Connectomic intermediate phenotypes for psychiatric disorders

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Psychiatric disorders are phenotypically heterogeneous entities with a complex genetic basis. To mitigate this complexity, many investigators study so-called intermediate phenotypes (IPs) that putatively provide a more direct index of the physiological effects of candidate genetic risk variants than overt psychiatric syndromes. Magnetic resonance imaging (MRI) is a particularly popular technique for measuring such phenotypes because it allows interrogation of diverse aspects of brain structure and function in vivo. Much of this work however, has focused on relatively simple measures that quantify variations in the physiology or tissue integrity of specific brain regions in isolation, contradicting an emerging consensus that most major psychiatric disorders do not arise from isolated dysfunction in one or a few brain regions, but rather from disturbed interactions within and between distributed neural circuits; i.e., they are disorders of brain connectivity. The recent proliferation of new MRI techniques for comprehensively mapping the entire connectivity architecture of the brain, termed the human connectome, has provided a rich repertoire of tools for understanding how genetic variants implicated in mental disorder impact distinct neural circuits. In this article, we review research using these connectomic techniques to understand how genetic variation influences the connectivity and topology of human brain networks. We highlight recent evidence from twin and imaging genetics studies suggesting that the penetrance of candidate risk variants for mental illness, such as those in SLC6A4, MAOA, ZNF804A, and APOE, may be higher for IPs characterized at the level of distributed neural systems than at the level of spatially localized brain regions. The findings indicate that imaging connectomics provides a powerful framework for understanding how genetic risk for psychiatric disease is expressed through altered structure and function of the human connectome.

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Genetic factors play a major role in liability for mental illness. Most psychiatric disorders are familial (Gottesman, 1991; Sullivan et al., 2000; Hettema et al., 2001), and twin studies of disease heritability – the proportion of illness susceptibility attributable to genes – indicate that genetic contributions are as high as 80–90% for schizophrenia and bipolar disorder (Cannon et al., 1998; Cardno et al., 1999; McGuffin et al., 2003); 40–70% for major depression (Kendler et al., 1993, 2006; Sullivan et al., 2000); 37 to >90% for autism and autistic traits (Hallmayer et al., 2011; Robinson et al., 2012); 30–70% for substance addiction (Agrawal and Lyskey, 2008); and ~30–50% for anxiety disorders and obsessive–compulsive disorder (Hettema et al., 2001; van Grootheest et al., 2005). This liability has a complex genetic basis, arising from the combined effect of multiple (hundreds or thousands) genetic variants of small-effect, rather than one or a few genes of large effect (e.g., Purcell et al., 2009). This complexity is compounded by the substantial phenotypic heterogeneity that characterizes most of these disorders. Some of this heterogeneity may be intrinsic to the disease process itself, but a large proportion likely reflects our current lack of biologically informed diagnostic criteria. In practice, this failure to appropriately “carve nature at its joints” (Kendler, 2006) introduces considerable noise into any attempts to map illness phenotypes to genetic risk mechanisms and positions psychiatric disorders, as currently diagnosed, far downstream of the pathophysiological effects of genetic variants influencing disease susceptibility.

One strategy proposed to mitigate the phenotypic heterogeneity of psychiatric disorders involves studying intermediate phenotypes (IPs; Meyer-Lindenberg and Weinberger, 2006). IPs are quantitative, biological traits that are interposed between gene and clinical phenotype on the causal pathway leading from inherited vulnerability to disease. They putatively provide a more direct index of the physiological effects of genetic risk variants and can be used to parse a phenotypically heterogeneous disorder with complex genetic basis into more homogeneous phenotypes with a presumably simpler genetic architecture (see Gottesman and Gould, 2003; Cannon and Keller, 2006; though, see Flint and Munafò, 2007; Walters and Owen, 2007; Kendler and Neale, 2010).
for critiques). Various criteria for viable IPs have been proposed (Gottesman and Gould, 2003; Cannon and Keller, 2006; Walters and Owen, 2007), generally stating that such a phenotype should (1) be quantitative and heritable; (2) differentiate patients from controls; (3) be associated with disease causes rather than effects; (4) co-segregate with illness within families; (5) be more frequent in unaffected individuals at increased genetic risk; and (6) be stable over time (although this last criterion has been challenged; see Pantelis et al., 2009; Gogtay et al., 2011).

Psychiatric disorders are disturbances of mental processes mediated by the brain. Neural measures therefore represent a major class of candidate IPs for mental illness, and in vivo neuroimaging has provided a powerful means for identifying and characterizing such IPs for a broad spectrum of psychiatric disease, particularly when related to variation in specific candidate risk genes (Meyer-Lindenberg and Weinberger, 2006). This “imaging genetics” approach has been used to elucidate the mechanisms through which genetically mediated variations in brain structure and function might give rise to psychiatric illness, and provide biological validation of candidate variants (Esslinger et al., 2009; Erk et al., 2010). In some cases, neuroimaging has also been used to augment the search for risk genes (Potkin et al., 2009).

Most imaging genetics work has studied relatively simple IPs, defined using measures of task-related activation or anatomical structure (e.g., gray matter volume or cortical thickness) in specific brain regions. Though the simplicity of these measures is attractive, they likely over-simplify relevant (patho)physiological processes in most cases. Over two decades of neuroimaging research has found that most major psychiatric disorders do not arise from isolated damage to one or a few brain regions, but rather from multiple abnormalities distributed throughout the cerebrum (Phillips et al., 2003b; Belmonte et al., 2004; Menzies et al., 2008; Fornito et al., 2009, 2012; Minzenberg et al., 2009). These abnormalities likely have their origin in disturbed interactions between discrete and distributed neural circuits; i.e., disordered brain connectivity. Moreover, many risk genes for psychiatric disorders are expressed diffusely throughout the brain, acting on physiological pathways involved in synaptic function/regulation, neurotransmitter release, degradation or re-uptake, and the development and maintenance of axonal pathways (Harrison and Weinberger, 2005; Bennett, 2011; Lips et al., 2011; Gai et al., 2012). These considerations indicate that a systems-level approach should prove useful for characterizing the neurophysiological impact of candidate risk variants, and in defining novel IPs.

Attempts to understand genetic influences on distributed brain networks have been greatly facilitated by recent attempts to map the structural and functional properties of the human connectome—the complete set of neural elements and inter-connections comprising the brain (Sporns et al., 2005; Sporns, 2011). The use of neuroimaging to achieve this goal, termed imaging connectomics, has led to the development and proliferation of a rich repertoire of tools for characterizing diverse aspects of human brain connectivity (Bullmore and Sporns, 2009; Bullmore et al., 2009; Fornito and Bullmore, 2010; Margulies et al., 2010). These tools are now increasingly being deployed within genetically informative designs to uncover new connectomic IPs (cIPs) that show promise as sensitive measures of genetic variation in brain structure and physiology (Meyer-Lindenberg, 2009). In this article we overview recent work attempting to understand genetic influences on brain connectivity, focusing principally on studies using magnetic resonance imaging (MRI) that provide illustrative examples of the potential utility of cIPs for characterizing genetic risk mechanisms in mental illness. Our intention is not to identify specific cIPs that fulfill all of the above criteria and which may thus be considered to be comprehensively validated, as this is difficult to achieve in practice. Rather, our aim is to draw attention to emerging evidence suggesting the connectomic measures provide particularly sensitive probes of the functional effects of disease risk genes. As an orientation to relevant concepts, we begin with a brief primer on some basic concepts central to the imaging connectomics approach.

**A PRIMER ON IMAGING CONNECTOMICS**

Magnetic resonance imaging studies have used a wide range of techniques to explore different properties of the human connectome. A simplified conceptual overview of how some of the most commonly used imaging techniques relate to these properties is presented in Figure 1.

Broadly, the connectome can be studied in terms of structure or function. Connectome structure refers to the anatomical connections between different brain regions, and is measured in MRI studies using either T1- or diffusion-weighted imaging (DWI). The former indirectly infers connectivity between regions either through voxel-wise mapping of variations in white matter density, or covariance in regional morphometric parameters, such as gray matter volume or cortical thickness. These morphometric covariance analyses (MCA) can be performed either between a single seed region and all other brain voxels (Pezawas et al., 2005; Meyer-Lindenberg et al., 2007), between (many) pairs of *a priori* defined regions (He et al., 2007; Bassett et al., 2008), or following multivariate decomposition of the data using techniques such as independent component analysis (ICA; Xu et al., 2009a,b). DWI provides a more direct measure of the integrity and trajectory of anatomical connections, subject to certain caveats (Mori and Zhang, 2006; Zalesky and Fornito, 2009; Jbabdi and Johansen-Berg, 2011). Voxel-based analysis (VBA) techniques applied to estimates of white matter density/volume or DWI-derived measures (e.g., axial/radial diffusivity and/or fractional anisotropy) allow whole-brain mapping of differences in white matter integrity or morphometry. This includes methods such as tract-based spatial statistics (TBSS; Smith et al., 2006). Alternatively, connectivity may be indexed with DWI by deterministic or probabilistic tractography of fiber trajectories linking different brain regions, either at the level of specific pairs of brain regions, or between every possible pair of regions defined using some comprehensive cerebral parcellation (Hagmann et al., 2008; Zalesky et al., 2010). With
Networks of voxels with temporally coherent activity. This approach, connectivity is estimated either as the number of tracts intersecting each regional pair (Zalesky et al., 2011), or some index of tissue integrity averaged across the extent of the reconstructed trajectory (van den Heuvel et al., 2010). Note that all of these anatomical measures only provide undirected estimates of inter-regional connectivity; i.e., they may imply that two regions are connected, but they cannot resolve whether the connection runs from region A to B or vice-versa.

Magnetic resonance imaging studies of connectome function generally use blood-oxygenation-level dependent (BOLD) imaging. Functional interactions between regions can be categorized into one of two broad classes: functional and effective connectivity (Friston, 1994). Effective connectivity refers to the influence that one neuronal system exerts over another and allows inferences concerning causal (directed) interactions between regions. The most rudimentary model of effective connectivity is provided by psychophysiological interaction (PPI) analysis (Friston et al., 1997), which involves analyzing task-related changes in connectivity between a seed region and all other brain voxels. Dynamic causal modeling (DCM; Friston et al., 2003) and Granger causality analysis (GCA; Bressler and Seth, 2011) provide more elaborate means for inferring causal interactions between brain regions but have seldom been studied in the context of genetically informative designs (though, see Curcic-Blake et al., 2012 for an exception).

Functional connectivity refers to a statistical dependence between regionally distinct neurophysiological recordings and is undirected in nature. Most frequently, this is measured through simple Pearson correlation of regional activity time courses. This covariance is typically studied between a single seed region and all other brain voxels (termed a seed-based correlation analysis), or in a pair-wise correlation (PWC) analysis where associations between either a single pair of a priori defined regions, or multiple pairs of regions, are computed. Another popular technique for studying functional connectivity involves multivariate spatio-temporal decomposition using techniques such as spatial ICA (Beckmann and Smith, 2004; Calhoun et al., 2004), which offers a data-driven method for identifying spatially independent networks of voxels with temporally coherent activity.

A final important distinction that applies to studies of both connectome function and structure concerns whether inter-regional interactions are studied at the level of connectivity or topology. Studies of connectivity are concerned with measuring variations in the strength and nature (e.g., structural or functional, positive or negative) of connectivity between regions. Studies of topology are concerned with how connections between different brain regions are configured with respect to each other. These analyses require relatively comprehensive mapping of inter-regional connectivity using a PWC approach combined with graph analysis to characterize such topological variations (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011). Briefly, graph analysis involves modeling the brain as a graph of nodes, representing brain regions, connected by edges, representing some measure of inter-regional structural or functional interaction. The method allows a wide range of topological properties representing diverse aspects of connectome organization to be computed (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Though topology and connectivity are not necessarily independent (Barrat et al., 2004; Alexander-Bloch et al., 2010; Lynall et al., 2010), the distinction between them provides a useful heuristic for evaluating findings in imaging connectomics. In the following, we first consider studies examining genetic influences on brain network connectivity before discussing studies of network topology.

**THE GENETICS OF HUMAN BRAIN NETWORK CONNECTIVITY**

Most of the connectomic phenotypes studied in imaging genetics studies to date have been relatively specific, focusing on particular neural circuits of theoretical interest. These have typically been investigated by analyzing connectivity between specific pairs of brain regions, or between one seed region and all other brain voxels. Most of this work has used fMRI and therefore focuses on neural circuits of theoretical interest. For example, in the default mode network, examples of how genetic variants impact other neural systems can be found elsewhere (e.g., Meyer-Lindenberg et al.,...
SLC6A4, MAOA, AND FRONTO-LIMBIC CONNECTIVITY

The first MRI study to examine genetic influences on a connectomic phenotype examined how variation in the human serotonin (5-HT) transporter gene SLC6A4 impacted functional connectivity between the amygdala and medial prefrontal cortex (mPFC; Heinz et al., 2005). A variable number of tandem repeats (VNTR) in the 5′ promoter region (5-HTTPLR) of SLC6A4 influences mRNA and protein expression such that a short (s) compared to long (l) allele is associated with reduced transcriptional efficiency (Heils et al., 1996) and reduced 5-HT transporter binding in the brain (Heinz et al., 2000). Accordingly, the s allele has been variably associated with personality traits associated with negative emotionality (Lesch et al., 1996; Munafo et al., 2009), alcohol dependence (McHugh et al., 2010), mood disorders (Clarke et al., 2010), and suicidality (Li and He, 2007). In some cases, these associations may be moderated by environmental factors (Caspi et al., 2010).

Consistent with an association between the s allele and negative emotions, an early fMRI study found that human carriers of this allele showed increased amygdala activation during perception of aversive emotional stimuli (Hariri et al., 2002). In a separate study using a similar task, an association was reported between the s allele and greater functional connectivity between the amygdala and anterior mPFC (Heinz et al., 2005). This finding was noteworthy given the abundant evidence pointing to the amygdala and mPFC as critical nodes within a broader neural network subserving emotional regulation (Phillips et al., 2003a). These findings were subsequently replicated by an independent group, who also reported an association between the s allele and reduced functional connectivity between the amygdala and more posterior medial prefrontal regions located in pre- and sub-genual anterior cingulate cortex (ACC; Pezawas et al., 2005). An anatomical basis for these functional effects was suggested by a corresponding reduction in gray matter volume covariance between the amygdala and pre-genual ACC in s allele carriers compared to l/l homozygotes, a finding replicated in an independent study using DTI-derived measures of anatomical connectivity (Pacheco et al., 2009). The functional connectivity measures predicted approximately 30% of the variance in temperamental measures of anxiety-related traits such as harm avoidance. No such association was found with regional indices of activation or volume, indicating that the connectomic measures provided a more direct physiological marker of clinically relevant behavioral phenotypes. Collectively, these results suggest that variation in SLC6A4 regulates fronto-limbic dynamics in highly specific ways, such that the s allele up-regulates functional connectivity between amygdala and anterior mPFC and down-regulates connectivity between amygdala and perigenual ACC (Figure 2).

Another genetic variant shown to impact fronto-limbic connectivity is a VNTR in the upstream promoter region of the X-linked Monoamine Oxidase A (MAOA) gene (Buckholtz et al., 2008).

**FIGURE 2 | Genetic influences on functional connectivity of fronto-limbic circuits.** Cortical surface renderings display the stereotactic peaks of regions in prefrontal cortex where functional connectivity with the amygdala is impacted by common genetic variants. Different colors denote the different genes studied in relation to fronto-limbic functional connectivity; namely, SLC6A4 (Heinz et al., 2005; Pezawas et al., 2005; Schardt et al., 2010), MAOA (Buckholtz et al., 2008), COMT (Rasch et al., 2010), and DRD2 (Blasi et al., 2009). Arrows indicate whether functional connectivity was increased (↑) or decreased (↓) in carriers of the putative risk allele for each gene. The distinction between cyan and blue foci for SLC6A4 studies differentiates a single study examining functional connectivity during cognitive regulation of emotion (Schardt et al., 2010) from others involving passive perception of emotional stimuli. This distinction illustrates how the risk allele of 5-HTTPLR polymorphism of this gene can be associated with either increased or decreased functional connectivity with the amygdala in adjacent regions of right pre-genual ACC, depending on task context.
MAOA is the main enzyme responsible for catabolizing synaptic 5-HT and norepinephrine, and MAOA expression is higher when the VNTR comprises 3.5–4 repeats (MAOA-H) than when 2, 3, or 5 repeats are present (MAOA-L; Sabol et al., 1998). The low activity allele has been shown to interact with childhood stressors to increase risk for adverse mental health outcomes such as aggressive behavior and mood disturbances (Caspil et al., 2002; Kim-Cohen et al., 2006; Nikulina et al., 2012). Accordingly, functional connectivity between the amygdala and anterior mPFC is higher in MAOA-L individuals compared to MAOA-H participants performing an emotional perception task (Buckholtz et al., 2008), a finding that parallels the functional connectivity increases between these two regions found in carriers of the 5-HTTPLR-s allele (Heinz et al., 2005; Pezawas et al., 2005; Figure 2).

The common effect of the MAOA-L and 5-HTTPLR-s alleles on amygdala–mPFC circuitry may result from a shared influence on synaptic serotonin levels, as both are thought to be associated with increased brain 5-HT. Greater functional connectivity between the amygdala and anterior mPFC may therefore represent a final common pathway for genetically mediated increases in synaptic 5-HT concentrations. Contrary to this view however, recent imaging evidence suggests that 5-HTTPLR genotype has little effect on basal synaptic serotonin levels (Jedema et al., 2010; Murthy et al., 2010). As such, the precise mechanism through which the polymorphism influences mPFC–amygdala connectivity remains unclear, but may be related to its emerging role in neurodevelopment (Anzorge et al., 2004). Regardless of the precise mechanism, it is noteworthy that the effects seem specific to variants impacting on 5-HT function, as functional polymorphisms in genes that do not directly impact this neurotransmitter show no effect on amygdala–mPFC connectivity. For example, two genetic variants that influence synaptic dopamine levels, the Val108/158 Met polymorphism of the catechol-o-methyl transferase (COMT) gene, and the rs1076560 polymorphism of the D2 receptor gene DRD2, influence functional connectivity between the amygdala and lateral, but not medial, PFC (Buckholtz et al., 2008; Blasi et al., 2009; Rasch et al., 2010; Figure 2). These findings point to highly specific genetic influences on different components of fronto-limbic circuitry.

Some of these genetic effects can be expressed in different ways depending on psychological context. For example, during conditions requiring cognitive regulation of emotion, s allele carriers actually show increased functional connectivity between the amygdala and perigenual ACC (Schardt et al., 2010). This result indicates that the previously reported reduction in functional coupling between these regions does not reflect a hard-wired deficit, despite evidence for anatomical connectivity reductions between these regions (Pezawas et al., 2005). Rather, the connectivity reduction may reflect a bias to process aversive stimuli in maladaptive ways, which may be ameliorated given appropriate environmental circumstances. In this regard, the connectivity increase in s allele carriers during cognitive regulation of emotion may reflect the deployment of greater processing resources to overcome this processing bias. These context-specific effects on connectomic phenotypes are consistent with evidence for environmental factors such as life stress moderating the influence of SLC6A4 genotype on functional connectivity of the amygdala (Canli et al., 2006).

To summarize, studies of the SLC6A4 and MAOA genes provide examples of how genetic influences on brain connectivity can be expressed in circuit specific ways, and in a manner contingent on environmental context. The circuit- and context-specificity of these effects is underscored by work on other genes, such as CA1CNAC (Erk et al., 2010), α5 acetylcholine receptor subunit (CHRNAS; Hong et al., 2010), brain-derived neurotrophic factor (BDNF; Mukherjee et al., 2011), and α2-adrenergic receptor (ADRA2B; Rasch et al., 2009). Variants in each of these genes have been shown to impact fronto-limbic circuitry in a task-dependent manner, and in regions outside the amygdala–mPFC loop influenced by SLC6A4 and MAOA. Understanding how each of these variants impact different components of fronto-limbic circuits, and under what conditions, will no doubt prove to be a challenging task.

FRONTO-TEMPORAL CONNECTIVITY AND ZNF804A

Fronto-temporal connectivity is of particular interest to schizophrenia researchers, as diverse lines of evidence point to altered structural and functional interactions between frontal and temporal brain regions as a core feature of the disease phenotype (Weinberger et al., 1992; Meyer-Lindenberg et al., 2005; Ellison-Wright and Bullmore, 2009; van den Heuvel et al., 2010; Fornito et al., 2011a; 2012; Pettersson-Yeo et al., 2011). Accordingly, variation in several candidate risk genes for schizophrenia has been shown to impact fronto-temporal connectivity, including loci in COMT (Bertolino et al., 2006; Dennis et al., 2010b), RGS4 (Buckholtz et al., 2007), PPPIR1B encoding DAARP-32 (Curcic-Blake et al., 2012), and ErbB4 (Konrad et al., 2009).

One genetic variant receiving increasing attention for its effects on fronto-temporal circuitry is the rs1344706 polymorphism of ZNF804A. The gene encodes a zinc finger domain protein with unknown function, although preliminary evidence suggests a role in oligodendrocyte regulation (Riley et al., 2010) and neurodevelopment (Chung et al., 2010). The rs1344706 polymorphism has now been implicated as a genome-wide significant risk variant for both schizophrenia and bipolar disorder in several independent samples (O’Donovan et al., 2008; Stefansson et al., 2009; Riley et al., 2010; Steinberg et al., 2011), with fine-mapping of nearly all common variants in the gene confirming that rs1344706 is the most strongly associated marker (Williams et al., 2011). The polymorphism is functional, affecting ZNF804A expression (Williams et al., 2011) and DNA–protein binding (Hill and Bray, 2011).

The first study to investigate the effects of the rs1344706 polymorphism on the brain used fMRI to examine activation and functional connectivity during performance of a working memory and emotion perception task (Esslinger et al., 2009). The variant was not found to impact measures of regional activation, but did influence inter-regional functional connectivity, suggesting its effects show higher penetrance at the level of distributed neural systems. Specifically, carriers of the risk-associated A allele demonstrated reduced functional connectivity of the dorsolateral PFC with other ipsi- and contra-lateral prefrontal regions, as well as increased functional connectivity between dorsolateral PFC and the hippocampal formation, during working memory performance. Increased fronto-hippocampal functional connectivity had previously been reported in a positron emission tomography...
study of patients with schizophrenia (Meyer-Lindenberg et al., 2005) and was thus interpreted as a possible cIP mediating the role of ZNF804A in risk for the disorder. The A allele was also associated with enhanced functional connectivity within fronto-limbic circuits during the emotional perception task, which was interpreted as a possible cIP for bipolar disorder. Thus, this study pointed to context-specific and pleiotropic effects of the rs1344706 polymorphism with relevance for understanding its role in risk for both schizophrenia and bipolar disorder.

A subsequent study in an independent sample using the same working memory task replicated the association between the A allele and both increased fronto-hippocampal functional coupling and decreased fronto-frontal connectivity (Rasetti et al., 2011). The lack of a significant effect on regional activation was also replicated. Similar connectivity changes were apparent in schizophrenia patients and their unaffected relatives suggesting that these changes may indeed represent a candidate cIP for the disorder (Figure 3). However, the A allele carriers in this study showed stronger negative fronto-hippocampal functional connectivity, contrasting the original report of higher positive functional connectivity between these two regions (Esslinger et al., 2011). These results suggest distinct interpretations: stronger positive connectivity implies greater functional integration or cooperation between regions; stronger negative connectivity points to antagonistic or competitive dynamics (Clare Kelly et al., 2008). The reasons for this discrepancy are unclear, although the fact that stronger negative functional connectivity has been found in patients and their unaffected relatives (Meyer-Lindenberg et al., 2005; Rasetti et al., 2011) suggests that it may provide a more faithful representation of genetically influenced pathophysiological processes in schizophrenia.

The effect of the rs1344706 variant on fronto-hippocampal connectivity may be less robust than its effect on fronto-frontal coupling, and may only be expressed in certain contexts. In one recent study, the variant was found to influence fronto-hippocampal functional connectivity only during working memory performance, whereas it impacted fronto-frontal coupling during working memory, emotion perception, and resting-state paradigms (Esslinger et al., 2011). Thus, the effect on fronto-frontal connectivity may be generalized, possibly resulting from an influence on anatomical connectivity between these regions (Wei et al., 2010), whereas the association with fronto-hippocampal coupling may be context-specific. This result is consistent with research into the effects of SLC6A4 variation on fronto-limbic circuitry (e.g., Schardt et al., 2010) demonstrating the highly context-specific influences of genetic variants of brain functional dynamics. Precisely mapping the circumstances under which these genetic effects are expressed will be an important step in characterizing the functional significance of any putative cIPs related to ZNF804A variation, particularly given recent evidence that schizophrenia may also be characterized by a profile of both generalized and context-specific functional connectivity deficits which affect prefrontal regions in particular (Fornito et al., 2011a).

**APOE AND THE DEFAULT MODE NETWORK**

The DMN comprises regions of posterior cingulate cortex (PCC), precuneous, medial PFC and lateral parietal cortices, and functionally couples with the hippocampus under certain task contexts (Buckner et al., 2008). The DMN characteristically shows elevated activity during passive rest conditions or tasks requiring introspective processing and deactivates during cognitively demanding tasks (Shulman et al., 1997; Buckner et al., 2008; Harrison et al., 2008, 2011). Alterations of DMN connectivity have been found in patients suffering a range of neuropsychiatric disorders including schizophrenia (Bluhm et al., 2007), autism (Kennedy and Courchesne, 2008), attention-deficit hyperactivity disorder (Castellanos et al., 2008), major depression (Greicius et al., 2007), and Alzheimer’s disease (Greicius et al., 2004; see Sonuga-Barke and Castellanos, 2007; Zhang and Raichle, 2010 for reviews). In the case of schizophrenia, similar alterations have been found in patients’ unaffected relatives, suggesting an association between DMN connectivity changes and genetic risk for the disorder (Whitfield-Gabrieli et al., 2009). Accordingly, specific variants in genes linked to risk for psychosis, such as the D-Amino Acid Oxidase (DAAO; Papagni et al., 2011; Prata et al., 2012) and neuregulin-1 (NRG1; Winterer et al., 2008), have been shown to impact structural and functional connectivity of DMN regions.

Confirmation that functional connectivity of the DMN is under genetic control came from a recent resting-state fMRI study of a sample of extended pedigrees comprising 333 individuals selected from 29 families (Glahn et al., 2010). Spontaneous neural dynamics measured during the so-called resting-state, when people lie...
quietly in the scanner without performing any specific task, are highly organized and correlate in a manner that recapitulates well-known functional networks (Biswal et al., 1995; Smith et al., 2009). The topography of these networks is robust over time and individuals (Damoiseaux et al., 2006; Shchzad et al., 2009) and has been linked to neurophysiological measures (He et al., 2008; Shmuel and Leopold, 2008). In addition, spontaneous BOLD signal fluctuations influence task-evoked activity (Fox et al., 2006; Mennes et al., 2011), perception (Hesselmann et al., 2008), and behavior (Fox et al., 2007), suggesting that they represent an intrinsic and functionally important component of neural dynamics (Fox and Raichle, 2007; though, see Morcom and Fletcher, 2007; Fornito and Bullmore, 2010 for caveats). The extended pedigree design exploited the varying degree of genetic relatedness between participants to estimate genetic and environmental influences on functional connectivity of the DMN, as characterized using ICA. Genetic influences on an averaged estimate of functional connectivity of the entire DMN were significant, with heritability \( h^2 \) estimated to be 0.42. The degree to which each constituent region of the DMN was functionally connected with the entire network was also heritable, ranging from 0.33 to 0.42 for key nodes such as posterior cingulate/precuneus, mPFC, and parietal cortex.

Despite the DMN’s involvement in a wide range of diseases, the most frequently studied genetic locus in relation to DMN connectivity has been the Apolipoprotein E (APOE) gene. The gene encodes a lipoprotein that in the central nervous system, plays a role in coordinating mobilization of cholesterol, phospholipids, and fatty acids, and has been implicated in neuronal development, plasticity, and repair (Mahley and Rall, 2000). The gene has three allelic variants – \( \varepsilon_2 \), \( \varepsilon_3 \), and \( \varepsilon_4 \). Homozygosity for the last is the most established genetic risk factor for late-onset Alzheimer’s disease, being associated with a 10-fold increase in risk (Farrer et al., 1997; Bertram et al., 2007). In contrast, average allelic summary odds ratios for non-APOE-related variants are \( \sim 1.25 \) (Bertram and Tanzi, 2008). APOE has also been implicated in the pathophysiology of schizophrenia and mood disorders (Gibbons et al., 2011).

Several studies have demonstrated an association between the \( \varepsilon 4 \) allele and both increased and decreased functional connectivity of the DMN and medial temporal regions, though reports of increases have been more common in younger samples (Filippini et al., 2009; Dennis et al., 2010a; Sheline et al., 2010a,b; Machulda et al., 2011; Westlye et al., 2011). One hypothesis proposed to explain this age effect is that \( \varepsilon 4 \) carriers inherit a CLP characterized by enhanced DMN connectivity early in life. This enhanced connectivity facilitates the spread of amyloid-\( \beta \) plaques, the primary pathological characteristic of Alzheimer’s disease, throughout the network and exacerbates risk of disease onset and progression (Machulda et al., 2011; Seeley, 2011). With advancing age, these plaques accumulate and result in a deterioration of DMN function and concomitant reduction of network connectivity relative to non-risk allele carriers. Though this postulate requires experimental verification, it is supported by reports that DMN regions are among the first to show aggregation of amyloid-\( \beta \) plaques in Alzheimer’s disease and that these plaques disperse throughout the network with disease progression (Buckner et al., 2005, 2009). It also accords with reports that gray matter volume loss in neurodegenerative disease occurs within functionally connected networks (Seeley et al., 2009).

The effects of APOE genotype on functional connectivity are often apparent in the absence of any differences in gray matter volume, cognitive impairment, or \( \beta \)-amyloid deposition (Den-nis et al., 2010a; Sheline et al., 2010a; Machulda et al., 2011). In addition, one recent study found that resting-state connectivity measures of the DMN were able to differentiate between cognitively unimpaired \( \varepsilon 4 \) carriers with a family history of Alzheimer’s disease and individuals without any apparent genetic risk with an effect size approximately three times greater than was possible using measures of task-related activation during a memory encoding paradigm (Fleischer et al., 2009). Such findings provide a powerful demonstration of the enhanced sensitivity provided by connectomic measures for indexing the physiological effects of disease risk variants, and support the contention that these variants often show higher penetrance at the level of distributed neural systems.

**THE GENETICS OF HUMAN BRAIN NETWORK TOPOLOGY**

The preceding discussion illustrates how genetic variation can influence the nature and strength of connectivity between different brain regions. We now consider studies of genetic influences on how connections are arranged in the brain; i.e., how genes influence the topology of the connectome. Such an investigation is motivated by the sparse character of brain connectivity. The human cerebral cortex comprises an estimated \( 10^{15} \) neurons connected by \( 10^{13} \) fibers (Braitenberg and Schüz, 1991). Though numerous, these connections represent only a small fraction of the total \( 5 \times 10^{21} \) connections that are possible. Similarly, neuronal connectivity in the nematode worm *Caenorhabditis elegans*, which has been comprehensively mapped at the level of each and every synapse, comprises \(< 3\% \) of the total number of connections possible while estimates of the degree of inter-regional connectivity (i.e., connectivity between distinct cytoarchitectonic regions) in the macaque monkey *Macaca mulatta* and the feline brain range from 18 to 38\% (Latora and Marchiori, 2003; Kaiser and Hilgetag, 2006). This sparsity suggests that connections between brain regions develop according to specific constraints and/or design principles that are likely to be under genetic control.

Ramón y Cajal (1995) proposed over a century ago that one critical organizational principle for brain networks involves the minimization of wiring costs. The adaptive benefit of this principle is clear, as less wiring reduces the total energy required to support neuronal communication (Laughlin and Sejnowski, 2003). Accordingly, a substantial body of evidence has accumulated to suggest that pressure to minimize wiring costs can explain numerous aspects of cortical organization, including axonal branching and cortical folding patterns (Van Essen, 1997; Cherniak et al., 1999), neuronal morphology (Buzsáki et al., 2004; Chklovskii, 2004), the spatial location of neurons and cytoarchitectonic fields (Knyshko and Stevens, 2003; Cherniak et al., 2004), and even the fraction of cortical volume occupied by axons and dendrites (Chklovskii et al., 2002). However, wiring cost minimization alone cannot account for all design features of nervous system networks (Chen et al., 2006; Kaiser and Hilgetag, 2006), and recent evidence points to a trade-off between cost minimization and the
emergence of topological properties such as communication efficiency, which may be behaviorally advantageous but entail a wiring cost premium (Kaiser and Hilgetag, 2006; Bassett et al., 2010).

The topological efficiency of a network can be readily quantified using graph theoretic techniques. In complex networks, communication is more efficient when fewer connections must be traversed to transfer information between any two nodes; the fewer the connections, the faster the rate of information transmission, and the lower the probability of signal degradation or transmission errors (Latora and Marchiori, 2003). In an economically wired network, long-range projections act as topological short-cuts that reduce the mean path length between regions and dramatically increase communication efficiency (Latora and Marchiori, 2003). However, these short-cuts come at the cost of increased wiring. In principle it would be possible to maximize network efficiency simply by adding more connections (Latora and Marchiori, 2003; Achard and Bullmore, 2007), though the metabolic costs associated with forming and maintaining each connection limit the total volume of wiring that can be supported (Laughlin and Sejnowski, 2003). This balance, between efficiency maximization and connection cost minimization, may be construed as one concerned with the optimization of connection cost-efficiency. The importance of this balance for the connectome was recently underscored by a study showing that the physical embedding of the brain’s connectivity architecture in the three-dimensional space of the skull is optimally cost-efficient, subject to certain higher-dimensional constraints (Bassett et al., 2010).

We examined the heritability of cost-efficient properties of functional brain network topology using resting-state fMRI in healthy twins (Fornito et al., 2011b). Network efficiency was measured using established graph theoretic methods (Latora and Marchiori, 2001), whereas connection costs were estimated indirectly using a measure of physical distance between regions. We found that the balance between these two measures, taken as an index of network cost-efficiency, was highly heritable at a global level, with genetic factors accounting for approximately 60% of the phenotypic variance. These influences were not uniformly distributed throughout the cortex, with regional estimates of significant genetic influences ranging from 0.30 to 0.80 (Figure 4). Some of the largest effects were seen in regions of lateral PFC and core components of the DMN, such as posterior cingulate and medial prefrontal cortices (Figure 4). Heritability estimates in these regions are comparable to those reported for whole-brain and regional gray matter volume (0.66 < $h^2$ < 0.97; Thompson et al., 2001; Peper et al., 2007), cognitive abilities (0.30 < $h^2$ < 0.80; McClearn et al., 1997; Bouchard, 1998; Boomsma et al., 2002), and various measures of personality and psychopathology (0.50 < $h^2$ < 0.60; Boomsma et al., 2002). They also compare favorably with heritability estimates for simple measures of functional connectivity within the DMN (0.33 < $h^2$ < 0.42; Glahn et al., 2010), as well as regional task-related activation (0.40 < $h^2$ < 0.80; Koten et al., 2009; Blokland et al., 2011) and DTI-derived measures of anatomical connectivity (0.55 < $h^2$ < 0.85; Chiang et al., 2009).

![Figure 4](image-url)
The adaptive benefit of a cost-efficient neural architecture is intuitive, and it is plausible that evolution would favor connections that can provide high communication efficiency for low metabolic cost. Evidence that greater topological efficiency and/or greater cost-efficiency predicts better performance on tests of intelligence and working memory (Bassett et al., 2009; Li et al., 2009; van den Heuvel et al., 2009; Zalesky et al., 2011), and that alterations of network efficiency and cost-efficiency are apparent in a range of patient groups, including schizophrenia (Bassett et al., 2009; Lynall et al., 2010; Zalesky et al., 2011), Alzheimer’s disease (Lo et al., 2010), and Alzheimers disease (Lo et al., 2010), indicates that these findings have clear implications for psychiatric disorders. To our knowledge however, no study to date has examined how variations in specific candidate genes influence brain network cost-efficiency, or any other topological properties of the connectome.

Cost-efficiency optimization is but one of many potential organizational principles for the connectome. Indeed, graph analytic studies of neuroimaging data have pointed to several other candidate topological properties that may be under genetic control. For example, both structural and functional human brain networks are characterized by a small-world topology (Achard et al., 2006; Hagmann et al., 2007), which concurrently supports locally segregated and globally integrated connectivity to provide high dynamical complexity, a property that may have been favored by evolutionary processes (Sporns et al., 2000). The human connectome also possesses a hierarchical, modular architecture; i.e., it can be decomposed into subsets of regions, termed modules, that show relatively high connectivity with each other than with other areas at multiple scales of resolution, allowing the formation of modules within modules and so on (Meunier et al., 2009; Bassett et al., 2010). This property has been associated with enhanced functional stability and diversity (Kaiser et al., 2007), the emergence of self-organized, critical dynamics (Rubinov et al., 2011), and may be intimately linked to optimization of connection cost-efficiency (Bassett et al., 2010).

These considerations raise questions as to whether genetic influences are specific to network cost-efficiency, or are related to other topological variations. In our analysis, we found no evidence for genetic influences on a range of other topological properties frequently studied in the graph theoretic literature, including clustering, path length, small-worldness, and global and local efficiency, although we did not examine modularity (Fornito et al., 2011b). Other studies have however reported heritability values as high as 0.80 for some of these measures, computed for functional networks derived from electroencephalographic (EEG) recordings (Smit et al., 2008). The reasons for these inconsistencies are unclear, but may be related to the imaging techniques employed or the enhanced power provided by the much larger sample analyzed in the EEG study. In general, the high degree of inter-correlation between different topological measures of brain network organization (Alexander-Bloch et al., 2010; Lynall et al., 2010), means that multivariate genetic analyses allowing categorization of different topological measures into distinct groupings defined by common genetic influences will be critical for identifying the primary genetic constraints on connectome development and organization.

CONCLUSION
This brief overview illustrates the potential power of imaging connectomics in the search for IPs for neuropsychiatric disorders. Specifically, the available data indicate that connectomic measures are able to index the physiological effects of disease risk genes when simpler regional measures of activation or volume, or cognition, cannot (Esslinger et al., 2009; Dennis et al., 2010a; Sheline et al., 2010a; Machulda et al., 2011; Rasetti et al., 2011). They also indicate that variations in cIPs correlate with relevant behavioral indices when regional measures do not (Pezawas et al., 2005; Buckholtz et al., 2008), and that certain connectomic phenotypes are highly heritable (Chiang et al., 2009; Glahn et al., 2010; Fornito et al., 2011b). Collectively, these data support the idea that the penetrance of many disease risk genes is higher at the level of distributed brain systems than at the level of isolated brain regions, a conclusion consistent with an emerging consensus that many psychiatric disorders arise from genetically mediated vulnerabilities in discrete neural circuits (Meyer-Lindenberg and Weinberger, 2006; Meyer-Lindenberg, 2009, 2010; Insel, 2011). As such, cIPs may offer greater sensitivity for characterizing genetic effects in imaging genetic designs than more traditional, regionally focused neuroimaging measures.

One potential criticism of cIPs is that, by design, they are more complicated, requiring additional processing steps and assumptions for their derivation. Characterizing activation or volume in a single region is intrinsically univariate, requiring measurement of one property describing the behavior of that region, whereas connectivity measures are intrinsically bi or multivariate as they involve two or more regions by definition. The problem is worse for graph analytic studies, which often incorporate multiple measures and processing steps when computing topological properties. Each additional measure and step can introduce noise into the analysis, making the resulting phenotypic characterizations less reliable (Habeck and Moeller, 2011), and placing an upper limit on power for detecting genetic effects (Kendler and Neale, 2010; Blokland et al., 2011). Moreover, more complex measures presumably have a more complex genetic basis. This emphasis on simplicity and reliability must however be balanced with a need to define valid and pathophysiologically relevant IPs. Most major psychiatric diseases are disorders of brain connectivity, and the physiological effects of putative disease risk variants are likely to be expressed throughout multiple, interconnected neural circuits. Connectomic measures will provide a more sensitive index of these effects. The findings discussed here support these conclusions, and demonstrate that even highly derived topological properties, such as network cost-efficiency, can show high heritability (Fornito et al., 2011b). Moreover, recent studies have shown that connectomic measures, despite their increased complexity, represent more robust biomarkers of schizophrenia (Calhoun et al., 2008; Erhardt et al., 2011; Bassett et al., 2012) and risk for Alzheimer’s disease (Fleisher et al., 2009), than simpler, regional measures. Thus, while parsimony and reliability are always important, candidate IPs should be selected for their reliability and their hypothesized role in relevant pathophysiological processes; not purely for their simplicity.
A more general criticism often leveled at the IP approach concerns whether any candidate IPs studied thus far are truly “intermediate” in the sense that they mediate the effects of candidate genetic variants on disease risk or expression (Walters and Owen, 2007; Kendler and Neale, 2010). Under such a mediation model, the risk gene is assumed to influence the IP, which in turn influences illness susceptibility (i.e., gene → IP > disorder); thus, the IP is truly interposed between gene and disorder. In this case the IP is likely to represent a physiological mechanism through which genetic risk is expressed. An alternative possibility however, is that the gene exerts pleiotropic and possibly independent effects on both the IP and disease risk (i.e., IP < gene > disorder). Under this liability model, the IP is not involved in disease pathophysiology but may represent a biomarker of illness susceptibility. Distinguishing between these two possibilities experimentally is challenging (Walters and Owen, 2007; Kendler and Neale, 2010) and it is thus unclear which category the cIPs discussed here fall into. Our use of the term “IP” in reference to the measures discussed here is therefore subject to this caveat. In practice however, the distinction may be overly simplistic as it assumes near-complete genetic overlap between the IP and psychiatric disorder. A more likely scenario is that IPs and psychiatric disorders possess both common and independent genetic influences which require multivariate analyses in genetically informative samples for complete characterization (Kendler and Neale, 2010). To our knowledge, no such studies of cIPs have yet been conducted.

Though it is as yet unclear whether any of the candidate IPs identified to date should be best conceptualized using mediation, liability, or multivariate models, they can certainly provide important clues as to how genetic risk factors influence variation in key phenotypic properties of psychiatric disease. Mapping differences and commonalities in these properties across disorders may prove useful in developing new, biologically informed diagnostic criteria. In addition, preliminary evidence suggests that IPs can augment the search for novel risk genes (Potkin et al., 2009). The research reviewed here indicates that this kind work will benefit from a greater focus on identifying novel IPs that describe systems-level properties of the brain, and that imaging connectomics provides a powerful methodological and conceptual framework for doing so.

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