Neural Connectivity as an Intermediate Phenotype: Brain Networks Under Genetic Control

Andreas Meyer-Lindenberg*

Central Institute of Mental Health, J5, 68159 Mannheim, Germany

Abstract: Recent evidence suggests that default mode connectivity characterizes neural states that account for a sizable proportion of brain activity and energy expenditure, and therefore represent a plausible neural intermediate phenotype. This implies the possibility of genetic control over systems-level connectivity features. Imaging genetics is an approach to combine genetic assessment with multi-modal neuroimaging to discover neural systems linked to genetic abnormalities or variation. In the present contribution, we report results obtained from applying this strategy to both structural connectivity and functional connectivity data. Using data for serotonergic (5-HTTLPR, MAO-A) and dopaminergic (DARPP-32) genes as examples, we show that systems-level connectivity networks under genetic control can be identified. Remarkable similarities are observed across modalities and scales of description. Features of connectivity often better account for behavioral effects of genetic variation than regional parameters of activation or structure. These data provide convergent evidence for genetic control in humans over connectivity systems, whose characterization has promise for identifying neural systems mediating genetic risk for complex human behavior and psychiatric disease. *Hum Brain Mapp* 30:1938–1946, 2009. © 2009 Wiley-Liss, Inc.

Key words: DARPP-32; 5-HTTLPR; MAO-A; imaging genetics; fMRI; connectivity

INTRODUCTION

Although there is clear evidence that many complex behaviors and psychiatric disorders have a high heritable component [Sullivan et al., 2000]; identifying these genes and understanding the neural mechanisms bridging the gap from gene transcript to behavior is not easy [Meyer-Lindenberg and Weinberger, 2006]. Because genetic effects on behavior should be neurally mediated, the functional

impact of genetic variation can only be understood if considered in terms of the effects on arguably the most complex entity known, the human brain.

One approach that has proven useful in this difficult-to-negotiate terrain is imaging genetics [Meyer-Lindenberg and Weinberger, 2006]. Here, the power of neuroimaging to characterize various aspects of brain structure and function in vivo is combined with genetic data to link interindividual variation in imaging parameters to genetic variants these individuals carry. If the genetic variants under study have been associated with neuropsychiatric, behavioral, or cognitive phenotypes, then the identification of neural systems linked to these variants implicates these systems in mediating genetic risk for the disorders to which the genetic variants have been linked. This “imaging genetics” approach benefits from the fact that genes are likely to have a bigger effect on the level of biological processing than on emergent mental or social and behavioral phenomena. In other words, the penetrance is

*Correspondence to: Andreas Meyer-Lindenberg, Central Institute of Mental Health, J5, 68159 Mannheim, Germany.

E-mail: a.meyer-lindenberg@zi-mannheim.de

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likely to be higher on the neural systems level. In this way, imaging genetics leverages the genetic information usually obtained in large-scale association studies to discover neural systems is important in normal and abnormal behavior [Meyer-Lindenberg and Weinberger, 2006].

The question then arises which of the myriad of features of neural systems that can be derived from neuroimaging data are especially useful for the translational genetic enterprise. Because endogenous oscillations, and the networks that they define, characterize a baseline system that accounts for a considerable proportion of brain energy expenditure [Raichle et al., 2001] and therefore form an enduring trait exhibited by the human brain, there is a high a priori likelihood that genetic factors, if they impact on the brain, should have an effect here. If these connectivity data reflect basic changes, relative to wildtype, in how the brain is wired, these circuit level alterations could be visible across several cognitive domains in activation tasks, or even in brain structure. Similarly, if these features identify a critical component of how the brain mediates genetic risk for a behavioral phenotype, the prediction follows that circuit (connectivity) features should explain behavioral variance, possibly to a higher degree than regional (activation/deactivation) data. We discuss data from our recent and ongoing work that largely confirms these expectations, focusing on genetic variants impacting on dopaminergic (DARPP-32) and serotonergic (5-HTTLPR, MAO-A) neurotransmission. Further examples for the usefulness of connectivity analyses for imaging genetics are available in the literature [Buckholz et al., 2007b; Tan et al., 2007a, 2007b].

ASSESSMENT OF CONNECTIVITY IN IMAGING GENETICS

Methodologically, imaging genetics relates neuroimaging data to genetic variants across the population using a random-effects second level approach. This approach can be generically applied to any kind of imaging information summarized for each subject in a brain map on the first level, ranging from regional volume (VBM) or cortical thickness through structural measures of connectivity [diffusion tensor imaging (DTI), structural covariance] to measures of regional activation/deactivation and functional or effective connectivity. Traditionally, default mode activity and connectivity is measured at rest, if necessary in regions relatively deactivated during a cognitive control paradigm. A straightforward way to identify genetic components would then be to use datasets acquired at rest; when such studies are ongoing, we are not aware of published results addressing the question of heritability and reliability of resting data in the context of imaging genetics or specific genetic effects. A complementary approach that has been used extensively to define connectivity, and is discussed here, starts with data from a (block design or event related) activation experiment and uses residual oscillations that remain af-

ter the cognitive effects of interest have been statistically removed (through an appropriate general linear model). In other words, regional activations/deactivations related to the task will have been subtracted from these data. A potential drawback of this approach is that by design, periods of rest in these time series are interspersed with those in which the brain assumed states related to a task performed in the scanner. This means that effects of the paradigm, although they are removed to the degree (which may be limited if task-related effects are highly nonlinear) that they can be accounted for statistically, could impact on connectivity profiles if they show interactions with endogenous oscillations in the task-related areas. On the other hand, fluctuating cognitive states are probably also associated with behavioral resting, where they cannot be controlled, but do not prevent a reliable determination of resting state connectivity that delineates systems highly concordant with those seen even in sedation [Greicius et al., 2008]. Human neuroimaging evidence also suggests that endogenous fluctuations, although attenuated, persist during cognitive activation [Fransson, 2006] and may in fact be related to variation in task performance [Mason et al., 2007]. From whichever source, time series data can then be used to define functional (correlative) or effective connectivity measures. For the latter, structural equation modeling and PPI methods have been used in imaging genetics. Here, we will focus on functional connectivity networks.

Because of the different time scale which structural data reflect, at least those currently used, structural measures of connectivity pose no problems related to cognitive state. Delineation of fiber tracks through DTI offers a straightforward way to define networks of structural connectivity. Because of computational and methodological issues related to performing whole brain fiber tracking in the comparatively large cohorts necessary for imaging genetics, this approach has not been widely applied, although first results using voxel-based derived DTI measures, such as fractional anisotropy, have appeared [McIntosh et al., 2007], as have fiber tracking data in neurogenetic syndromes [Marenco et al., 2007]. In the data discussed here, we use a “structural connectivity” or “structural covariance” measure, in which VBM data are employed by correlating volume in a region of interest with regional volumes across subjects. This approach identifies areas which have regional volume that is significantly (positively or negatively) correlated with the target area across subjects. Although this provides, compared to DTI, only an indirect measure of anatomical connectivity, it has been shown to correspond to neuroanatomical data on regional connectivity [Mechelli et al., 2005] and to be sensitive to genetic variation [Pezawas et al., 2005]. Studies of conditions with known impact on anatomical connectivity have shown that structural covariance characterizes these processes in aging [Knafo et al., 2007] and in schizophrenia [Woodruff et al., 1997]. Furthermore, in the human optic system, it has been demonstrated directly that anatomically connected struc-

tures (i.e., optical tract, lateral geniculate nucleus, and primary visual cortex) co-vary in volume across individuals [Andrews et al., 1997].

CONNECTIVITY FEATURES ACROSS SCALES AND MODALITIES OF DESCRIPTION: DARPP-32

Dopamine- and cAMP-regulated phosphoprotein of molecular weight 32 kDa (DARPP-32) was initially identified as a major target for dopamine-activated adenylyl cyclase in striatum [Walaas et al., 1983]. Over more than two decades, an intense research effort has demonstrated that DARPP-32 is at a unique position as a central molecular switch in dopaminergic neurons, integrating multiple information streams converging through a variety of neurotransmitters, neuromodulators, neuropeptides, and steroid hormones [Svenningsson et al., 2004]. Because dopaminergic neurotransmission is critical for motivated behavior, working memory [Goldman-Rakic, 1998], and reward-related learning [Schultz, 1998], and is implicated in, among others, schizophrenia [Weinberger, 1987], alcoholism [Grace, 2000], Parkinson's disease, and pathological gambling [Fiorillo et al., 2003], DARPP-32 has received considerable attention not only in basic neuroscience, but also in studies of the pathogenesis of these disorders and as a potential drug target.

By far the highest levels of DARPP-32 are found in the neostriatum [caudate and putamen] [Ouimet et al., 1992]. In a topographically well-organized manner, the neostriatum receives excitatory glutamatergic projections from the cortex and thalamus, integrates them with monoaminergic inputs and sends them via the globus pallidus and substantia nigra pars reticulata to the thalamus which projects back to the cortex [Alexander et al., 1986]. These parallel processing loops are critical for the ongoing processing of sensorimotor, cognitive, and emotional information [Alexander et al., 1986]. In addition, a general role in learning through a reciprocal influence on cortical processing via striato-pallidal-thalamo-cortical pathways has been suggested [Graybiel, 2005]. Of particular interest for neuropsychiatry is a circuit linking dorsolateral prefrontal cortex with the rostral striatum [Haber, 2003]. One function attributed to these prefrontal-striatal interactions is that of acting as a "filter" of information competing for prefrontal cortical processing [Swerdlow et al., 2001]. Consequently, lesions to the neostriatal-prefrontal system at all levels impair prefrontally dependent cognitive functions such as working memory, set shifting, and executive control [Dunnett et al., 2005], which are characteristic of the cognitive deficits found in conditions such as Parkinson's disease and schizophrenia [Pantelis et al., 1997].

Given this central role of the protein in molecular mechanisms related to dopaminergic neurotransmission in striatum and its diverse pharmacological actions, we hypothesized that it would be associated in humans with higher

level cognitive behaviors implicated in cortical-striatal circuitry and function. In fact, we found a common haplotype that predicted variance across a wide range of cognitive functions, in gene expression in postmortem brain, as well as risk for schizophrenia in our family-based sample, indicating that this variant had functional impact on striatal-cortical interactions. Imaging genetics confirmed this prediction [Meyer-Lindenberg et al., 2007b].

First, using voxel-based morphometry, we found a bilateral relative decrease in neostriatal volume (maximum in dorsal putamen) (Fig. 1A) for the risk haplotype. We used this finding as a point of departure for delineating circuit properties. An analysis of "structural connectivity" of the bilateral striatum in fact showed a pronounced increase in this measure of structural connectivity between striatum and lateral prefrontal cortex, especially dorsolateral prefrontal cortex in carriers of the frequent haplotype (Fig. 1B). The question now arose whether that structural connectivity result could be found in brain function as well. For this, we analyzed two large archival fMRI datasets, which show differential activation in neostriatum in the context of prefrontal cortex involvement, as predicted by the fronto-striatal loop concept [Alexander et al., 1986]. Firstly, during a well-established working memory paradigm which robustly activates dorsolateral prefrontal cortex, the N-back task [Callicott et al., 2000], functional connectivity of the bilateral striatum indeed showed a result similar to structural connectivity of the same region: connectivity with prefrontal cortex was strongly increased in carriers of the risk haplotype. Finally, we analyzed an emotional face matching task using threatening visual stimuli [Pezawas et al., 2005], which probes neural circuitry of the human emotional alerting response and engages ventrolateral prefrontal and lateral orbitofrontal cortex [Meyer-Lindenberg et al., 2005a]. Again, we observed a significant effect of haplotype on functional connectivity: a region in left dorsolateral prefrontal cortex showed increased connectivity for carriers of the implicated haplotype (Fig. 1F). Because these were largely nonoverlapping datasets, these results provide convergent evidence that genetic variation impacts on structure and function of fronto-striatal circuitry in a way that can be identified convergently across modalities and temporal scales of description. Given the central role of this circuit for "gating" and efficient information processing in prefrontal cortex, this convergent neurobiological finding provides a plausible basis for the broad impact on cognitive function as well as on increased schizophrenia risk in this study.

CONNECTIVITY FEATURES PREDICT BEHAVIOR: SEROTONERGIC RISK GENES FOR DEPRESSION AND REGULATORY LIMBIC INTERACTIONS

Further strong support for the usefulness of a neural circuit/connectivity perspective in imaging genetics comes

Figure 1.

Neuroimaging analyses (structure and function) of a common haplotype in *PPP1R1B* in Caucasian control samples. Top row shows haplotype effects on volume (**A**) or activation (**C**, **E**) in striatum, bottom row shows haplotype effects on structural (**B**), and functional (**D**, **F**) connectivity of striatum with prefrontal cortex. Structural MRI analyses (voxel-based morphometry): **A**: significantly reduced volume in striatum ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype. **B**: Greater structural connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. Functional imaging analyses (fMRI), n-back task. **C**: Significantly reduced reactivity in putamen ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype.

D: Greater functional connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. Functional imaging analyses (fMRI), face matching task. **E**: Significantly reduced reactivity in striatum ($P < 0.05$) for carriers of the frequent (CGCACTC) haplotype. **F**: Greater functional connectivity between prefrontal cortex and striatum for homozygotes for the frequent (CGCACTC) haplotype. *t* color scales depict statistical significance level (*t* statistic value) (Reproduced with permission from Meyer-Lindenberg et al., *J Clin Invest*, 2007, 117, 672–682 ©American Society for Clinical Investigation). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

from work on a medial prefrontal-amygdala circuit, which is involved in amygdala regulation, emotional control and social behavior, risk for depression and violence.

The serotonin transporter gene (*SLC6A4*) (Fig. 2A–C) contains several functional variants, but the one studied most extensively is a variable number of tandem repeats in the 5' promoter region (5-HTTLPR) which influences transcriptional activity and subsequent availability of the 5-HTT [Lesch et al., 1996], with reduced transcription of the 5-HTTLPR short (S) allele in comparison to the long (L) allele. Individuals carrying the S allele tend to have increased anxiety-related temperamental traits [Lesch et al., 1996], which are inconsistently related to risk for depression [Lotrich and Pollock, 2004]. This is one of the serotonergic variants where interaction with environmental adversity has been demonstrated [Caspi et al., 2003]. In contrast to the results of traditional clinical association, which are largely inconsistent and weak, imaging-based

phenotyping has provided strong evidence of a mechanism by which variation in *SLC6A4* could increase biologic risk for anxiety and depression.

The amygdala has been implicated as a centerpiece of this genetic effect as several fMRI studies have found that S allele carriers evince an exaggerated amygdala response compared with L homozygote individuals [Hariri et al., 2002, 2005; Heinz et al., 2005]. These findings suggest that amygdala hyperreactivity might be a neural substrate of trait anxiety predisposing to psychiatric disease. Recent research has made progress towards characterizing the neural circuit contributing to this finding. Using voxel-based morphometry, a reduction in gray matter was found in the subgenual and perigenual cingulate region of healthy carriers of the S allele compared with matched LL homozygotes [Pezawas et al., 2005] (Fig. 1C). Analyses of functional and structural connectivity confirmed close interactions of this cingulate region with amygdala and

Figure 2.

Serotonergic neurotransmission and associated genetic variants. **A:** Schematic drawing of serotonergic neuron (Modified with permission from Lesch), showing termination of serotonin (5-HT) action by the serotonin transporter (5-HTT) and by catabolism by MAO to 5-HIAA, as well as synthesis through tryptophane (TRP) and 5-hydroxytryptophane (5-HTP). Presynaptic serotonin receptors (1A, B, D, E, F) also shown. **B:** Schematic drawing of neurodevelopmental effects of increased serotonin level due to inactivation of MAO-A or 5-HTT (Modified with permission from Lesch). **C:** A common variable number of tan-

dem repeat polymorphism in the promoter of the 5-HTT (5-HTTLPR) [redrawn from Lesch and Mossner, 1998]. A long (L) and short (S) regulatory variant are distinguished, with relatively reduced transcription and activity of the transporter in the S form. **D:** A common variable number of tandem repeat polymorphism in the promoter of the X-linked MAO-A gene affects transcription, with an optimum range (MAOA-H) of 3.5 or 4 repeats. Redrawn from (Sabol et al., 1998). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

suggested a feedback circuit, which inhibits amygdala function and may be involved in fear extinction (Fig. 1D) [Pezawas et al., 2005]. In humans, the subgenual cingulate (BA25) displays a high density of 5-HTT terminals [Varnas et al., 2004] and is impacted by serotonin reuptake inhibitor antidepressants [Mayberg et al., 2000]. The subgenual cingulate [Drevets et al., 1997; Mayberg et al., 1999; Pezawas et al., 2005], furthermore, receives strong afferent input from the amygdala and is reciprocally connected to more dorsal parts of the cingulate which project back to amygdala [Paus, 2001]. Importantly, convergent evidence strongly suggests that amygdala-cingulate interactions represent a functional feedback circuitry regulating amygdala processing of environmental adversity; stimulation of peri-limbic PFC inhibits amygdala

[Stefanacci and Amaral, 2002] and lesions of this region markedly impair fear extinction [Sotres-Bayon et al., 2004].

These preclinical data were reflected in convergent neuroimaging data on connectivity. Both in structure and in function, the S allele was associated with reduced coupling between amygdala and the subgenual cingulate. Furthermore, the degree of that coupling, that is, the connectivity circuit feature most strongly implicated by the imaging genetics approach, predicted close to 30% in the variability of trait anxiety in these normal individuals [Pezawas et al., 2005]. This implied that using a gene whose associations, on the level of behavior, are comparatively weak, as a heuristic to investigate connectivity as a target phenotype extracted a neural circuit feature that explained a consider-

Figure 3.

Neural mechanisms linked to genetic variation in serotonergic risk genes. **(A)** Structural (using voxel-based morphometry) and **(B)** functional results (during an emotional faces matching task) show an impact of genetic variation in MAO on amygdala and cingulate volume and function (based on data from Meyer-Lindenberg et al., 2006). Volume is relatively reduced in carriers of the MAOA-L allele implicated in risk for impulsive violence. Amygdala activation is increased, while activation of regulatory cingulate regions is decreased. **(C)** Structure and **(D)** functional connectivity (during a faces matching task) are also affected by genetic varia-

tion in 5-HTTLPR (from Pezawas et al., 2005, with permission). Carriers of the S allele show relative volume reductions in subgenual cingulate and amygdala, and reduced connectivity of amygdala to subgenual cingulate. Reduced connectivity (5-HTTLPR) or cingulate activation (MAOA-A) predict amygdala hyperactivation by reduced feedback inhibition as an endomechanism underlying anxiety and impulsivity associations of these genes. An anterior medial prefrontal area might modulate this effect (Heinz et al., 2005). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

able proportion of variance on the level of that target behavior. Notably, nonconnectivity imaging phenotypes, such as regional activation or volumes, did not explain relevant variance in harm avoidance [Pezawas et al., 2005]. These findings validate both the intermediate phenotype [Gottesman and Gould, 2003] approach (the expectation that neural phenotypes show higher penetrance because they are closer to the biological genetic substrate than the behavior that they mediate) and the usefulness of connectivity as a superior phenotype of that kind.

Convergent evidence for the importance of the circuit perspective in understanding serotonergic neurotransmission genetic effects comes from studies showing an impact of other functional genetic variants in serotonergic metabolism on amygdala activation and regulation. We recently investigated [Meyer-Lindenberg et al., 2006] genetic variation in MAOA-A, encoding monoamine oxidase A, a key enzyme for the catabolism of serotonin and other neurotransmitters during neurodevelopment. The human MAOA-A gene contains a common variable number of tandem

repeats polymorphism that again affects transcriptional efficiency; enzyme expression is relatively high for carriers of 3.5 or 4 repeats (MAOA-H) and lower for carriers of 2, 3, or 5 repeats (MAOA-L) [Sabol et al., 1998] (Fig. 2D). Our multimodal imaging results [Meyer-Lindenberg et al., 2006] indicated, very similarly to that of 5-HTTLPR, an impact on structure (Fig. 3A) and function (Fig. 3B) of amygdala and perigenual cingulate cortex, suggesting a shared mechanism of emotional regulation under serotonergic control and predicting some overlap in clinical association in risk for depression, as is indeed observed [Yu et al., 2005]. As in the case of 5-HTTLPR, no strong correlations between regional structure or functional activation data and behavior were observed. Again, it was the connectivity perspective that provided a link to behavior. Using functional connectivity, we found increased coupling of amygdala with ventromedial prefrontal cortex [Buckholtz et al., 2007a]. Degree of coupling predicted harm avoidance and reward dependence personality scores, suggesting a mediation of genetic association with MAOA through this circuit. In addition, the degree of coupling predicted personality variables related to the aggression phenotype, such as angry hostility. Of interest, a prior study of the 5-HTTLPR variant [Heinz et al., 2005] also found increased coupling between more anterior medial prefrontal areas (BA10), providing convergent evidence for this circuit. Using effective connectivity methods (path analysis), we found evidence that ventromedial prefrontal cortex regulates amygdala indirectly through an influence on cingulate cortex, and that this system contributes to the genetic associations of MAOA with behavior.

CONCLUSION

In summary, we have discussed data indicating that connectivity networks form attractive phenotypes for imaging genetics. The predictions outlined at the beginning of this article were largely confirmed, in that a given genetic variant (5-HTTLPR, DARPP-32) shows convergent effects across modalities and scales, and that connectivity parameters predict behavior and can be shown to mediate genetic risk. Nevertheless, work in this area is just beginning. It would be important to study resting state connectivity to ascertain whether or not this phenotype is heritable and affected by individual genetic variants. Resting state activity is also an important phenotype that can be contrasted with activation during a cognitive paradigm with regard to its reactivity to genetic variation. For example, we have found that the link between midbrain dopamine synthesis and activity during rest and activation was qualitatively different depending on genotype [Meyer-Lindenberg et al., 2005b]. Finally, new methodological developments in this area hold the promise of further dissecting the neural basis of genetic contribution. Dynamic causal modeling, for example, relates modeled neural activity to imaging observables [Friston et al., 2003]. It would be extremely helpful to explicitly include parameters directly

linked to genetic variations (e.g., in the genes discussed here, dopamine and 5-HT and their presynaptic and postsynaptic effects) in the neural model that could then be validated both pharmacologically and genetically. Whole brain DTI based fiber tracking, once computationally feasible in large cohorts, could be directly related to functional measures of connectivity for a joint characterization of networks affected by genetic variants. Finally, methodological developments are necessary to allow relating much more extensive genetic datasets, such as the more than a million SNPs per subject becoming available through the current wave of genome-wide association studies, to genetic data. Although we have recently shown that false positives are well controlled by current procedures in imaging genetics [Meyer-Lindenberg et al., 2007a], the challenge posed by this new level of genetic information is still formidable, especially if one attempts to relate it not only to individual circuits, as done in the work here, but to the entire functional-structural connectome delineated through neuroimaging. Recent advances in applying topological measures, for example from graph theory, to the connectome may help in extracting relevant parameters of global connectivity for imaging genetics [Bassett et al., 2006]. In addition to these methodological challenges and the intrinsic neuroscientific interest of the topic, it is to be expected, and hoped, that imaging genetics will be able to contribute an important piece in translational characterization of severe heritable disorders such as autism and schizophrenia to identify new treatment targets and monitor their efficacy.

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