodt, K. H. (2021). Heritability of Functional Connectivity in Resting State: Assessment of the Dynamic Mean, Dynamic Variance, and Static Connectivity across Networks. *Cerebral Cortex*, bhaa391. <https://doi.org/10.1093/cercor/bhaa391>
- Baruch, L., Itzkovitz, S., Golan-Mashiach, M., Shapiro, E., & Segal, E. (2008). Using Expression Profiles of *Caenorhabditis elegans* Neurons To Identify Genes That Mediate Synaptic Connectivity. *PLOS Computational Biology*, 4(7), e1000120. <https://doi.org/10.1371/journal.pcbi.1000120>
- Bassett, D. S., & Bullmore, E. T. (2017). Small-World Brain Networks Revisited. *The Neuroscientist*, 23(5), 499–516. <https://doi.org/10.1177/1073858416667720>
- Bassett, D. S., Greenfield, D. L., Meyer-Lindenberg, A., Weinberger, D. R., Moore, S. W., & Bullmore, E. T. (2010). Efficient Physical Embedding of Topologically Complex Information Processing Networks in Brains and Computer Circuits. *PLOS Computational Biology*, 6(4), e1000748. <https://doi.org/10.1371/journal.pcbi.1000748>
- Bedeschi, M. F., Giangioffe, S., Paganini, L., Tabano, S., Silipigni, R., Colombo, L., Crippa, B. L., Lalatta, F., Gueneri, S., & Miozzo, M. (2017). STAR syndrome plus: The first description of a female patient with the lethal form. *American Journal of Medical Genetics. Part A*, 173(12), 3226–3230. <https://doi.org/10.1002/ajmg.a.38484>
- Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: A meta-analysis. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, 10(3), 423–433. <https://doi.org/10.1375/twin.10.3.423>
- Betzel, R. F., Medaglia, J. D., Papadopoulos, L., Baum, G. L., Gur, R., Gur, R., Roalf, D., Satterthwaite, T. D., & Bassett, D. S. (2017). The modular organization of human anatomical brain networks: Accounting for the cost of wiring. *Network Neuroscience*, 1(1), 42. https://doi.org/10.1162/NETN_a_00002
- Bohlken, M. M., Mandl, R. C. W., Brouwer, R. M., Heuvel, M. P. van den, Hedman, A. M., Kahn, R. S., & Pol, H. E. H. (2014). Heritability of structural brain network topology: A DTI study of 156 twins. *Human Brain Mapping*, 35(10), 5295–5305. <https://doi.org/10.1002/hbm.22550>
- Bomba, L., Walter, K., & Soranzo, N. (2017). The impact of rare and low-frequency genetic variants in common disease. *Genome Biology*, 18(1), 77. <https://doi.org/10.1186/s13059-017-1212-4>
- Braskie, M. N., Jahanshad, N., Stein, J. L., Barysheva, M., Johnson, K., McMahon, K. L., Zubicaray, G. I. de, Martin, N. G., Wright, M. J., Ringman, J. M., Toga, A. W., & Thompson, P. M. (2012). Relationship of

- a Variant in the NTRK1 Gene to White Matter Microstructure in Young Adults. *Journal of Neuroscience*, 32(17), 5964–5972. <https://doi.org/10.1523/JNEUROSCI.5561-11.2012>
- Briley, D. A., & Tucker-Drob, E. M. (2013). Explaining the Increasing Heritability of Cognitive Ability Across Development: A Meta-Analysis of Longitudinal Twin and Adoption Studies. *Psychological Science*, 24(9), 1704–1713. <https://doi.org/10.1177/0956797613478618>
- Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, 10(3), 186–198. <https://doi.org/10.1038/nrn2575>
- Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, 13(5), 336–349. <https://doi.org/10.1038/nrn3214>
- Bullmore, E. T., & Bassett, D. S. (2011). Brain graphs: Graphical models of the human brain connectome. *Annual Review of Clinical Psychology*, 7, 113–140. <https://doi.org/10.1146/annurev-clinpsy-040510-143934>
- Burt, J. B., Demirtaş, M., Eckner, W. J., Navejar, N. M., Ji, J. L., Martin, W. J., Bernacchia, A., Anticevic, A., & Murray, J. D. (2018). Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. *Nature Neuroscience*, 21(9), 1251–1259. <https://doi.org/10.1038/s41593-018-0195-0>
- Burt, J. B., Helmer, M., Shinn, M., Anticevic, A., & Murray, J. D. (2020). Generative modeling of brain maps with spatial autocorrelation. *NeuroImage*, 220, 117038. <https://doi.org/10.1016/j.neuroimage.2020.117038>
- Bush, W. S., & Moore, J. H. (2012). Chapter 11: Genome-Wide Association Studies. *PLOS Computational Biology*, 8(12), e1002822. <https://doi.org/10.1371/journal.pcbi.1002822>
- Carmelli, D., DeCarli, C., Swan, G. E., Jack, L. M., Reed, T., Wolf, P. A., & Miller, B. L. (1998). Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. *Stroke*, 29(6), 1177–1181. <https://doi.org/10.1161/01.str.29.6.1177>
- Chen, J., Rashid, B., Yu, Q., Liu, J., Lin, D., Du, Y., Sui, J., & Calhoun, V. D. (2018). Variability in Resting State Network and Functional Network Connectivity Associated With Schizophrenia Genetic Risk: A Pilot Study. *Frontiers in Neuroscience*, 12, 114. <https://doi.org/10.3389/fnins.2018.00114>
- Chiang, A.-S., Lin, C.-Y., Chuang, C.-C., Chang, H.-M., Hsieh, C.-H., Yeh, C.-W., Shih, C.-T., Wu, J.-J., Wang, G.-T., Chen, Y.-C., Wu, C.-C., Chen, G.-Y., Ching, Y.-T., Lee, P.-C., Lin, C.-Y., Lin, H.-H., Wu, C.-C., Hsu, H.-W., Huang, Y.-A., ... Hwang, J.-K. (2011). Three-dimensional reconstruction of brain-wide wiring networks in Drosophila at single-cell resolution. *Current Biology: CB*, 21(1), 1–11. <https://doi.org/10.1016/j.cub.2010.11.056>
- Chiang, M.-C., Barysheva, M., McMahon, K. L., Zubicaray, G. I. de, Johnson, K., Montgomery, G. W., Martin, N. G., Toga, A. W., Wright, M. J., Shapshak, P., & Thompson, P. M. (2012). Gene Network Effects on Brain Microstructure and Intellectual Performance Identified in 472 Twins. *Journal of Neuroscience*, 32(25), 8732–8745. <https://doi.org/10.1523/JNEUROSCI.5993-11.2012>
- Chiang, M.-C., Barysheva, M., Shattuck, D. W., Lee, A. D., Madsen, S. K., Avedissian, C., Klunder, A. D., Toga, A. W., McMahon, K. L., de Zubicaray, G. I., Wright, M. J., Srivastava, A., Balov, N., & Thompson, P. M. (2009). Genetics of Brain Fiber Architecture and Intellectual Performance. *The Journal of Neuroscience*, 29(7), 2212–2224. <https://doi.org/10.1523/JNEUROSCI.4184-08.2009>

- Chiang, M.-C., Barysheva, M., Toga, A. W., Medland, S. E., Hansell, N. K., James, M. R., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Wright, M. J., & Thompson, P. M. (2011). BDNF gene effects on brain circuitry replicated in 455 twins. *NeuroImage*, 55(2), 448–454.
<https://doi.org/10.1016/j.neuroimage.2010.12.053>
- Choi, J. K., & Kim, S. C. (2007). Environmental Effects on Gene Expression Phenotype Have Regional Biases in the Human Genome. *Genetics*, 175(4), 1607–1613. <https://doi.org/10.1534/genetics.106.069047>
- Choi, S. W., Mak, T. S.-H., & O'Reilly, P. F. (2020). Tutorial: A guide to performing polygenic risk score analyses. *Nature Protocols*, 15(9), 2759–2772. <https://doi.org/10.1038/s41596-020-0353-1>
- Cioli, C., Abdi, H., Beaton, D., Burnod, Y., & Mesmoudi, S. (2014). Differences in Human Cortical Gene Expression Match the Temporal Properties of Large-Scale Functional Networks. *PLOS ONE*, 9(12), e115913. <https://doi.org/10.1371/journal.pone.0115913>
- Ciric, R., Wolf, D. H., Power, J. D., Roalf, D. R., Baum, G. L., Ruparel, K., Shinohara, R. T., Elliott, M. A., Eickhoff, S. B., Davatzikos, C., Gur, R. C., Gur, R. E., Bassett, D. S., & Satterthwaite, T. D. (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *NeuroImage*, 154, 174–187.
<https://doi.org/10.1016/j.neuroimage.2017.03.020>
- Colantuoni, C., Lipska, B. K., Ye, T., Hyde, T. M., Tao, R., Leek, J. T., Colantuoni, E. A., Elkahoul, A. G., Herman, M. M., Weinberger, D. R., & Kleinman, J. E. (2011). Temporal dynamics and genetic control of transcription in the human prefrontal cortex. *Nature*, 478(7370), 519–523.
<https://doi.org/10.1038/nature10524>
- Colclough, G. L., Smith, S. M., Nichols, T. E., Winkler, A. M., Sotiropoulos, S. N., Glasser, M. F., Van Essen, D. C., & Woolrich, M. W. (2017). The heritability of multi-modal connectivity in human brain activity. *eLife*, 6, e20178. <https://doi.org/10.7554/eLife.20178>
- Cole, S. W. (2009). Social Regulation of Human Gene Expression. *Current Directions in Psychological Science*, 18(3), 132–137. <https://doi.org/10.1111/j.1467-8721.2009.01623.x>
- Collin, G., Sporns, O., Mandl, R. C. W., & van den Heuvel, M. P. (2014). Structural and Functional Aspects Relating to Cost and Benefit of Rich Club Organization in the Human Cerebral Cortex. *Cerebral Cortex (New York, NY)*, 24(9), 2258–2267. <https://doi.org/10.1093/cercor/bht064>
- Conley, D., Rauscher, E., Dawes, C., Magnusson, P. K. E., & Siegal, M. L. (2013). Heritability and the Equal Environments Assumption: Evidence from Multiple Samples of Misclassified Twins. *Behavior Genetics*, 43(5), 415–426. <https://doi.org/10.1007/s10519-013-9602-1>
- Cook, S. J., Jarrell, T. A., Brittin, C. A., Wang, Y., Bloniarz, A. E., Yakovlev, M. A., Nguyen, K. C. Q., Tang, L. T.-H., Bayer, E. A., Duerr, J. S., Bülow, H. E., Hobert, O., Hall, D. H., & Emmons, S. W. (2019). Whole-animal connectomes of both *Caenorhabditis elegans* sexes. *Nature*, 571(7763), 63–71.
<https://doi.org/10.1038/s41586-019-1352-7>
- Corsello, G., & Piro, E. (2010). The world of twins: An update. *The Journal of Maternal-Fetal & Neonatal Medicine*, 23(sup3), 59–62. <https://doi.org/10.3109/14767058.2010.508218>
- Dandash, O., Pantelis, C., & Fornito, A. (2017). Dopamine, fronto-striato-thalamic circuits and risk for psychosis. *Schizophrenia Research*, 180, 48–57. <https://doi.org/10.1016/j.schres.2016.08.020>

- Darmanis, S., Sloan, S. A., Zhang, Y., Enge, M., Caneda, C., Shuer, L. M., Gephart, M. G. H., Barres, B. A., & Quake, S. R. (2015). A survey of human brain transcriptome diversity at the single cell level. *Proceedings of the National Academy of Sciences*, 112(23), 7285–7290. <https://doi.org/10.1073/pnas.1507125112>
- Dennis, E. L., Jahanshad, N., Rudie, J. D., Brown, J. A., Johnson, K., McMahon, K. L., de Zubicaray, G. I., Montgomery, G., Martin, N. G., Wright, M. J., Bookheimer, S. Y., Dapretto, M., Toga, A. W., & Thompson, P. M. (2011). Altered Structural Brain Connectivity in Healthy Carriers of the Autism Risk Gene, CNTNAP2. *Brain Connectivity*, 1(6), 447–459. <https://doi.org/10.1089/brain.2011.0064>
- Dickson, B. J. (2002). Molecular mechanisms of axon guidance. *Science (New York, N.Y.)*, 298(5600), 1959–1964. <https://doi.org/10.1126/science.1072165>
- Dudbridge, F. (2013). Power and Predictive Accuracy of Polygenic Risk Scores. *PLOS Genetics*, 9(3), e1003348. <https://doi.org/10.1371/journal.pgen.1003348>
- Eberle, C., Peterse, Y., Jukic, F., Müller-Myhsok, B., Czamara, D., Martins, J., Schmoll, V., Czisch, M., Binder, E. B., & Sämann, P. G. (2019). Endophenotype Potential of Nucleus Accumbens Functional Connectivity: Effects of Polygenic Risk for Schizophrenia Interacting with Childhood Adversity. *Journal of Psychiatry and Brain Science*, 4(3). <https://doi.org/10.20900/jpbs.20190011>
- Edsgård, D., Johnsson, P., & Sandberg, R. (2018). Identification of spatial expression trends in single-cell gene expression data. *Nature Methods*, 15(5), 339–342. <https://doi.org/10.1038/nmeth.4634>
- Elliott, L. T., Sharp, K., Alfaro-Almagro, F., Shi, S., Miller, K. L., Douaud, G., Marchini, J., & Smith, S. M. (2018). Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature*, 562(7726), 210–216. <https://doi.org/10.1038/s41586-018-0571-7>
- Elsheikh, S. S. M., Chimusa, E. R., Mulder, N. J., & Crimi, A. (2020). Genome-Wide Association Study of Brain Connectivity Changes for Alzheimer's Disease. *Scientific Reports*, 10(1), 1433. <https://doi.org/10.1038/s41598-020-58291-1>
- Ercsey-Ravasz, M., Markov, N. T., Lamy, C., Van Essen, D. C., Knoblauch, K., Toroczkai, Z., & Kennedy, H. (2013). A predictive network model of cerebral cortical connectivity based on a distance rule. *Neuron*, 80(1), 184–197. <https://doi.org/10.1016/j.neuron.2013.07.036>
- Eyler, L. T., Chen, C.-H., Panizzon, M. S., Fennema-Notestine, C., Neale, M. C., Jak, A., Jernigan, T. L., Fischl, B., Franz, C. E., Lyons, M. J., Grant, M., Prom-Wormley, E., Seidman, L. J., Tsuang, M. T., Fiecas, M. J. A., Dale, A. M., & Kremen, W. S. (2012). A comparison of heritability maps of cortical surface area and thickness and the influence of adjustment for whole brain measures: A magnetic resonance imaging twin study. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, 15(3), 304–314. <https://doi.org/10.1017/thg.2012.3>
- Fakhry, A., & Ji, S. (2015). High-resolution prediction of mouse brain connectivity using gene expression patterns. *Methods*, 73, 71–78. <https://doi.org/10.1016/j.ymeth.2014.07.011>
- Fakhry, A., Zeng, T., Peng, H., & Ji, S. (2015). Global analysis of gene expression and projection target correlations in the mouse brain. *Brain Informatics*, 2(2), 107–117. <https://doi.org/10.1007/s40708-015-0014-2>
- Filippini, N., Rao, A., Wetten, S., Gibson, R. A., Borrie, M., Guzman, D., Kertesz, A., Loy-English, I., Williams, J., Nichols, T., Whitcher, B., & Matthews, P. M. (2009). Anatomically-distinct genetic

- associations of APOE epsilon4 allele load with regional cortical atrophy in Alzheimer's disease. *NeuroImage*, 44(3), 724–728. <https://doi.org/10.1016/j.neuroimage.2008.10.003>
- Foo, H., Thalamuthu, A., Jiang, J., Koch, F. C., Mather, K. A., Wen, W., & Sachdev, P. S. (2020). Novel genetic variants associated with brain functional networks in 18,445 adults from the UK Biobank. *BioRxiv*, 2020.09.17.268029. <https://doi.org/10.1101/2020.09.17.268029>
- Forest, M., Iturria-Medina, Y., Goldman, J. S., Kleinman, C. L., Lovato, A., Klein, K. O., Evans, A., Ciampi, A., Labbe, A., & Greenwood, C. M. T. (2017). Gene networks show associations with seed region connectivity. *Human Brain Mapping*, 38(6), 3126–3140. <https://doi.org/10.1002/hbm.23579>
- Fornito, A., Arnatkevičiūtė, A., & Fulcher, B. D. (2019). Bridging the Gap between Connectome and Transcriptome. *Trends in Cognitive Sciences*, 23(1), 34–50. <https://doi.org/10.1016/j.tics.2018.10.005>
- Fornito, A., Zalesky, A., Bassett, D. S., Meunier, D., Ellison-Wright, I., Yücel, M., Wood, S. J., Shaw, K., O'Connor, J., Nertney, D., Mowry, B. J., Pantelis, C., & Bullmore, E. T. (2011). Genetic Influences on Cost-Efficient Organization of Human Cortical Functional Networks. *Journal of Neuroscience*, 31(9), 3261–3270. <https://doi.org/10.1523/JNEUROSCI.4858-10.2011>
- Fornito, A., Zalesky, A., & Bullmore, E. (2016). *Fundamentals of Brain Network Analysis* (1st edition). Academic Press.
- Fraser, H. B., Khaitovich, P., Plotkin, J. B., Pääbo, S., & Eisen, M. B. (2005). Aging and Gene Expression in the Primate Brain. *PLOS Biology*, 3(9), e274. <https://doi.org/10.1371/journal.pbio.0030274>
- French, L., & Pavlidis, P. (2011). Relationships between Gene Expression and Brain Wiring in the Adult Rodent Brain. *PLOS Computational Biology*, 7(1), e1001049. <https://doi.org/10.1371/journal.pcbi.1001049>
- Fu, Y., Ma, Z., Hamilton, C., Liang, Z., Hou, X., Ma, X., Hu, X., He, Q., Deng, W., Wang, Y., Zhao, L., Meng, H., Li, T., & Zhang, N. (2015). Genetic influences on resting-state functional networks: A twin study. *Human Brain Mapping*, 36(10), 3959–3972. <https://doi.org/10.1002/hbm.22890>
- Fulcher, B. D., Arnatkevičiūtė, A., & Fornito, A. (2021). Overcoming bias in gene-set enrichment analyses of brain-wide transcriptomic data. *Nature Communications (in Press)*. <https://doi.org/10.1101/2020.04.24.058958>
- Fulcher, B. D., & Fornito, A. (2016). A transcriptional signature of hub connectivity in the mouse connectome. *Proceedings of the National Academy of Sciences*, 113(5), 1435–1440. <https://doi.org/10.1073/pnas.1513302113>
- Fulker, D. W., DeFries, J. C., & Plomin, R. (1988). Genetic influence on general mental ability increases between infancy and middle childhood. *Nature*, 336(6201), 767–769. <https://doi.org/10.1038/336767a0>
- Ge, T., Holmes, A. J., Buckner, R. L., Smoller, J. W., & Sabuncu, M. R. (2017). Heritability analysis with repeat measurements and its application to resting-state functional connectivity. *Proceedings of the National Academy of Sciences*, 114(21), 5521–5526. <https://doi.org/10.1073/pnas.1700765114>
- Glahn, D. C., Winkler, A. M., Kochunov, P., Almasy, L., Duggirala, R., Carless, M. A., Curran, J. C., Olvera, R. L., Laird, A. R., Smith, S. M., Beckmann, C. F., Fox, P. T., & Blangero, J. (2010). Genetic control over the resting brain. *Proceedings of the National Academy of Sciences*, 107(3), 1223–1228. <https://doi.org/10.1073/pnas.0909969107>

- Goel, P., Kuceyeski, A., LoCastro, E., & Raj, A. (2014). Spatial patterns of genome-wide expression profiles reflect anatomic and fiber connectivity architecture of healthy human brain. *Human Brain Mapping*, 35(8), 4204–4218. <https://doi.org/10.1002/hbm.22471>
- Gollo, L. L., Roberts, J. A., Copley, V. L., Di Biase, M. A., Pantelis, C., Zalesky, A., & Breakspear, M. (2018). Fragility and volatility of structural hubs in the human connectome. *Nature Neuroscience*, 21(8), 1107–1116. <https://doi.org/10.1038/s41593-018-0188-z>
- Goodhill, G. J. (2016). Can Molecular Gradients Wire the Brain? *Trends in Neurosciences*, 39(4), 202–211. <https://doi.org/10.1016/j.tins.2016.01.009>
- Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Ching, C. R. K., McMahon, M. A. B., Shatikhina, N., Zsembik, L. C. P., Thomopoulos, S. I., Zhu, A. H., Strike, L. T., Agartz, I., Alhusaini, S., Almeida, M. A. A., Alnæs, D., ... Group, E. N. G. through M.-A. C. (ENIGMA)—Genetics working. (2020). The genetic architecture of the human cerebral cortex. *Science*, 367(6484). <https://doi.org/10.1126/science.aay6690>
- Griffiths, A. J., Miller, J. H., Suzuki, D. T., Lewontin, R. C., & Gelbart, W. M. (2000). Quantifying heritability. *An Introduction to Genetic Analysis. 7th Edition*. <https://www.ncbi.nlm.nih.gov/books/NBK21866/>
- Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q. K., Yu, A. B., Kahn, A. E., Medaglia, J. D., Vettel, J. M., Miller, M. B., Grafton, S. T., & Bassett, D. S. (2015). Controllability of structural brain networks. *Nature Communications*, 6, 8414. <https://doi.org/10.1038/ncomms9414>
- Haak, K. V., & Beckmann, C. F. (2019). Plasticity versus stability across the human cortical visual connectome. *Nature Communications*, 10(1), 3174. <https://doi.org/10.1038/s41467-019-11113-z>
- Harriger, L., Heuvel, M. P. van den, & Sporns, O. (2012). Rich Club Organization of Macaque Cerebral Cortex and Its Role in Network Communication. *PLOS ONE*, 7(9), e46497. <https://doi.org/10.1371/journal.pone.0046497>
- Harris, T. W., Antoshechkin, I., Bieri, T., Blasiar, D., Chan, J., Chen, W. J., De La Cruz, N., Davis, P., Duesbury, M., Fang, R., Fernandes, J., Han, M., Kishore, R., Lee, R., Müller, H.-M., Nakamura, C., Ozersky, P., Petcherski, A., Rangarajan, A., ... Sternberg, P. W. (2010). WormBase: A comprehensive resource for nematode research. *Nucleic Acids Research*, 38(Database issue), D463–467. <https://doi.org/10.1093/nar/gkp952>
- Hart, A. B., de Wit, H., & Palmer, A. A. (2013). Candidate Gene Studies of a Promising Intermediate Phenotype: Failure to Replicate. *Neuropsychopharmacology*, 38(5), 802–816. <https://doi.org/10.1038/npp.2012.245>
- Haworth, C., Wright, M., Luciano, M., Martin, N., de Geus, E., van Beijsterveldt, C., Bartels, M., Posthuma, D., Boomsma, D., Davis, O., Kovas, Y., Corley, R., DeFries, J., Hewitt, J., Olson, R., Rhea, S.-A., Wadsworth, S., Iacono, W., McGue, M., ... Plomin, R. (2010). The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Molecular Psychiatry*, 15(11), 1112–1120. <https://doi.org/10.1038/mp.2009.55>
- Hawrylycz, M. J., Lein, E. S., Guillozet-Bongaarts, A. L., Shen, E. H., Ng, L., Miller, J. A., van de Lagemaat, L. N., Smith, K. A., Ebbert, A., Riley, Z. L., Abajian, C., Beckmann, C. F., Bernard, A., Bertagnolli, D., Boe, A. F., Cartagena, P. M., Chakravarty, M. M., Chapin, M., Chong, J., ... Jones, A. R. (2012). An

- anatomically comprehensive atlas of the adult human brain transcriptome. *Nature*, 489(7416), 391–399. <https://doi.org/10.1038/nature11405>
- Hawrylycz, M., Miller, J. A., Menon, V., Feng, D., Dolbeare, T., Guillozet-Bongaarts, A. L., Jegga, A. G., Aronow, B. J., Lee, C.-K., Bernard, A., Glasser, M. F., Dierker, D. L., Menche, J., Szafer, A., Collman, F., Grange, P., Berman, K. A., Mihalas, S., Yao, Z., ... Lein, E. (2015). Canonical genetic signatures of the adult human brain. *Nature Neuroscience*, 18(12), 1832–1844. <https://doi.org/10.1038/nn.4171>
- Henderson, J. A., & Robinson, P. A. (2014). Relations between the geometry of cortical gyrification and white-matter network architecture. *Brain Connectivity*, 4(2), 112–130. <https://doi.org/10.1089/brain.2013.0183>
- Heuvel, M. P. van den, Kahn, R. S., Goñi, J., & Sporns, O. (2012). High-cost, high-capacity backbone for global brain communication. *Proceedings of the National Academy of Sciences*, 109(28), 11372–11377. <https://doi.org/10.1073/pnas.1203593109>
- Heuvel, M. P. van den, & Sporns, O. (2011). Rich-Club Organization of the Human Connectome. *Journal of Neuroscience*, 31(44), 15775–15786. <https://doi.org/10.1523/JNEUROSCI.3539-11.2011>
- Hibar, D. P., Adams, H. H. H., Jahanshad, N., Chauhan, G., Stein, J. L., Hofer, E., Renteria, M. E., Bis, J. C., Arias-Vasquez, A., Ikram, M. K., Desrivieres, S., Vernooij, M. W., Abramovic, L., Alhusaini, S., Amin, N., Andersson, M., Arfanakis, K., Aribisala, B. S., Armstrong, N. J., ... Ikram, M. A. (2017). Novel genetic loci associated with hippocampal volume. *Nature Communications*, 8(1), 13624. <https://doi.org/10.1038/ncomms13624>
- Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics*, 6(2), 95–108. <https://doi.org/10.1038/nrg1521>
- Honey, C. J., Kötter, R., Breakspear, M., & Sporns, O. (2007). Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proceedings of the National Academy of Sciences of the United States of America*, 104(24), 10240–10245. <https://doi.org/10.1073/pnas.0701519104>
- Hong, E. P., & Park, J. W. (2012). Sample Size and Statistical Power Calculation in Genetic Association Studies. *Genomics & Informatics*, 10(2), 117–122. <https://doi.org/10.5808/GI.2012.10.2.117>
- Horita, N., & Kaneko, T. (2015). Genetic model selection for a case-control study and a meta-analysis. *Meta Gene*, 5, 1–8. <https://doi.org/10.1016/j.mgene.2015.04.003>
- Horvát, S., Gămănuț, R., Ercsey-Ravasz, M., Magrou, L., Gămănuț, B., Essen, D. C. V., Burkhalter, A., Knoblauch, K., Toroczkai, Z., & Kennedy, H. (2016). Spatial Embedding and Wiring Cost Constrain the Functional Layout of the Cortical Network of Rodents and Primates. *PLOS Biology*, 14(7), e1002512. <https://doi.org/10.1371/journal.pbio.1002512>
- Huang, M., Nichols, T., Huang, C., Yu, Y., Lu, Z., Knickmeyer, R. C., Feng, Q., Zhu, H., & Alzheimer's Disease Neuroimaging Initiative. (2015). FVGWAS: Fast voxelwise genome wide association analysis of large-scale imaging genetic data. *NeuroImage*, 118, 613–627. <https://doi.org/10.1016/j.neuroimage.2015.05.043>
- Jahanshad, N., Hibar, D. P., Ryles, A., Toga, A. W., McMahon, K. L., de Zubicaray, G. I., Hansell, N. K., Montgomery, G. W., Martin, N. G., Wright, M. J., & Thompson, P. M. (2012). DISCOVERY OF GENES THAT AFFECT HUMAN BRAIN CONNECTIVITY: A GENOME-WIDE ANALYSIS OF

- THE CONNECTOME. *Proceedings. IEEE International Symposium on Biomedical Imaging*, 542–545. <https://doi.org/10.1109/ISBI.2012.6235605>
- Jahanshad, N., Rajagopalan, P., Hua, X., Hibar, D. P., Nir, T. M., Toga, A. W., Jack, C. R., Saykin, A. J., Green, R. C., Weiner, M. W., Medland, S. E., Montgomery, G. W., Hansell, N. K., McMahon, K. L., Zubicaray, G. I. de, Martin, N. G., Wright, M. J., Thompson, P. M., & Initiative, the A. D. N. (2013). Genome-wide scan of healthy human connectome discovers SPON1 gene variant influencing dementia severity. *Proceedings of the National Academy of Sciences*. <https://doi.org/10.1073/pnas.1216206110>
- Jansen, A. G., Mous, S. E., White, T., Posthuma, D., & Polderman, T. J. C. (2015). What Twin Studies Tell Us About the Heritability of Brain Development, Morphology, and Function: A Review. *Neuropsychology Review*, 25(1), 27–46. <https://doi.org/10.1007/s11065-015-9278-9>
- Jansen, P. R., Muetzel, R. L., Polderman, T. J. C., Jaddoe, V. W., Verhulst, F. C., Lugt, A. van der, Tiemeier, H., Posthuma, D., & White, T. (2019). Polygenic Scores for Neuropsychiatric Traits and White Matter Microstructure in the Pediatric Population. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(3), 243–250. <https://doi.org/10.1016/j.bpsc.2018.07.010>
- Ji, S., Fakhry, A., & Deng, H. (2014). Integrative analysis of the connectivity and gene expression atlases in the mouse brain. *NeuroImage*, 84, 245–253. <https://doi.org/10.1016/j.neuroimage.2013.08.049>
- Jinks, J. L., & Fulker, D. W. (1970). Comparison of the biometrical genetical, MAVA, and classical approaches to the analysis of the human behavior. *Psychological Bulletin*, 73(5), 311–349. <https://doi.org/10.1037/h0029135>
- Joseph, J. (2002). Twin Studies in Psychiatry and Psychology: Science or Pseudoscience? *Psychiatric Quarterly*, 73(1), 71–82. <https://doi.org/10.1023/A:1012896802713>
- Kanehisa, M., & Goto, S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 28(1), 27–30.
- Kang, H. J., Kawasawa, Y. I., Cheng, F., Zhu, Y., Xu, X., Li, M., Sousa, A. M. M., Pletikos, M., Meyer, K. A., Sedmak, G., Guennel, T., Shin, Y., Johnson, M. B., Krsnik, Ž., Mayer, S., Fertuzinhos, S., Umlauf, S., Lisgo, S. N., Vortmeyer, A., ... Šestan, N. (2011). Spatio-temporal transcriptome of the human brain. *Nature*, 478(7370), 483–489. <https://doi.org/10.1038/nature10523>
- Kaufman, A., Dror, G., Meilijson, I., & Ruppin, E. (2006). Gene Expression of *Caenorhabditis elegans* Neurons Carries Information on Their Synaptic Connectivity. *PLOS Computational Biology*, 2(12), e167. <https://doi.org/10.1371/journal.pcbi.0020167>
- Kaufman, S. B. (2007). Sex differences in mental rotation and spatial visualization ability: Can they be accounted for by differences in working memory capacity? *Intelligence*, 35(3), 211–223. <https://doi.org/10.1016/j.intell.2006.07.009>
- Keil, J. M., Qalieh, A., & Kwan, K. Y. (2018). Brain Transcriptome Databases: A User's Guide. *The Journal of Neuroscience*, 38(10), 2399–2412. <https://doi.org/10.1523/JNEUROSCI.1930-17.2018>
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior Genetics*, 23(1), 21–27. <https://doi.org/10.1007/BF01067551>
- Khundrakpam, B., Vainik, U., Gong, J., Al-Sharif, N., Bhutani, N., Kiar, G., Zeighami, Y., Kirschner, M., Luo, C., Dagher, A., & Evans, A. (2020). Neural correlates of polygenic risk score for autism spectrum

- disorders in general population. *Brain Communications*, 2(2).
<https://doi.org/10.1093/braincomms/fcaa092>
- Kim, J. S., & Kaiser, M. (2014). From *Caenorhabditis elegans* to the human connectome: A specific modular organization increases metabolic, functional and developmental efficiency. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369(1653). <https://doi.org/10.1098/rstb.2013.0529>
- Kirsch, L., & Chechik, G. (2016). On Expression Patterns and Developmental Origin of Human Brain Regions. *PLOS Computational Biology*, 12(8), e1005064. <https://doi.org/10.1371/journal.pcbi.1005064>
- Kochunov, P., Glahn, D. C., Lancaster, J. L., Winkler, A. M., Smith, S., Thompson, P. M., Almasy, L., Duggirala, R., Fox, P. T., & Blangero, J. (2010). Genetics of microstructure of cerebral white matter using diffusion tensor imaging. *NeuroImage*, 53(3), 1109–1116.
<https://doi.org/10.1016/j.neuroimage.2010.01.078>
- Kovács, I. A., Barabási, D. L., & Barabási, A.-L. (2020). Uncovering the genetic blueprint of the *C. elegans* nervous system. *Proceedings of the National Academy of Sciences*, 117(52), 33570–33577.
<https://doi.org/10.1073/pnas.2009093117>
- Krienen, F. M., Yeo, B. T. T., Ge, T., Buckner, R. L., & Sherwood, C. C. (2016). Transcriptional profiles of supragranular-enriched genes associate with corticocortical network architecture in the human brain. *Proceedings of the National Academy of Sciences*, 113(4), E469–E478.
<https://doi.org/10.1073/pnas.1510903113>
- Lake, B. B., Ai, R., Kaeser, G. E., Salathia, N. S., Yung, Y. C., Liu, R., Wildberg, A., Gao, D., Fung, H.-L., Chen, S., Vijayaraghavan, R., Wong, J., Chen, A., Sheng, X., Kaper, F., Shen, R., Ronaghi, M., Fan, J.-B., Wang, W., ... Zhang, K. (2016). Neuronal subtypes and diversity revealed by single-nucleus RNA sequencing of the human brain. *Science*, 352(6293), 1586–1590.
<https://doi.org/10.1126/science.aaf1204>
- Lau, H. Y. G., Fornito, A., & Fulcher, B. D. (2021). Scaling of gene transcriptional gradients with brain size across mouse development. *NeuroImage*, 224, 117395.
<https://doi.org/10.1016/j.neuroimage.2020.117395>
- Lee, K.-H., Oh, H., Suh, J. S., Cho, K. I. K., Yoon, Y. B., Shin, W.-G., Lee, T. Y., & Kwon, J. S. (2018). Functional and Structural Connectivity of the Cerebellar Nuclei With the Striatum and Cerebral Cortex in First-Episode Psychosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 31(2), 143–151. <https://doi.org/10.1176/appi.neuropsych.17110276>
- Lee, W. H., Rodrigue, A., Glahn, D. C., Bassett, D. S., & Frangou, S. (2020). Heritability and Cognitive Relevance of Structural Brain Controllability. *Cerebral Cortex*, 30(5), 3044–3054.
<https://doi.org/10.1093/cercor/bhz293>
- Lein, E., Borm, L. E., & Linnarsson, S. (2017). The promise of spatial transcriptomics for neuroscience in the era of molecular cell typing. *Science*, 358(6359), 64–69. <https://doi.org/10.1126/science.aan6827>
- Lein, E. S., Hawrylycz, M. J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., Boe, A. F., Boguski, M. S., Brockway, K. S., Byrnes, E. J., Chen, L., Chen, L., Chen, T.-M., Chi Chin, M., Chong, J., Crook, B. E., Czaplinska, A., Dang, C. N., Datta, S., ... Jones, A. R. (2007). Genome-wide atlas of gene expression in the adult mouse brain. *Nature*, 445(7124), 168–176. <https://doi.org/10.1038/nature05453>

- Lewis, C. M., & Vassos, E. (2020). Polygenic risk scores: From research tools to clinical instruments. *Genome Medicine*, 12(1), 44. <https://doi.org/10.1186/s13073-020-00742-5>
- Liu, T. T., Nalci, A., & Falahpour, M. (2017). The Global Signal in fMRI: Nuisance or Information? *NeuroImage*, 150, 213–229. <https://doi.org/10.1016/j.neuroimage.2017.02.036>
- Marees, A. T., Kluiver, H. de, Stringer, S., Vorspan, F., Curis, E., Marie-Claire, C., & Derks, E. M. (2018). A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. *International Journal of Methods in Psychiatric Research*, 27(2), e1608. <https://doi.org/10.1002/mpr.1608>
- Mark, K. M., Pike, A., Latham, R. M., & Oliver, B. R. (2017). Using Twins to Better Understand Sibling Relationships. *Behavior Genetics*, 47(2), 202–214. <https://doi.org/10.1007/s10519-016-9825-z>
- Markello, R. D., & Misic, B. (2020). Comparing spatially-constrained null models for parcellated brain maps. *BioRxiv*, 2020.08.13.249797. <https://doi.org/10.1101/2020.08.13.249797>
- Markello, R., Shafiei, G., Zheng, Y.-Q., & Mišić, B. (2021). *abagen: A toolbox for the Allen Brain Atlas genetics data*. Zenodo. Available from: <https://doi.org/10.5281/zenodo.4646030>
- Markov, N. T., Ercsey-Ravasz, M. M., Ribeiro Gomes, A. R., Lamy, C., Magrou, L., Vezoli, J., Misery, P., Falchier, A., Quilodran, R., Gariel, M. A., Sallet, J., Gamanut, R., Huissoud, C., Clavagnier, S., Giroud, P., Sappey-Marinier, D., Barone, P., Dehay, C., Toroczkai, Z., ... Kennedy, H. (2014). A Weighted and Directed Interareal Connectivity Matrix for Macaque Cerebral Cortex. *Cerebral Cortex (New York, NY)*, 24(1), 17–36. <https://doi.org/10.1093/cercor/bhs270>
- McColgan, P., Gregory, S., Seunarine, K. K., Razi, A., Papoutsis, M., Johnson, E., Durr, A., Roos, R. A. C., Leavitt, B. R., Holmans, P., Scahill, R. I., Clark, C. A., Rees, G., Tabrizi, S. J., Coleman, A., Decolongon, J., Fan, M., Petkau, T., Jauffret, C., ... Crawford, D. (2018). Brain Regions Showing White Matter Loss in Huntington's Disease Are Enriched for Synaptic and Metabolic Genes. *Biological Psychiatry*, 83(5), 456–465. <https://doi.org/10.1016/j.biopsych.2017.10.019>
- McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. *Trends in Neurosciences*, 42(3), 205–220. <https://doi.org/10.1016/j.tins.2018.12.004>
- Meunier, D., Lambiotte, R., Fornito, A., Ersche, K., & Bullmore, E. T. (2009). Hierarchical modularity in human brain functional networks. *Frontiers in Neuroinformatics*, 3. <https://doi.org/10.3389/neuro.11.037.2009>
- Mills, B. D., Grayson, D. S., Shunmugavel, A., Miranda-Dominguez, O., Feczko, E., Earl, E., Neve, K. A., & Fair, D. A. (2018). Correlated Gene Expression and Anatomical Communication Support Synchronized Brain Activity in the Mouse Functional Connectome. *Journal of Neuroscience*, 38(25), 5774–5787. <https://doi.org/10.1523/JNEUROSCI.2910-17.2018>
- Miranda-Dominguez, O., Feczko, E., Grayson, D. S., Walum, H., Nigg, J. T., & Fair, D. A. (2018). Heritability of the human connectome: A connectotyping study. *Network Neuroscience*, 2(2), 175–199. https://doi.org/10.1162/netn_a_00029
- Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage*, 154, 169–173. <https://doi.org/10.1016/j.neuroimage.2016.11.052>

- Neale, M. C. (2009). Biometrical Models in Behavioral Genetics. In Y.-K. Kim (Ed.), *Handbook of Behavior Genetics* (pp. 15–33). Springer. https://doi.org/10.1007/978-0-387-76727-7_2
- Neale, M. C., & Cardon, L. R. (1992). Multivariate Analysis. In M. C. Neale & L. R. Cardon (Eds.), *Methodology for Genetic Studies of Twins and Families* (pp. 231–259). Springer Netherlands. https://doi.org/10.1007/978-94-015-8018-2_12
- Neale, M., & Cardon, L. (1992). *Methodology for Genetic Studies of Twins and Families*. Springer Netherlands. <https://doi.org/10.1007/978-94-015-8018-2>
- Ng, L., Bernard, A., Lau, C., Overly, C. C., Dong, H.-W., Kuan, C., Pathak, S., Sunkin, S. M., Dang, C., Bohland, J. W., Bokil, H., Mitra, P. P., Puelles, L., Hohmann, J., Anderson, D. J., Lein, E. S., Jones, A. R., & Hawrylycz, M. (2009). An anatomic gene expression atlas of the adult mouse brain. *Nature Neuroscience*, 12(3), 356–362. <https://doi.org/10.1038/nn.2281>
- Northoff, G., & Duncan, N. W. (2016). How do abnormalities in the brain’s spontaneous activity translate into symptoms in schizophrenia? From an overview of resting state activity findings to a proposed spatiotemporal psychopathology. *Progress in Neurobiology*, 145–146, 26–45. <https://doi.org/10.1016/j.pneurobio.2016.08.003>
- Oldham, M. C., Konopka, G., Iwamoto, K., Langfelder, P., Kato, T., Horvath, S., & Geschwind, D. H. (2008). Functional organization of the transcriptome in human brain. *Nature Neuroscience*, 11(11), 1271–1282. <https://doi.org/10.1038/nn.2207>
- Oldham, S., Arnatkevičiūtė, A., Smith, R. E., Tiego, J., Bellgrove, M. A., & Fornito, A. (2020). The efficacy of different preprocessing steps in reducing motion-related confounds in diffusion MRI connectomics. *NeuroImage*, 117252. <https://doi.org/10.1016/j.neuroimage.2020.117252>
- Ott, J., & Rabinowitz, D. (1999). A principal-components approach based on heritability for combining phenotype information. *Human Heredity*, 49(2), 106–111. <https://doi.org/10.1159/000022854>
- Pankow, A., Deserno, L., Walter, M., Fydrich, T., BERPohl, F., Schlagenhauf, F., & Heinz, A. (2015). Reduced default mode network connectivity in schizophrenia patients. *Schizophrenia Research*, 165(1), 90–93. <https://doi.org/10.1016/j.schres.2015.03.027>
- Pantazatos, S. P., & Li, X. (2017). Commentary: BRAIN NETWORKS. Correlated Gene Expression Supports Synchronous Activity in Brain Networks. *Science* 348, 1241–4. *Frontiers in Neuroscience*, 11. <https://doi.org/10.3389/fnins.2017.00412>
- Parkes, L., Fulcher, B. D., Yücel, M., & Fornito, A. (2017). Transcriptional signatures of connectomic subregions of the human striatum. *Genes, Brain and Behavior*, 16(7), 647–663. <https://doi.org/10.1111/gbb.12386>
- Parkes, Linden, Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*, 171, 415–436. <https://doi.org/10.1016/j.neuroimage.2017.12.073>
- Patnala, R., Clements, J., & Batra, J. (2013). Candidate gene association studies: A comprehensive guide to useful in silico tools. *BMC Genetics*, 14, 39. <https://doi.org/10.1186/1471-2156-14-39>
- Pfefferbaum, A., Sullivan, E. V., Swan, G. E., & Carmelli, D. (2000). Brain structure in men remains highly heritable in the seventh and eighth decades of life☆. *Neurobiology of Aging*, 21(1), 63–74. [https://doi.org/10.1016/S0197-4580\(00\)00086-5](https://doi.org/10.1016/S0197-4580(00)00086-5)

- Pizzagalli, F., Auzias, G., Yang, Q., Mathias, S. R., Faskowitz, J., Boyd, J. D., Amini, A., Rivière, D., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Mangin, J.-F., Glahn, D. C., Blangero, J., Wright, M. J., Thompson, P. M., Kochunov, P., & Jahanshad, N. (2020). The reliability and heritability of cortical folds and their genetic correlations across hemispheres. *Communications Biology*, 3(1), 1–12. <https://doi.org/10.1038/s42003-020-01163-1>
- Posthuma, D., Beem, A. L., de Geus, E. J. C., van Baal, G. C. M., von Hjelmberg, J. B., Iachine, I., & Boomsma, D. I. (2003). Theory and Practice in Quantitative Genetics. *Twin Research*, 6(5), 361–376. <https://doi.org/10.1375/136905203770326367>
- Power, J. D., Plitt, M., Laumann, T. O., & Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. *NeuroImage*, 146, 609–625. <https://doi.org/10.1016/j.neuroimage.2016.09.038>
- Rashid, S., Kotton, D. N., & Bar-Joseph, Z. (2017). TASIC: Determining branching models from time series single cell data. *Bioinformatics*, 33(16), 2504–2512. <https://doi.org/10.1093/bioinformatics/btx173>
- Raychaudhuri, A., Ghosh, R., Vasulu, T. S., & Bharati, P. (2003). Heritability Estimates of Height and Weight in Mahishya Caste Population. *International Journal of Human Genetics*, 3(3), 151–154. <https://doi.org/10.1080/09723757.2003.11885842>
- Richiardi, J., Altmann, A., & Greicius, M. (2017). Distance is not everything in imaging genomics of functional networks: Reply to a commentary on Correlated gene expression supports synchronous activity in brain networks. *BioRxiv*, 132746. <https://doi.org/10.1101/132746>
- Richiardi, J., Altmann, A., Milazzo, A.-C., Chang, C., Chakravarty, M. M., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Bromberg, U., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Lemaître, H., ... Consortium, I. (2015). Correlated gene expression supports synchronous activity in brain networks. *Science*, 348(6240), 1241–1244. <https://doi.org/10.1126/science.1255905>
- Rijsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in Bioinformatics*, 3(2), 119–133. <https://doi.org/10.1093/bib/3.2.119>
- Rittman, T., Rubinov, M., Vértes, P. E., Patel, A. X., Ginestet, C. E., Ghosh, B. C. P., Barker, R. A., Spillantini, M. G., Bullmore, E. T., & Rowe, J. B. (2016). Regional expression of the MAPT gene is associated with loss of hubs in brain networks and cognitive impairment in Parkinson disease and progressive supranuclear palsy. *Neurobiology of Aging*, 48, 153–160. <https://doi.org/10.1016/j.neurobiolaging.2016.09.001>
- Roberti, I., Lovino, M., Di Cataldo, S., Ficarra, E., & Urgese, G. (2019). Exploiting Gene Expression Profiles for the Automated Prediction of Connectivity between Brain Regions. *International Journal of Molecular Sciences*, 20(8). <https://doi.org/10.3390/ijms20082035>
- Roberts, D. F., Billewicz, W. Z., & McGregor, I. A. (1978). Heritability of stature in a West African population. *Annals of Human Genetics*, 42(1), 15–24. <https://doi.org/10.1111/j.1469-1809.1978.tb00928.x>
- Roberts, J. A., Perry, A., Lord, A. R., Roberts, G., Mitchell, P. B., Smith, R. E., Calamante, F., & Breakspear, M. (2016). The contribution of geometry to the human connectome. *NeuroImage*, 124, 379–393. <https://doi.org/10.1016/j.neuroimage.2015.09.009>
- Romero-Garcia, R., Whitaker, K. J., Váša, F., Seidlitz, J., Shinn, M., Fonagy, P., Dolan, R. J., Jones, P. B., Goodyer, I. M., Bullmore, E. T., & Vértes, P. E. (2018). Structural covariance networks are coupled to

- expression of genes enriched in supragranular layers of the human cortex. *NeuroImage*, 171, 256–267. <https://doi.org/10.1016/j.neuroimage.2017.12.060>
- Romme, I. A. C., de Reus, M. A., Ophoff, R. A., Kahn, R. S., & van den Heuvel, M. P. (2017). Connectome Disconnectivity and Cortical Gene Expression in Patients With Schizophrenia. *Biological Psychiatry*, 81(6), 495–502. <https://doi.org/10.1016/j.biopsych.2016.07.012>
- Rubinov, M., Ypma, R. J. F., Watson, C., & Bullmore, E. T. (2015). Wiring cost and topological participation of the mouse brain connectome. *Proceedings of the National Academy of Sciences*, 112(32), 10032–10037. <https://doi.org/10.1073/pnas.1420315112>
- Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at rest: How correlation patterns and group differences become distorted after global signal regression. *Brain Connectivity*, 2(1), 25–32. <https://doi.org/10.1089/brain.2012.0080>
- Satizabal, C. L., Adams, H. H. H., Hibar, D. P., White, C. C., Knol, M. J., Stein, J. L., Scholz, M., Sargurupremraj, M., Jahanshad, N., Roshchupkin, G. V., Smith, A. V., Bis, J. C., Jian, X., Luciano, M., Hofer, E., Teumer, A., van der Lee, S. J., Yang, J., Yanek, L. R., ... Ikram, M. A. (2019). Genetic architecture of subcortical brain structures in 38,851 individuals. *Nature Genetics*, 51(11), 1624–1636. <https://doi.org/10.1038/s41588-019-0511-y>
- Schulze, A., & Downward, J. (2001). Navigating gene expression using microarrays—A technology review. *Nature Cell Biology*, 3(8), E190–195. <https://doi.org/10.1038/35087138>
- Schutte, N. M., Hansell, N. K., de Geus, E. J. C., Martin, N. G., Wright, M. J., & Smit, D. J. A. (2013). Heritability of Resting State EEG Functional Connectivity Patterns. *Twin Research and Human Genetics*, 16(5), 962–969. <https://doi.org/10.1017/thg.2013.55>
- Seidlitz, J., Nadig, A., Liu, S., Bethlehem, R. A. I., Vértés, P. E., Morgan, S. E., Váša, F., Romero-Garcia, R., Lalonde, F. M., Clasen, L. S., Blumenthal, J. D., Paquola, C., Bernhardt, B., Wagstyl, K., Polioudakis, D., Torre-Ubieta, L. de la, Geschwind, D. H., Han, J. C., Lee, N. R., ... Raznahan, A. (2020). Transcriptomic and cellular decoding of regional brain vulnerability to neurogenetic disorders. *Nature Communications*, 11(1), 1–14. <https://doi.org/10.1038/s41467-020-17051-5>
- Shen, K.-K., Rose, S., Fripp, J., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Thompson, P. M., Wright, M. J., & Salvado, O. (2014). Investigating brain connectivity heritability in a twin study using diffusion imaging data. *NeuroImage*, 100, 628–641. <https://doi.org/10.1016/j.neuroimage.2014.06.041>
- Silventoinen, K., Sammalisto, S., Perola, M., Boomsma, D. I., Cornes, B. K., Davis, C., Dunkel, L., De Lange, M., Harris, J. R., Hjelmborg, J. V. B., Luciano, M., Martin, N. G., Mortensen, J., Nisticò, L., Pedersen, N. L., Skytthe, A., Spector, T. D., Stazi, M. A., Willemsen, G., & Kaprio, J. (2003). Heritability of adult body height: A comparative study of twin cohorts in eight countries. *Twin Research: The Official Journal of the International Society for Twin Studies*, 6(5), 399–408. <https://doi.org/10.1375/136905203770326402>
- Sinclair, B., Hansell, N. K., Blokland, G. A. M., Martin, N. G., Thompson, P. M., Breakspear, M., de Zubicaray, G. I., Wright, M. J., & McMahon, K. L. (2015). Heritability of the network architecture of intrinsic brain functional connectivity. *NeuroImage*, 121, 243–252. <https://doi.org/10.1016/j.neuroimage.2015.07.048>

- Smit, D. J. A., Stam, C. J., Posthuma, D., Boomsma, D. I., & Geus, E. J. C. de. (2008). Heritability of “small-world” networks in the brain: A graph theoretical analysis of resting-state EEG functional connectivity. *Human Brain Mapping*, 29(12), 1368–1378. <https://doi.org/10.1002/hbm.20468>
- Smith, S. M., Douaud, G., Chen, W., Hanayik, T., Alfaro-Almagro, F., Sharp, K., & Elliott, L. T. (2020). Enhanced Brain Imaging Genetics in UK Biobank. *BioRxiv*, 2020.07.27.223545. <https://doi.org/10.1101/2020.07.27.223545>
- Sousa, A. M. M., Zhu, Y., Raghanti, M. A., Kitchen, R. R., Onorati, M., Tebbenkamp, A. T. N., Stutz, B., Meyer, K. A., Li, M., Kawasawa, Y. I., Liu, F., Perez, R. G., Mele, M., Carvalho, T., Skarica, M., Gulden, F. O., Pletikos, M., Shibata, A., Stephenson, A. R., ... Sestan, N. (2017). Molecular and cellular reorganization of neural circuits in the human lineage. *Science*, 358(6366), 1027–1032. <https://doi.org/10.1126/science.aan3456>
- Sporns, O. (2011). The human connectome: A complex network. *Annals of the New York Academy of Sciences*, 1224(1), 109–125. <https://doi.org/10.1111/j.1749-6632.2010.05888.x>
- Sporns, O., & Betzel, R. F. (2016). Modular Brain Networks. *Annual Review of Psychology*, 67, 613–640. <https://doi.org/10.1146/annurev-psych-122414-033634>
- Sporns, O., Tononi, G., & Kötter, R. (2005). The Human Connectome: A Structural Description of the Human Brain. *PLOS Computational Biology*, 1(4), e42. <https://doi.org/10.1371/journal.pcbi.0010042>
- Stein, J. L., Hua, X., Lee, S., Ho, A. J., Leow, A. D., Toga, A. W., Saykin, A. J., Shen, L., Foroud, T., Pankratz, N., Huentelman, M. J., Craig, D. W., Gerber, J. D., Allen, A. N., Corneveaux, J. J., Dechairo, B. M., Potkin, S. G., Weiner, M. W., Thompson, P., & Alzheimer’s Disease Neuroimaging Initiative. (2010). Voxelwise genome-wide association study (vGWAS). *NeuroImage*, 53(3), 1160–1174. <https://doi.org/10.1016/j.neuroimage.2010.02.032>
- Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Medicine*, 12(3), e1001779. <https://doi.org/10.1371/journal.pmed.1001779>
- Sudre, G., Choudhuri, S., Szekely, E., Bonner, T., Goduni, E., Sharp, W., & Shaw, P. (2017). Estimating the Heritability of Structural and Functional Brain Connectivity in Families Affected by Attention-Deficit/Hyperactivity Disorder. *JAMA Psychiatry*, 74(1), 76–84. <https://doi.org/10.1001/jamapsychiatry.2016.3072>
- Sullivan, P. F. (2007). Spurious Genetic Associations. *Biological Psychiatry*, 61(10), 1121–1126. <https://doi.org/10.1016/j.biopsych.2006.11.010>
- Sun, J., Kranzler, H. R., & Bi, J. (2015). An Effective Method to Identify Heritable Components from Multivariate Phenotypes. *PLOS ONE*, 10(12), e0144418. <https://doi.org/10.1371/journal.pone.0144418>
- Taylor, S. R., Santpere, G., Reilly, M., Glenwinkel, L., Poff, A., McWhirter, R., Xu, C., Weinreb, A., Basavaraju, M., Cook, S. J., Barrett, A., Abrams, A., Vidal, B., Cros, C., Rafi, I., Sestan, N., Hammarlund, M., Hobert, O., & Miller, D. M. (2019). Expression profiling of the mature *C. elegans* nervous system by single-cell RNA-Sequencing. *BioRxiv*, 737577. <https://doi.org/10.1101/737577>

- Thomas, C., Ye, F. Q., Irfanoglu, M. O., Modi, P., Saleem, K. S., Leopold, D. A., & Pierpaoli, C. (2014). Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. *Proceedings of the National Academy of Sciences*, 111(46), 16574–16579. <https://doi.org/10.1073/pnas.1405672111>
- Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V.-P., Huttunen, M., Lönqvist, J., Standertskjöld-Nordenstam, C.-G., Kaprio, J., Khaledy, M., Dail, R., Zoumalan, C. I., & Toga, A. W. (2001). Genetic influences on brain structure. *Nature Neuroscience*, 4(12), 1253–1258. <https://doi.org/10.1038/nn758>
- Thompson, P. M., Ge, T., Glahn, D. C., Jahanshad, N., & Nichols, T. E. (2013). Genetics of the connectome. *NeuroImage*, 80, 475–488. <https://doi.org/10.1016/j.neuroimage.2013.05.013>
- Towlson, E. K., Vértes, P. E., Ahnert, S. E., Schafer, W. R., & Bullmore, E. T. (2013). The rich club of the C. elegans neuronal connectome. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 33(15), 6380–6387. <https://doi.org/10.1523/JNEUROSCI.3784-12.2013>
- Trachtenberg, A. J., Filippini, N., Ebmeier, K. P., Smith, S. M., Karpe, F., & Mackay, C. E. (2012). The effects of APOE on the functional architecture of the resting brain. *NeuroImage*, 59(1), 565–572. <https://doi.org/10.1016/j.neuroimage.2011.07.059>
- Unger, S., Böhm, D., Kaiser, F. J., Kaulfuß, S., Borozdin, W., Buiting, K., Burfeind, P., Böhm, J., Barrionuevo, F., Craig, A., Borowski, K., Keppler-Noreuil, K., Schmitt-Mechelke, T., Steiner, B., Bartholdi, D., Lemke, J., Mortier, G., Sandford, R., Zabel, B., ... Kohlhasse, J. (2008). Mutations in the cyclin family member FAM58A cause an X-linked dominant disorder characterized by syndactyly, telecanthus and anogenital and renal malformations. *Nature Genetics*, 40(3), 287–289. <https://doi.org/10.1038/ng.86>
- Vaishnavi, S. N., Vlassenko, A. G., Rundle, M. M., Snyder, A. Z., Mintun, M. A., & Raichle, M. E. (2010). Regional aerobic glycolysis in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 107(41), 17757–17762.
- van den Heuvel, M. P., Bullmore, E. T., & Sporns, O. (2016). Comparative Connectomics. *Trends in Cognitive Sciences*, 20(5), 345–361. <https://doi.org/10.1016/j.tics.2016.03.001>
- van den Heuvel, M. P., van Soelen, I. L. C., Stam, C. J., Kahn, R. S., Boomsma, D. I., & Hulshoff Pol, H. E. (2013). Genetic control of functional brain network efficiency in children. *European Neuropsychopharmacology*, 23(1), 19–23. <https://doi.org/10.1016/j.euroneuro.2012.06.007>
- Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E. J., Yacoub, E., & Ugurbil, K. (2013). The WU-Minn Human Connectome Project: An overview. *NeuroImage*, 80, 62–79. <https://doi.org/10.1016/j.neuroimage.2013.05.041>
- van Soelen, I. L. C., Brouwer, R. M., van Baal, G. C. M., Schnack, H. G., Peper, J. S., Collins, D. L., Evans, A. C., Kahn, R. S., Boomsma, D. I., & Hulshoff Pol, H. E. (2012). Genetic influences on thinning of the cerebral cortex during development. *NeuroImage*, 59(4), 3871–3880. <https://doi.org/10.1016/j.neuroimage.2011.11.044>
- Varadan, V., Miller, D. M., & Anastassiou, D. (2006). Computational inference of the molecular logic for synaptic connectivity in C. elegans. *Bioinformatics*, 22(14), e497–e506. <https://doi.org/10.1093/bioinformatics/btl224>

- Várkuti, B., Cavusoglu, M., Kullik, A., Schiffler, B., Veit, R., Yilmaz, Ö., Rosenstiel, W., Braun, C., Uludag, K., Birbaumer, N., & Sitaram, R. (2011). Quantifying the Link between Anatomical Connectivity, Gray Matter Volume and Regional Cerebral Blood Flow: An Integrative MRI Study. *PLOS ONE*, 6(4), e14801. <https://doi.org/10.1371/journal.pone.0014801>
- Varshney, L. R., Chen, B. L., Paniagua, E., Hall, D. H., & Chklovskii, D. B. (2011). Structural Properties of the *Caenorhabditis elegans* Neuronal Network. *PLOS Computational Biology*, 7(2), e1001066. <https://doi.org/10.1371/journal.pcbi.1001066>
- Váša, F., Seidlitz, J., Romero-Garcia, R., Whitaker, K. J., Rosenthal, G., Vértes, P. E., Shinn, M., Alexander-Bloch, A., Fonagy, P., Dolan, R. J., Jones, P. B., Goodyer, I. M., Consortium, the N., Sporns, O., & Bullmore, E. T. (2018). Adolescent Tuning of Association Cortex in Human Structural Brain Networks. *Cerebral Cortex*, 28(1), 281–294. <https://doi.org/10.1093/cercor/bhx249>
- Vértes, P. E., Rittman, T., Whitaker, K. J., Romero-Garcia, R., Váša, F., Kitzbichler, M. G., Wagstyl, K., Fonagy, P., Dolan, R. J., Jones, P. B., Goodyer, I. M., & Bullmore, E. T. (2016). Gene transcription profiles associated with inter-modular hubs and connection distance in human functional magnetic resonance imaging networks. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 371(1705). <https://doi.org/10.1098/rstb.2015.0362>
- Vuoksima, E., Panizzon, M. S., Jr, D. J. H., Hatton, S. N., Fennema-Notestine, C., Rinker, D., Eyler, L. T., Franz, C. E., Lyons, M. J., Neale, M. C., Tsuang, M. T., Dale, A. M., & Kremen, W. S. (2017). Heritability of white matter microstructure in late middle age: A twin study of tract-based fractional anisotropy and absolute diffusivity indices. *Human Brain Mapping*, 38(4), 2026–2036. <https://doi.org/10.1002/hbm.23502>
- Wang, C., Liu, B., Zhang, X., Cui, Y., Yu, C., & Jiang, T. (2018). Multilocus genetic profile in dopaminergic pathway modulates the striatum and working memory. *Scientific Reports*, 8(1), 5372. <https://doi.org/10.1038/s41598-018-23191-y>
- Wang, N., Anderson, R. J., Ashbrook, D. G., Gopalakrishnan, V., Park, Y., Priebe, C. E., Qi, Y., Laoprasert, R., Vogelstein, J. T., Williams, R. W., & Johnson, G. A. (2020). Variability and heritability of mouse brain structure: Microscopic MRI atlases and connectomes for diverse strains. *NeuroImage*, 222, 117274. <https://doi.org/10.1016/j.neuroimage.2020.117274>
- Wang, T., Zhang, X., Li, A., Zhu, M., Liu, S., Qin, W., Li, J., Yu, C., Jiang, T., & Liu, B. (2017). Polygenic risk for five psychiatric disorders and cross-disorder and disorder-specific neural connectivity in two independent populations. *NeuroImage: Clinical*, 14, 441–449. <https://doi.org/10.1016/j.nicl.2017.02.011>
- Wang, Y., Fang, Y., & Jin, M. (2007). A ridge penalized principal-components approach based on heritability for high-dimensional data. *Human Heredity*, 64(3), 182–191. <https://doi.org/10.1159/000102991>
- Ward, J., Lyall, L. M., Bethlehem, R. A. I., Ferguson, A., Strawbridge, R. J., Lyall, D. M., Cullen, B., Graham, N., Johnston, K. J. A., Bailey, M. E. S., Murray, G. K., & Smith, D. J. (2019). Novel genome-wide associations for anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. *Translational Psychiatry*, 9. <https://doi.org/10.1038/s41398-019-0635-y>
- Wei, Y., de Lange, S. C., Scholtens, L. H., Watanabe, K., Ardesch, D. J., Jansen, P. R., Savage, J. E., Li, L., Preuss, T. M., Rilling, J. K., Posthuma, D., & van den Heuvel, M. P. (2019). Genetic mapping and

- evolutionary analysis of human-expanded cognitive networks. *Nature Communications*, 10(1), 4839. <https://doi.org/10.1038/s41467-019-12764-8>
- Wei, Y., Lange, S. C. de, Pijnenburg, R., Scholtens, L. H., Ardesch, D. J., Watanabe, K., Posthuma, D., & Heuvel, M. P. van den. (2021). Statistical testing and annotation of gene transcriptomic-neuroimaging associations. *BioRxiv*, 2021.02.22.432228. <https://doi.org/10.1101/2021.02.22.432228>
- Westlye, E. T., Lundervold, A., Rootwelt, H., Lundervold, A. J., & Westlye, L. T. (2011). Increased Hippocampal Default Mode Synchronization during Rest in Middle-Aged and Elderly APOE ϵ 4 Carriers: Relationships with Memory Performance. *Journal of Neuroscience*, 31(21), 7775–7783. <https://doi.org/10.1523/JNEUROSCI.1230-11.2011>
- Whelan, C. D., Hibar, D. P., van Velzen, L. S., Zannas, A. S., Carrillo-Roa, T., McMahon, K., Prasad, G., Kelly, S., Faskowitz, J., deZubiracay, G., Iglesias, J. E., van Erp, T. G. M., Frodl, T., Martin, N. G., Wright, M. J., Jahanshad, N., Schmaal, L., Sämann, P. G., & Thompson, P. M. (2016). Heritability and reliability of automatically segmented human hippocampal formation subregions. *NeuroImage*, 128, 125–137. <https://doi.org/10.1016/j.neuroimage.2015.12.039>
- Whitaker, K. J., Vértés, P. E., Romero-Garcia, R., Váša, F., Moutoussis, M., Prabhu, G., Weiskopf, N., Callaghan, M. F., Wagstyl, K., Rittman, T., Tait, R., Ooi, C., Suckling, J., Inkster, B., Fonagy, P., Dolan, R. J., Jones, P. B., Goodyer, I. M., Consortium, the N., & Bullmore, E. T. (2016). Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proceedings of the National Academy of Sciences*, 113(32), 9105–9110. <https://doi.org/10.1073/pnas.1601745113>
- White, J. G., Southgate, E., Thomson, J. N., & Brenner, S. (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, 314(1165), 1–340. <https://doi.org/10.1098/rstb.1986.0056>
- Wray, N. R., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., Murray, G. K., & Visscher, P. M. (2020). From Basic Science to Clinical Application of Polygenic Risk Scores: A Primer. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2020.3049>
- Wright, I. C., Sham, P., Murray, R. M., Weinberger, D. R., & Bullmore, E. T. (2002). Genetic Contributions to Regional Variability in Human Brain Structure: Methods and Preliminary Results. *NeuroImage*, 17(1), 256–271. <https://doi.org/10.1006/nimg.2002.1163>
- Yang, J., Zeng, J., Goddard, M. E., Wray, N. R., & Visscher, P. M. (2017). Concepts, estimation and interpretation of SNP-based heritability. *Nature Genetics*, 49(9), 1304–1310. <https://doi.org/10.1038/ng.3941>
- Yang, Z., Zuo, X.-N., McMahon, K. L., Craddock, R. C., Kelly, C., de Zubicaray, G. I., Hickie, I., Bandettini, P. A., Castellanos, F. X., Milham, M. P., & Wright, M. J. (2016). Genetic and Environmental Contributions to Functional Connectivity Architecture of the Human Brain. *Cerebral Cortex*, 26(5), 2341–2352. <https://doi.org/10.1093/cercor/bhw027>
- Zalesky, A., Fornito, A., & Bullmore, E. (2012). On the use of correlation as a measure of network connectivity. *NeuroImage*, 60(4), 2096–2106. <https://doi.org/10.1016/j.neuroimage.2012.02.001>

- Zalesky, A., Fornito, A., Cocchi, L., Gollo, L. L., van den Heuvel, M. P., & Breakspear, M. (2016). Connectome sensitivity or specificity: Which is more important? *NeuroImage*, *142*, 407–420. <https://doi.org/10.1016/j.neuroimage.2016.06.035>
- Zhan, L., Jahanshad, N., Faskowitz, J., Zhu, D., Prasad, G., Martin, N. G., Zubicaray, G. I. de, McMahon, K. L., Wright, M. J., & Thompson, P. M. (2015). Heritability of brain network topology in 853 twins and siblings. *2015 IEEE 12th International Symposium on Biomedical Imaging (ISBI)*, 449–453. <https://doi.org/10.1109/ISBI.2015.7163908>
- Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012). NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, *61*(4), 1000–1016. <https://doi.org/10.1016/j.neuroimage.2012.03.072>
- Zhu, H., & Zhou, X. (2020). Statistical methods for SNP heritability estimation and partition: A review. *Computational and Structural Biotechnology Journal*, *18*, 1557–1568. <https://doi.org/10.1016/j.csbj.2020.06.011>
- Zingg, B., Hintiryan, H., Gou, L., Song, M. Y., Bay, M., Bienkowski, M. S., Foster, N. N., Yamashita, S., Bowman, I., Toga, A. W., & Dong, H.-W. (2014). Neural Networks of the Mouse Neocortex. *Cell*, *156*(5), 1096–1111. <https://doi.org/10.1016/j.cell.2014.02.023>
- Zyphur, M. J., Zhang, Z., Barsky, A. P., & Li, W.-D. (2013). An ACE in the hole: Twin family models for applied behavioral genetics research. *The Leadership Quarterly*, *24*(4), 572–594. <https://doi.org/10.1016/j.leaqua.2013.04.001>