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Genetics as a tool for the dissociation of mental operations over the course of development

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In recent years it has become possible to differentiate separable aspects of attention and to characterize the anatomical structure and dynamic states of their underlying networks. When individual differences in the structure and dynamics of these networks are used as dependent measures in associations with individual genetic variation, it becomes possible to assign cellular and molecular changes that occur over the course of normal development to specific aspects of network structure and function. In this way, a more granular understanding of the physiology of neural networks can be obtained. Here we review a translational research strategy focused on how genetic variation contributes to the normal development of attentional function. We seek to use genetic information to help construct a multinode, multinetwork model that can explain, in part, individual differences in the development of attention over the course of development.

Keywords: genetics; brain; development; cognition; dopamine; cingulate

Introduction

A role for genetics in mental function has been noted since the earliest days of the modern synthesis of Mendelian and population genetics.[1] The remarkable patterns of behavior observed in identical twins who may have been separated at birth as well as the alterations of behavioral development associated chromosomal anomalies show that the genetic material, in addition to environmental forces, is important in shaping mental function. In more recent years, the advancement of gene mapping methodologies has led to the identification of specific genes that account for risk for a variety of forms of mental disability that are both contiguous with healthy mental function such as addiction,[2,3] ADHD,[4] and anxiety[5] as well as disabilities that fall outside the normal distribution such as autism,[6] schizophrenia,[7] and Williams syndrome[8] to cite but a few.

The now widespread joint application of genetic and neuroimaging methods has provided a deeper understanding of how genetic risk influences the structure and function of certain neural networks. For example, a recent imaging-genetic study on a T-to-C nucleotide base change in the schizophrenia risk-factor *neuregulin 1* gene, found that individuals who carry the TT genotype, when asked to perform a working memory task, showed less brain activity in the frontal cortex than individuals with the CC genotype.[9] This study is notable for providing a translational bridge that connects the genetic risk for schizophrenia with activation of an anatomical network that is known to function abnormally in patients. The findings also reinforce the notion that normal executive control and complex psychopathology can have deep developmental roots. This is because *neuregulin* has many functions in the developing CNS, which may be related to early prodromal markers of schizophrenia, particularly in executive control.[10] Other similar translational research studies for disorders such as autism,[6] addiction[11] that use such a cognitive-neuro-genetic and imaging-genetic approach are now increasingly common in the literature. These efforts also reveal a rather productive co-application of two historically separate research traditions in psychiatry—a molecular genetic approach that seeks to ascertain the genetic origins of mental illness and a cognitive

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neuroscience approach that seeks to understand human behavior in terms of specific neural systems and component neural mechanisms. Because both research methods seek to dissociate and dissect mental function along the lines of naturally occurring biological processes (*i.e.*, to "cut nature at its joints") there has been remarkable synergy in the joint application of both cognitive and genetic methods in the area of psychopathology.

As such joint findings continue to emerge along the lines of the major psychopathologies, it becomes increasingly possible to ask what role do genes (that carry risk for mental illness) play in *healthy* cognitive function. Indeed, this question may be of some relevance, especially in research seeking to ameliorate and/or remediate cognitive disability in patient populations. To this end, there may be some value in understanding how genetics can be used to gain insight into the *development* of healthy mental function. From the perspective of cognitive science, much is already known about neural systems and neural mechanisms that carry out healthy cognitive function in adults. What can the introduction of genetic methods offer to this already robust research approach? In this review, we suggest that the inherently biological nature of genetic information is useful to further the longstanding aims of cognitive neuroscience—that is, to explain human behavior in terms of neural systems and component neural mechanisms. In particular, we emphasize the value of imaging-genetic approaches that synthesize anatomical, physiological, and molecular information within the constraints of mechanistic models of neural network dynamics. Our focus has been on a single area of cognition—attention—and we have sought to apply a genetic approach to an existing and longstanding program of research in the area of attention led by Michael I. Posner, who has been our mentor and collaborator for more than a decade.

Genetic dissection of attention networks in healthy adult populations

The ability to focus and shift one's attention is an important aspect of healthy psychological function. In recent decades, this ability has begun to be understood in terms of anatomical and physiological changes in specific neural networks that mature over the course of human development. One method that has been critical to this endeavor has been neuroimaging, which has allowed many mental operations to be analyzed in terms of the brain areas they activate. Studies of attention have been among the most commonly examined by neuroimaging and such research has supported the presence of three networks related to different aspects of attention. These networks carry out the functions of alerting, orienting and executive control.[12–14] In brief, alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli; orienting is the selection of information from sensory input; and executive control, a widely used term with many definitions, involves mechanisms for resolving conflict among thoughts, feelings, and responses. Some of the underlying circuitry in the case of alerting are networks that contain frontal, parietal and thalamic regions whose function can be probed by the use warning of signals prior to targets in an functional magnetic resonance imaging (fMRI) setting.[15] The influence of warning signals on the level of alertness is also thought to be due to modulation of neural activity by the norepinepherine system.[14]

The orienting of attention involves aligning attention with a source of sensory signals. This may be overt as in eye movements or may occur covertly without any movement. The orienting system for visual events has been associated with posterior brain areas including the superior parietal lobe and temporal parietal junction and, in addition, the frontal eye fields. Orienting can be manipulated by presenting a cue indicating where in space a person should attend, thereby directing attention to the cued location.[16] Event related fMRI studies have suggested that the superior parietal lobe is associated with orienting following the presentation of a cue.[15,17] The superior parietal lobe in humans is closely related to the lateral intraparietal area (LIP) in monkeys, which is known to produce eye movements.[18] When a target occurs at an uncued location and attention has to be disengaged and moved to a new location, there is activity in the temporal parietal junction.[17] Lesions of the parietal lobe and superior temporal lobe have been consistently related to difficulties in orienting.[19]

Executive control of attention is often studied by tasks that involve stimulus–response conflict, such as in various versions of the Stroop task.[20] In the Stroop task subjects must respond to the color of

ink (*e.g.*, red) whereas ignoring the color word name (*e.g.*, b-l-u-e). Resolving conflict in the Stroop task activates midline frontal areas such as the anterior cingulate cortex (ACC) and lateral prefrontal cortex.[21,22] There is evidence for the activation of this network in tasks involving conflict between central targets and surrounding flankers that may be congruent or incongruent with the target. Experimental tasks may provide a means of fractionating the functional contributions of different areas within the executive attention network.[23]

Reliability and heritability of measures of attention

As mental operations, such as alerting, orienting and executive processes are dissociated using behavioral and neuroimaging measures, there may arise some interest in other methods to facilitate finer-grained explorations into the nature of the structure and physiology associated with these processes. One such tool can be found in the human genome and its now-complete catalog of individual variation spanning some 20,500 genes. The so-called genetic approach has been used in many other areas of medicine, ecology, and natural history to assign specific molecular factors that are encoded by specific genes to individual differences in many types of structure, function and/or behavior. Certainly, there are many types of individual differences in cognitive performance, brain structure and brain activation—which makes the so-called cognitive- and imaging-genetic methods timely endeavors.

To begin to study such individual differences in attention networks we have developed an attention network test (ANT) that examines the efficiency of the three brain networks we have discussed above.[24] Differences in reaction times (RT) derived from the task provide three numbers that represent the skill of each individual in the alerting, orienting, and executive networks. In a sample of 40 normal volunteers we found these numbers to be reliable over two successive presentations. The correlations between two test sessions were 0.52, 0.61, and 0.77 for alerting, orienting, and conflict, respectively. In addition, we found no significant correlation among the three network numbers in this sample, indicating these three attentional networks are separable.

Although it is most often the case that genetics and the environment play somewhat equal and interacting roles in the expression of individual differences, it can be informative to compare the correlation of performance among monzygotic twins, having identical genomes, with a correlation of performance among dizygotic twins who share only as much genetic similarity as siblings do. A heritability index can be computed from the differences between these two correlations. Such measures of genetic influences on cognitive performance have been explored in this manner several times in ways that relate to attention. For example, studies using the Continuous Performance Task (CPT) have shown that the d' signal detection component of CPT performance has a heritability among normal subjects of 0.49.[25] The Span of Apprehension task (SPAN), a visual search task, has been shown to have an heritability among normal subjects of 0.65[26] and the P/N ratio of the Spontaneous Selective Attention Task (SSAT) was shown to have an heritability among normal subjects of 0.41.[27] Twin studies using normal control twins show that spatial working memory, divided attention, choice RT and selective attention,[28] attentional set-shifting,[29] sensorimotor gating,[30] smooth pursuit eye tracking[31] are heritable. The heritability observed at the behavioral level is supported by evidence that brain structures associated with attention can show genetic bases. Anatomical studies in rodents, nonhuman primates, and humans have established that genes are major determinants of overall brain size[32,33] for structural aspects of the frontal cortex[34] and corpus callosum.[35]

Using the ANT in the context of a twin study, we reported some evidence of heritability for the executive attention component.[24] Twenty-six pairs of adult monozygotic twins showed strong correlations for both the alerting ($r = 0.46$) and executive ($r = 0.73$) networks. For another group of 26 dizygotic same sex adult twins, we found a similar although somewhat smaller correlation for the alerting network ($r = 0.38$), but smaller correlation (0.28) for the executive network. The executive control network yielded a high heritability score of 0.89. Although the sample size is small and the estimates of heritability are not very precise, these data provided preliminary support for a genetic accounting of variation in the efficiency of the executive

attention network. It should be noted as well that the data on the orienting response did not show strong reliability or heritability.

Selection of candidate genes for population-based association studies

With an anatomically characterized,[15] reliable,[24] and heritable[36] assay in hand, our strategy progressed to an exploration of individual genetic factors that might account for individual differences in performance. Given the vast size of the human genome, a great many design and implementation issues abound. In practice, two main phenomena have tended to limit the success of so-called "candidate gene" explorations. First, the effects of a single genetic variant have been found to be vanishingly small, historically accounting for less than 2% of variance. Genetic modeling studies suggest that when many genes underlie a complex trait, such as attention, or a complex disorder (*e.g.*, ADHD), great difficulty is expected in detecting significant associations of single candidate genes.[37]

The second limitation relates to wide disparities in the frequency of genetic variants across ethnic groups. In the course of human evolution, errors in the replication of chromosomal DNA are rare, occurring at a rate[38] of 2.5×10^{-8} but they do occur often enough in our genome of 3 billion nucleotides, such that dozens of base-pair changes can accumulate per generation per genome.[39] Although many of these minor base pair changes have been lost over time—perhaps due to a normal loss of isolated mating enclaves—some changes have persisted, and even, perhaps due to natural selection, increased in frequency. Since their arrival, such ancestral errors in DNA replication—now referred to as polymorphisms—have since been distributed across the globe in an uneven and fragmented way by varied migratory patterns of human populations as far back as 10,000 and even 60,000 years ago. In the course of our own genetic studies, we have recognized that the complexities of genetic structure within human populations are especially troublesome for experimental designs in mixed populations of volunteers. This is especially true in North America and Europe where extensive ethnic admixture has occurred over the past 200 years. In an effort to minimize the limitations introduced by populations with a mixture of ethnicities, we have favored the choosing of candidate genetic variants that are common and found at high frequency across many different ethnic groups.

With these limitations in mind, we then attempted to select several promising candidate genes by considering existing knowledge of neural networks, pharmacology, gene expression patterns, animal models, and human genetic anomalies. Once candidates were proposed, individuals with specific alleles could be tested with the appropriate measures to determine whether certain alleles are correlated with performance. Critical overviews of this approach are discussed in great detail elsewhere.[40] One of the most widely cited examples of such a candidate gene selection rationale is that of Egan and colleagues in the study of working and episodic memory.[41] Based on a dopaminergic hypothesis of schizophrenia, Egan and colleagues examined genes related to schizophrenia that might involve the dopamine pathway. Because schizophrenia is highly heritable, studies of families of patients had led to genetic linkage to several chromosomal areas. One of these areas is on chromosome 22, in the 22q11 region that contains the *catechol-O-methyl transferase* (COMT) gene that produces an enzyme important in the metabolism of dopamine. Egan and colleagues reported that a variant of the COMT gene was related to performance in cognitive tasks involving working memory. This gene accounted for about 4% of the variance in perseveration errors during the Wisconsin card-sorting task. Thus, variation in the COMT gene was expected to mediate several aspects of individual differences in executive function.

We have pursued this same rationale to evaluate candidate genes for attention. Specifically, we have focused on dopaminergic genes and their role in executive attention. Neural networks that contain the frontal cortex have been shown to be important for executive function and also are known to be particularly rich in dopamine innervation[42] implicating dopamine as a dominant neuromodulator for the executive network. Some data suggest that dopamine concentrations are higher in the dorsolateral frontal cortex (DLPFC) than in other cortical regions.[43] Depleting DLPFC of dopamine produces deficits in performance on executive function tasks such as on the delayed response task. These deficits can be as severe as

DLPFC lesions.[44] Destruction of the dopaminergic neurons in the ventral tegmental area (VTA) that project to PFC also impairs performance on executive function tasks.[45] Local injection of selective DA (D1) antagonists into DLPFC impairs performance on the delayed response task,[46,47] whereas leaving performance on sensory guided control tasks unimpaired.[48] Disruption of the prefrontal—striatal–dopamine system by injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) also impairs performance on the delayed response task[49] and halting L-dopa treatment to Parkinson's patients produces deficits on frontal cortex dependent cognitive tasks.[50] Finally, Watanabe and colleagues found that the concentration of extracellular DA in DL-PFC increased significantly whereas monkeys were performing the delayed alternation task (another classic measure of PFC function) but not during a sensory-guided control task, nor in other frontal regions (Area 8 [arcuate] or orbitofrontal) during the delayed alternation task.[51]

To begin to test these predictions in a human gene-association design, we carried out a pilot study using a population of 200 adult subjects who performed the ANT on a laboratory computer.[52] Although this strategy lacked the needed statistical power to meet the standards set for the reporting of true associations,[37] no associations or statistical trends were observed for global measures of performance such as overall RT. This may suggest some specificity in the role of genetic factors in contributing to separable neural functions. Cheek swabs were obtained from each volunteer and genomic DNA was extracted and used for genotyping. An analysis of genotype vs. performance was conducted for several dopaminergic genes including the *dopamine d4 receptor* (DRD4), *monoamine oxidase a* (MAOA), *dopamine transporter* (DAT), and COMT genes. The DRD4 and MAOA genes revealed modest associations with behavior. For the DRD4 exon III VNTR polymorphism, a comparison of 4-repeat versus non-4-repeat carriers showed some relation to executive attention, but not to orienting, alerting or overall RT. The promoter repeat polymorphism in MAOA,[53] an enzyme that is responsible for both dopamine and serotonin breakdown, also showed associations with executive attention. This polymorphism has also been identified as a genetic risk factor in studies of aggression in boys where the 3-repeat allele (which is associated with less efficient conflict resolution in our adult studies) was found to confer some additional risk of aggression in boys who experienced some degree of maltreatment during childhood.[54]

Other cognitive studies using somewhat different tasks have also reinforced our initial findings on genetics and aspects of attentional function. In two studies involving tasks that require executive attentional control, alleles of the COMT gene were related to the ability to resolve conflict.[55,56] The COMT gene has also been shown to be related to a measure of the ability to solve novel problems (fluid intelligence).[57] In addition, the orienting network, which has been shown to be influenced by cholinergic drugs in monkeys[58] was associated with a cholinergic genetic polymorphism. Different alleles of a cholinergic gene, the *alpha 4* subunit of the *neural nicotinic cholinergic receptor* (CHRNA4), was related to performance differences in the ability to orient attention during tasks involving visual search,[59] confirming a link between orienting and the cholinergic system.

Imaging-genetic analyses on selected dopaminergic candidate genes

In advancing our strategic plan beyond the genetic and behavioral levels of analysis, others and we have begun to explore whether fMRI can be used to confirm and extend the association between genes and particular underlying networks. As was noted earlier, Egan and colleagues showed that subjects with the Valine allele at the Met158Val polymorphism in COMT showed worse performance and higher levels of brain activation in the prefrontal cortex.[41] In our studies of the attentional networks, subjects who performed the ANT in the scanner showed that the DRD4 and MAOA alleles that were associated with more efficient handling of conflict in the earlier behavioral studies also differed in amount of activation in the anterior cingulate while performing the ANT.[60] Because we ran 16 genotypically unselected subjects we did not have sufficient data to equally subdivide groups based on genotype at the several genes we found to be related to conflict in our behavioral study. However, we did find significant differences in activation for alleles that, as argued, have considerable influence on dopamine activity within the network being studied. Moreover, our scanning data showed significant differences with about eight subjects per cell,

whereas the same alleles only approach significance in a behavioral study with nearly 100 subjects in each cell. These data support the speculation first proffered by Egan and colleagues that a combination of behavioral and fMRI work can provide statistical confirmation even though the influence of any individual gene is rather small. Recent work has now replicated the MAOA finding where the low expression (3-repeat) allele was found to be associated with changes in orbitofrontal volume, amygdala and hippocampus hyperreactivity during aversive recall, and impaired cingulate activation during cognitive inhibition.[61] Further structural MRI investigations showed that the DRD4 gene was associated with cortical structure while the DAT1 gene influenced subcortical structure.[4] This result seems in harmony with the known cortical expression of the DRD4 gene and high subcortical expression of the DAT1 gene.[62,63] A recent report shows that when executive tasks are conducted in the presence of emotional distraction COMT is associated with activity in neural structures associated with cognitive control and task-related processing.[64] Finally, imaging-genetic (but not behavioral-genetic) studies on the ANT showed that carriers of the A1 allele of the TaqIA polymorphism (dbSNP rs1800497) located inside an haplotype block containing the DRD2 and ANKK1 gene have gene-associated functional activation in an anatomically specific, dopamine-rich region of the brain comprising the anterior cingulate gyrus.[65]

From nodes to networks: preliminary explorations of genetic variation and its relation to neural network dynamics

As the imaging-genetic literature expands, it is increasingly clear that single genetic polymorphisms can be statistically related to individual differences in the activation of *specific brain structures*. Findings such as the seminal work of Hariri and colleagues[66] on the 5HTT-LPR, and its many replications since, show that such individual differences in brain activation provide a means to understand how genetic variability can underlie complex emotions and behavior. Subsequent work from the same group, however, extended the finding from a single structure (amygdala) to the interaction of the amygdala and structures in the frontal cortex such as the cingulate cortex.[67] This initial finding, and others like it[68] provide glimpses of how genes might serve to influence, not only the physiological properties of individual structures, but also the dynamic interactions among structures or nodes in more widely distributed neural networks. Our approach has been greatly influenced by these findings and so we have also sought to integrate various MRI-based connectivity measures as well as EEG measures into our studies going forward.

To this end, we have begun to consider methods that can supplement fMRI, which is heavily relied upon because of its noninvasiveness and high spatial resolution, and is used mainly to detect changes in neuronal activity that correlate with metabolic demand, and not wider changes in information representation within the brain. Methods that detect oscillatory signals at the surface of the scalp provide one such supplementary method. For example, changes in local coherence in neuronal firing in absence of net increases in average population firing rate would go undetected by fMRI but not by MEG or EEG.[69] Beyond being complementary to fMRI, the signals measured using the latter two techniques may also be more tightly coupled to changes in information representation within the neocortex; whereas one can argue that the signal measured by fMRI is epiphenomenal, low-frequency oscillations measured using EEG or MEG have been shown to entrain local population firing and to mediate long distance synchronization of activity.[70,71] It is therefore important to employ these techniques in addition to fMRI to gain a more complete understanding of the neuronal processes underlying cognition. We have begun to examine local and long-distance dynamics of cortical oscillations in order to develop a more mechanistic view of cortical control of information processing, and have found that this approach lends itself to testing a unique set of predictions regarding the role of genetic factors in development and function of neocortical networks.

The following sections will be mainly theoretical in scope. First, we present a brief review of the sources of cortical oscillations and the relationship between these and behavior, then discuss the role of gap junction proteins in mediating these oscillations, and finally propose a conceptual framework for interpreting genetic data in the context of oscillation data. We suggest a mechanism by which the brain might use genes that encode neuromodulatory

systems to dynamically adjust information processing efficiency via modulation of oscillatory coherence. We close the section by suggesting a method by which the imaging genetics approach could be used to study the contribution of oscillations within specific frequency bands to behavior.

The relationship between oscillations and behavior

The cortical oscillations examined using MEG or EEG arise from the summed postsynaptic potentials neocortical pyramidal cells, and are imposed by synchronized, rhythmic inhibition via networks of electrically coupled interneurons.[72–77] Oscillations of various frequency bands have been associated with various cognitive and behavioral functions. For example, the power of gamma oscillations (typically defined as 30–100 Hz) correlates with attentional processes,[78,79] working memory,[80] and language skills;[81] beta frequency oscillations (14–30 Hz) have been associated with sensorimotor integration[82] and visual object recognition;[83] alpha (8–14) with rest/arousal[84] and perceptual processes[85]; and theta (4–8 Hz in humans, and typically 4–12 Hz in rat hippocampus) with attention[78] and locomotion/exploration in rats.[86] Theta also plays an important role in many other cognitive functions via long distance coordination of activity[70] or entrainment of gamma band activity.[71] Given the importance of internuronal networks in imposing these rhythms, it is reasonable to conjecture that variation in genes whose products differentially affect synchronicity of inhibition should have consequences in terms of individual differences in oscillations of various frequencies and, in turn, behavior. One class of candidates includes the gap junction proteins.

A candidate genetic pathway involving gap junctions in oscillatory activity

Gap junctions are composed of two apposed heximeric connexin protein hemichannels, one inserted in each cell membrane, that together form physical conduits allowing for direct metabolic and electrical coupling of cells.[87,88] Given a half-life of just a few hours, connexins are continually synthesized, trafficked to the membrane, internalized, and degraded,[89] which allows for tight regulation of cell-cell coupling. One connexin isoform that may play an important role in cortical oscillations and behavior is *connexin 36* (CX36). CX36 is expressed throughout the CNS: in the retina, inferior olivary complex, cerebellum, hippocampus, thalamus, striatum, and in the neocortex, particularly in layers IV and VI.[90–95] CX36 within the CNS is primarily neuronal[92,96] and appears to be most prevalent in interneruons,[97] although it has also been identified in mouse and human microglia.[98]

Coupling between internurons of individual classes[75,99] allows for the control of neuronal oscillations across a wide range of frequencies, and CX36 appears to be important for this. For example, theta synchrony among multipolar bursting neurons is deficient in CX36 knockout mice[75] as is the gamma synchrony imposed by low threshold spiking cells.[77] There does not appear to be compensation for CX36 knockout by insertion of other connexin proteins, at least in the inferior olive,[100] and lentiviral expression of a CX36 dominant negative in this same structure demonstrates that decreased gap-junction conductance, and not just secondary developmental consequences of the knockout, negatively impacts synchrony.[101] Therefore, it is likely that the finding of behavioral deficits associated with CX36 knockout in mice in terms of motor learning and spatial navigation are due at least in part to a decrease in oscillatory synchrony.[102]

Given the high rate of connexin turnover, one would predict that functional polymorphisms negatively impacting translation of CX36 should be associated with decreased local and long-distance coupling of neuronal oscillations in the neocortex, which should translate into deficits in performance. Fortunately, a relatively common SNP of the CX36 gene has been identified that may permit for examination of the role of this protein in higher-order cognition in humans. Belluardo and colleagues[93] first cloned and sequenced the human CX36 gene and mapped it to chromosomal band 15q14, which was previously identified as a susceptibility locus for juvenile myoclonic epilepsy (JME).[103] Two independent genetic association studies subsequently found statistically significant associations between JME and a synonymous coding SNP (rs3743123) of the gene.[104,105] Although it is not yet known whether this or another gene in linkage disequilibrium is responsible for conferring risk, there is reason to believe that CX36 does play a role. First, the locus of this SNP lies in an evolutionarily conserved site, suggesting that it may be of some functional importance. Second, modeling of the expected

folding pattern of the mRNA encoded by the mutated gene reveals clear deviations from normal patterns, and a database search revealed that disruption of this site may disrupt binding of two exonic splicing enhancers, resulting in decreased levels of expression.[104] Assuming that there is a decrease in expression, compensation by another connexin isoform seems unlikely because this is not observed in knockout animals[100] and CX36 does not form heterotypic channels.[106]

In order to determine whether or not this SNP has functional consequences in terms of cognition and behavior, we have performed pilot behavioral testing using the ANT on a group of healthy adults. Preliminary data on a small pilot sample of adults show that the T-allele of rs3743123 is associated with impaired behavioral performance in terms of overall RT relative to the ancestral C-allele, and that the T-allele likely also has consequences for higher-order cognition in terms of executive control of attention (unpublished data). We are currently following up on this preliminary finding with a controlled study of the effects of this T-to-C polymorphism on behavior, cortical oscillations, and functional brain activation. In terms of oscillations we expect to see a decrease in prefrontal gamma power and long-distance theta coherence associated with the mutated allele. If the predicted findings are borne out, then future efforts may focus on signaling pathways affecting conductance of these channels and potential relationships between these and various psychopathologies.

Stochastic resonance, CX36, and neuromodulators

Stochastic resonance refers to a property of nonlinear systems such that there is a roughly quadratic relationship between the level of noise in the system and its efficiency of function; that is, optimal efficiency is achieved with a moderate, rather than very low or very high, signal-to-noise ratio. This idea was initially conceived of to explain periodic occurrence of ice ages,[107] but has because found theoretical usage elsewhere, including the neurosciences.[108,109] In many cases, stochastic resonance is discussed in terms of improved efficiency of a system in signal detection upon adding moderate levels of noise to a weak periodic driving input. However, the noise can be supplied by the system itself, and may vary as a function of, for example, coupling of neuronal oscillations. As noted above, the continuous turnover of connexin proteins leaves opportunity for tight regulation of coupling, and factors that modulate cell-cell coupling could allow for online optimization of the efficiency of network function in a context-dependent manner. Another mechanism may be via direct modulation of excitability of the network to increase its sensitivity to input.

The CX36 protein contains a number of regulatory sites subject to phosphorylation by CaMKII and PKA,[110,111] and may also be regulated by Ca^{2+}/calmoulin.[112] It has been demonstrated in amacrine cells of the retina that both CX36 and Cx 35 (the perch ortholog of CX36), are phosphorylated in response to dopamine (DA) signaling, and that this decreases gap junctional conductance.[111,113] In developing rat prefrontal cortex, dye coupling among pyramidal cells is decreased by stimulation of D1 and D2 receptors, likely via the cAMP/PKA pathway,[114] and stimulation of D1, but not D2 receptors, increases the excitability of pyramidal cells in the primate prefrontal cortex.[115] The excitability of rat prefrontal fast spiking (FS) interneurons is also increased by D1, but not D2, stimulation.[116] The only study to date that examined DAergic modulation of electrical coupling in cortical FS interneurons examined those of the motor cortex and focused on D1-like mediated signaling, and found no effect on electrical coupling.[117] It is possible that a modulation effect may be found in the prefrontal cortex, or that stimulation of D2-like or both D1- and D2-like receptors is required to produce such an effect. For example, stimulation of D2 receptors modulates electrical coupling in the retina[118] and D1/D2 heterodimer receptors have been shown to activate a signaling cascade not initiated by stimulation of either receptor alone,[119] which, in the nucleus accumbens, results in an increase in CaMKIIα.[120] To date, these possibilities remain unexplored in the literature.

The above findings are of interest because they suggest that DAergic signaling may be used to modulate the processing efficiency of neuronal ensembles via at least two mechanisms. First, it appears that D1-like mediated signaling increases the excitability of neuronal ensembles, which would permit for propagation of information carried by relatively weak inputs. Second, if DAergic modulation

of electrical coupling/oscillatory coherence can be demonstrated in the prefrontal cortex, this would suggest a mechanism by which signal to noise can be optimized in a task dependent manner.[51] If this is true then studying polymorphisms that affect DA signaling pathways that modulate gap junction conductance/oscillatory coherence may advance our understanding of certain psychopathologies by helping us to understand the sources of emergent deficits in the efficiency of prefrontal network-level processing.[121,122]

Gap junction proteins and factors that modulate gap junction conductance appear to be important for regulating synchrony of oscillations in general. Another application of the imaging genetics approach would be to understand the contribution of oscillations in specific frequency bands to local and long distance coordination of function, and, in turn, their contribution to behavioral performance. As noted earlier, theta oscillations appear to be important for mediating long distance coordination of processing,[70,71] and it has been hypothesized that networks of multipolar bursting neurons generate theta rhythm in the cortex in response to cholinergic input.[75] Application of acetylcholine to rabbit cortex increases the power of theta band activity[123] and there is increased phase-locking of frontal theta oscillations in Alzheimer's patients under treatment with cholinesterase inhibitors relative to untreated patients.[124] A synonymous mutation (rs1044396) of the gene encoding the α4 subunit in the nicotinic acetylcholine α4β2 receptor (CHRNA4) has been shown to have consequences in terms of attentional functions,[59,125–127] as well as functional activation of the brain during an attention task.[128] Although the consequences of this SNP in terms of expression are currently unknown, this may be a good starting point in imaging genetics work aimed at better understanding the contribution of these oscillations to efficiency of network function and, in turn, behavior.

Considering the *where* and *when* of candidate genes in studies of individual differences in network structure and dynamics

As described at the outset, we seek, ultimately, to understand how individual differences in attentional function, vis-à-vis neural network structure and dyamics, can be explained, in part, by individual differences in genetic background. Certainly, the multiple neuroimaging methods (such as the MRI and EEG-based methods described above) that are increasingly used to measure neural network structure and dynamics present an attractive context for the application of genetic data. To this end, we further consider this possibility. When neural networks are widely distributed and show many dynamic states, is it possible to use genetic data to dissociate specific states or anatomical regions of interest using genetic data? To begin to explore this question, we ask if anatomical nodes can be differentiated by patterns of gene expression. If so, there may be an opportunity to exploit such gene-expression differences to test for separable roles of nodes within larger networks. For example, Vogt and colleagues examined the expression a wide array of neurotransmitter receptors (protein expression rather than of mRNA expression) and found that the expression patterns of the receptors was able to differentiate among 4 subregions of the cingulate cortex.[129] This pattern of gene expression was consistent with prior converging evidence from lesions, evoked activity and architectonics that suggest the cingulate cortex contains 4 functionally separable regions. In the case of this study, the ACC region showed highest AMPA receptor expression and lowest GABA-A receptor expression whereas the MCC region had the lowest AMPA receptor expression and the PCC had the highest cholinergic M1 receptor expression.

Relationships between where a gene is *expressed* and where it *exerts an effect* during an imaging-genetic study may not be easily intuited, however, because many of the genes used in imaging-genetic studies are widely expressed. For example, a query of gene expression data for COMT in UniGene, a public access repository of genomic data (NCBI-UniGene, 2005) shows a broad pattern of expression (bladder, bone, cervix, heart, kidney, liver, lung, ovary, prostate, skin, stomach, and other areas) and cortical and subcortical neurons in the human brain. Imaging genetic studies, however, have shown that despite the high levels of expression of COMT in the striatum, gene-associated brain activation is mainly found in the DLPFC.[41] However, this finding is consistent with data showing that

COMT activity accounts for less-than 15% of total dopamine turnover in the striatum, but greater-than 60% in the PFC.[130] Hence, complexities can arise when trying to reconcile gene-associated brain activity with gene expression.

Shifting to a developmental perspective

In addition to the consideration of where a gene is expressed vs. the location of its gene-associated structure/function, there may be some additional insight into the dynamics of cognitive function gained from a consideration of *when a gene is expressed* and the period(s) of development *when it exerts* its gene-associated structure/function. Cognitive and imaging research on many well-studied developmental disabilities that arise from mutations in single genes or multiple genes within a continuous interval, show that the effects of single genes can exert dramatic effects on early and late phases of cognitive development. Research on developmental disorders, such as Williams Syndrome and fragile-X mental retardation that arise from minute chromosomal lesions shows that even when the genetic lesion is well defined, the developmental outcome can affect many neural systems and show variation in severity.[131] Simple genotype-phenotype mappings do not sufficiently explain this variability and emphasis should be placed not on these mappings, but rather, on the role of genes in developmental *processes*.[132] For example, a VNTR polymorphism in exon III of the dopamine d4 receptor (DRD4), a gene that is reliably associated with risk for the developmental disability ADHD, shows a correlation with cortical thinning in young children[133] and interacts with parenting style to influence temperament[134] suggesting a biological link between cortical development and cognitive development. Other developmental disabilities such as phenylketoneuria, Angelman syndrome and fragile-X mental retardation reveal the profound way in which single genes alter the normal trajectory of brain and cognitive development.[132]

Some genes may even function very early in embryogenesis, but only cause noticeable disruptions rather late in behavior. The *forkhead box a2* (FOXA2) gene, for example, regulates the earliest stages of the birth of dopamine neurons but contributes to a Parkinsonian form of neural degeneration when the organism reaches late adulthood.[135] Finally, we know that genes act under the influence of the environment during development, as evidenced by the interaction of early childhood stress with the MAOA and 5HTT genes increasing the risk of aggressive behavior and depression later in life.[54,136] Furthermore, early maternal stress can lead to epigenetic modification of the fetal genome, as seen in promoter of the glucocorticoid receptor gene.[137] Hence, it is of interest to specify the role of genetic variation in terms of its influence on structural and cognitive change during development.

Among the most widely explored pathways in cognitive development, and thus well-suited for genetic studies, is the dopamine system. In the seminal work of Diamond, infants show marked improvement in tasks that require them to both inhibit a prepotent response, and also hold-in-mind the location of a target[138] and performance on these measures was shown to be dependent on the frontal cortex in monkeys.[139] Animal models of phenylketoneuria show that cognitive disruptions associated with PKU were dependent on reductions of DA in the prefrontal cortex,[140] which is consistent with Goldman-Rakic and colleagues who, using a primate model, found that the reduction of DA was equally as effective in diminishing executive function as were lesions to the frontal cortex.[44] In primate models, age-related improvement on executive control tasks is paralleled by postnatal increase in DA levels[141] and an increase in DA receptor gene expression.[142] Within the developing brain, DA participates in cellular changes such as myelination, synaptogenesis and pruning[143–145] but may mainly subserve executive function as a modulator of excitability of recurrent synaptic inputs.[146] The time course of these processes may be quite variable and beyond the range of our current work on 5–13 year olds however, because synaptogenesis and myelination in the ACC may peak before age 5, although pruning may continue well after age 13.[147] Thus, as described above, we have made use of this converging evidence in our studies on adults and are presently using this evidence to craft suitable hypotheses for child studies.

For one of our primary candidate genes, COMT, the evidence suggests that it performs an ongoing physiological function, and that variation in the structure of the enzyme leads to individual differences that can be measured, and that arise from, the real-time function of the enzyme. Alternately, current differences observed in brain activity for

separate genetic groups may be consequences of a genetic polymorphism that acted *early* in the development of a specific brain structure or altered the function of an early developmental process upon which other more mature processes depend. For example, COMT, along with several other genes, are deleted in a disorder called 22q11 deletion syndrome. These children have only a single functioning copy of the chromosomal region containing COMT and show a number of signs of mental retardation as well as physical abnormalities and are also at greatly increased risk of developing schizophrenia.[148] Two experiments have examined a version of the ANT task suitable for children and both found greatly reduced ability to resolve conflict.[149,150] One of these efforts related deficits in prepulse inhibition to performance on the ANT and the results suggest that striatal-cingulate pathways may underlie combined deficits in executive attention and prepulse inhibition.[151]

To begin to assess the possible developmental roles of other candidate genes associated with executive attention, we have sought to use tasks that can measure the efficiency of the attention system at different age ranges and have employed a child-friendly version of the ANT as just one example of a suitable task. In choosing this strategy, we acknowledge a few of the many complexities in choosing suitable behavioral assessments for child populations. Practically speaking, it is important to consider tasks that can be adapted to a neuroimaging environment and to consider tasks where performance can be compared across a wide range of ages by parametrically manipulating task difficulty. More importantly though, the behavioral assessments should be consistent with an established psychological model or framework (in our case, attention). Substantial evidence points to a unified conceptual framework for the development of executive control where central attentional mechanisms are involved[152–154] as well as dissociable processes such as inhibition and working memory.[155] Therefore, we expect attention, and moreover, genes that contribute to the development of the attention system to play a central, but limited, role in the development of executive function.

A number of studies have already adapted the central construct of attention, upon which the ANT is built, to studies of attentional function in infants, toddlers and young children. Infants show a propensity to gaze longer during incorrect trials and show increased negative activity on measurements of event related potentials[156] while 2–3 year olds demonstrate correlation in their ability to resolve stimulus–response conflict and anticipatory eye movements.[157] A few behavioral performance measures have been found to relate to aspects of temperament using scales that are appropriate for infants and children. In infants, the orienting of attention was found to relate to positive affect and function as a means to distract children from distress and reduce negative affect.[158] In young children, effortful control was related to executive attention as measured by the child-friendly ANT.[159] By age 7, executive attention as measured by performance on the ANT appears stable.[160] However, performance on many traditional executive function tasks involving component functions such as working memory and inhibition (*e.g.*, the Wisconsin Card Sorting, Tower of Hanoi and N-back) continues to improve in adolescence and into early adulthood.

Our use of the child version of the ANT is based on this earlier work of Rueda and colleagues[161] as well as the work of Konrad and colleagues who have reported functional activations in children who performed the ANT in the MRI scanner.[162] Each trial begins with a cue (or a blank interval, as in the no-cue condition) that informs the child either that a target will appear soon, and/or where it will appear on the screen. The target always occurs either above or below fixation, and consists of a central arrow (in the shape of a smiling fish), surrounded by flanking arrows (smiling fish). The flankers point either in the same direction as the target arrow (congruent) or in the opposite direction (incongruent) and a subtraction of RTs of congruent from incongruent target trials provides a measure of conflict resolution that assesses the efficiency of the executive attention network. Our current data were obtained from a collection of 110 healthy children somewhat evenly distributed in gender and ages 5–13 years old who performed the task while under adult supervision.[163] A view of both the distribution of raw and of normalized (conflict RT/overall RT) shows that children experience a RT cost of about 90 ms related to the resolution of stimulus–response conflict and that there is little change in the efficiency of conflict resolution as children mature beyond this age range. This

is largely in agreement with previous reports[164] and suggest that genetic correlates of performance on the child-friendly ANT may relate to developmental processes that occur before the age of 5.

Genetic tools tailored for studies of the anterior cingulate cortex and its role in attention

With some experience gained from the preliminary work described above, and an increased awareness of several inherent constraints, our strategy is now poised to for use – in our case – on gene associated activity in the ACC. This brain region, situated bilaterally on the medial surface of the frontal lobes around the rostrum of the corpus callosum and bounded by the callosal sulcus and the cingulate sulcus, has numerous projections into the motor cortex and thus advantageously sits where it may have a significant contribution in the control of sensory, cognitive, and emotionally guided actions. Indeed, it may not be surprising to repeatedly find dopaminergic-gene-associated brain activity in the ACC, because it receives afferents from more thalamic nuclei than any other cortical region and also receives diffuse monoaminergic innervation from all major neuromodulatory nuclei.[21,165]

Several lines of converging evidence suggest that variation in the structure and function of the ACC may be a suitable region for intense genetic study. First, several tasks that activate the ACC such as spatial working memory, divided attention and attentional set shifting have been examined in identical and fraternal twin populations and found to have high heritabilities.[28,166] The structure of the ACC was recently examined in healthy relatives of schizophrenic patients. These healthy relatives, who, presumably carry some of the genetic risk for schizophrenia showed 11.4% less right cingulate gray matter volume, 8% reduction in surface area and bilateral reductions in thickness of up to 2.5%.[167] Twin studies reveal that about 60% of the variance in N2 and P3 amplitudes can be attributed to genetic factors.[168] Prior investigations on these ERP components have implicated the ACC as the most likely neural generator of the N2 potential.[169] Pezawas and colleagues showed that carriers of the short allele showed volume reductions of 25% in grey matter in the perigenual ACC and that this same short allele genetic group also showed decreased positive feedback between the rostral ACC and the amygdala as well as decreased negative coupling between caudal regions of the ACC and amygdala.[67]

Within the scope of our interest in the *development* of executive attention, the robust and reliable brain activity observed in the cingulate cortex of healthy children suggests that the ACC may be a feasible region of interest for developmental studies.[170] For example, event related potential recordings in infants as young as 6–9 months of age show increased negativity in response to conflict that is spectrally very similar to the error-related negativity seen in adults, a neural process that has been localized to the ACC.[156] In a population of children ages 7–11, Casey and colleagues, reported that the blood-oxygen-level-dependent (BOLD) response in the ACC varied as a function of increased number of errors on a go no-go task and demonstrated that activity in ventral prefrontal regions was correlated with accuracy.[171] This type of error-related activity in the ACC is suggested to inhibit dopaminergic function via projections to the striatum, which, in-turn, supports learning of the no-go response.[172] Like the prefrontal cortex, the cingulate cortex shows evidence for a somewhat prolonged time-course of development.[147,173,174] A recent functional connectivity study in children showed that correlated activity among voxels across the ACC was found to be weaker than in other areas of the brain.[175] In human children, a recent report shows that a VNTR polymorphism in exon III of the DRD4 gene shows a strong correlation with cortical thinning in young children but demonstrates a decreasing correlation as children grow.[133] Along these lines, a behavioral study of 2-year-old children showed that in the presence of a DRD4 7-repeat allele in children with relatively poor parenting showed higher levels of impulsivity whereas those with high quality parenting did not.[176] These various developmental findings presumably relate in some way to our adult imaging-genetic finding of DRD4-dependent individual differences in ACC activation.[60]

With these limitations and the existing literature in mind, we have started to formulate provisional imaging-genetic hypotheses for understanding how genetic factors might modulate attentional efficiency via the ACC. First, we seek to shape our hypotheses within the context of a particular task where the role of the ACC is well characterized. In our recent work using the ANT, the effective

connectivity among regions within the ACC shows that interactions between the anterior rostral cingulate zone (RCZa) and the caudal cingulate zone (CCZ) of the ACC is modulated by the context of conflict.[78] Also, high-density scalp electrical recordings during the executive attention component of the ANT reveal an early (<400 ms) increase in gamma-band activity, a later (>400 ms) decrease in beta- and low gamma-band activity after the target onset, and a decrease of all frequency bands before response followed by an increase after the response.[177] Our usage of several MRI- and non-MRI-based imaging modalities permits us to examine the validity and robustness of individual imaging genetic findings across imaging modalities. Second, to the extent that these different imaging modalities (EEG vs. structural MRI vs. functional MRI vs. diffusion tensor imaging, etc.) are sensitive to different aspects of cellular and neural network physiology, we can, with caution, begin to specify the association of a genetic variant with a certain physiological process.

Candidate pathways for development of frontal midline structures

To begin to better assess the role of genes in the development of the ACC, we focus on candidate genetic pathways that act to establish and shape structures in the frontal midline. The developing ACC is positioned dorsally, at the midline, where the cerebral hemispheres meet. Detailed anatomical studies have been conducted on populations with *holoprosencephaly*, a genetic disorder where the embryonic forebrain does not sufficiently divide into the double lobes of the cerebral hemispheres, and instead, are conjoined across the midline, resulting in a single-lobed brain structure and lethal skull and facial defects. In less severe cases, near-normal brain development and facial deformities that may affect the eyes, nose, and upper lip appear. Kinsman[178] reported abnormalities in the corpus callosum, corticospinal tract, medial lemniscus, and cerebellar peduncles in less severe cases of holoprosencephaly. Takahashi[179] used MRI to describe a series of seven human brains with the less severe semilobular form and provide details of general patterns of malformation across different levels of severity. These findings reveal that without proper functioning of the Hedgehog genetic pathway, a normally formed ACC fails to develop. Mutations in *sonic hedgehog* (SHH) and several downstream factors including 7-*dehydrocholesterol reductase* (DHCR7), *patched* (PTCH), *zic family member* 2 (ZIC2), *Kruppel family member gli2* (GLI2) give rise to holoprosencephaly (reviewed[180]). Cognitive deficits in humans have been reported in association with DHCR7[181] and ZIC2 hemizygous mice show deficits in sensorimotor gating.[182] We proposed[183] that subtle hypomorphic or hypermorphic alleles of genes in the hedgehog and BMP pathways could affect the volume of the cingulate cortex as well as the absolute number of neurons contained in the ACC. These types of changes might cause relatively minor biochemical changes but would be measurable using neuroimaging, and could influence human brain function in clinically meaningful ways. Further behavioral and imaging genetic studies on common polymorphisms in these genes may reveal links between basic developmental processes and structure/function variation in the frontal midline. Presently, however, we cannot report any significant associations for common SNPs within the SHH gene in our child population, despite having explored this possibility.

Looking deeper into the development of the ACC, Sugino and colleagues[184] compared gene expression profiles for 3 types of interneurons and two types of projection neurons (layer 5 and layer 6) in the ACC as well as a number of other cortical and subcortical regions. Some of the genes reported include *secreted frizzled-related protein 2* (SFRP2) *natriuretic peptide precursor C* (NPPC), *endothelin converting enzyme-like 1* (ECEL1), *tachykinin, precursor 1* (TAC1), and *neurexophilin 3* (NXPH3). In a mouse model of neuronal migration in the frontal midline, the presence of SFRP2 protein impaired the anterior turning of commissural axons after midline crossing.[185] ECEL1 is a member of the M13 family of zinc-containing endopeptidases known to be important regulators of neuropeptide and peptide hormone activity. The TAC1 gene encodes the neuropeptides *substance P* and *neurokinin A*. Mice without TAC1 function showed decreased depression- and anxiety-related behaviors.[186] TAC1 also emerged as a top candidate gene for depressive illness in a unique multistage analysis of animal model gene expression and human genetic linkage.[187] Finally, *neurexophilin 3* (NXPH3) is a tightly bound extracellular ligand of α-neurexins, a family of presynaptic α-latrotoxin receptors. NXPH3 expression is restricted mostly to

layer 6b of the cerebral cortex, where it occurs in subplate-derived excitatory neurons as well as granule cells in the vestibulocerebellum and knockout mice display impaired sensory information processing and motor coordination.[188]

Finally, several candidate pathways for ACC development emerge from developmental studies of the rostral forebrain. Drastic midline deficits in animal models and humans have been linked to the hedgehog signaling pathway. In addition, bone morphogenetic proteins (BMPs) are expressed at the dorsal apex (apices in cortices) in the embryonic central nervous system. In the absence of BMP signaling, the dorsal cortex does not properly develop,[189,190] whereas constitutive activation of BMP signaling causes dorsalization of the cortex.[191] Frontal identity has also been shown to be imparted by *fibroblast growth factor-8* (FGF8), which is expressed by the anterior neural ridge (ANR) within the fetal forebrain.[192] FGF8 gene expression is regulated by the homeobox transcription factor, EMX2, and FGF8 protein forms a rostrocaudal gradient that induces anterior cell types at the expense of posterior cell types.[193] FGF proteins signal primarily through MAP-kinase and PI-3-kinase pathways and mutations in the PI-3-kinase pathway are associated with autism[194,195] and schizophrenia.[196] Also, mice with a conditional inactivation of FGF2 as well as a null CNP1 background display no obvious anatomical abnormalities, but display hyperactivity that can be suppressed by dopaminergic antagonists.[197] FGF14 gene targeted mouse models of spinocerebellar ataxia exhibit impaired spatial learning and defective theta burst induced LTP in hippocampal slices.[198] Finally, the growth factor FGF20, which promotes dopaminergic cell survival has been implicated in psychiatric illness.[199] Like hedgehog and BMP signaling, the FGF pathway is a promising source of converging evidence.

Plasticity within the ACC

Because the use of functional and structural imaging in conjunction with genetic data permits not only an analysis of structural variation in the ACC, but also functional variation, we have constructed provisional hypotheses about neural plasticity in the ACC. These provisional hypotheses are rooted largely on the extensive findings of Zhuo and colleagues who have characterized a form of long-term potentiation (LTP) in the mouse and rat cingulate cortex.[200–202] In their experimental system, several different forms of stimulation such as spike-EPSP-pairing and theta-burst stimulation are used to mimic endogenous activity of ACC neurons and are able to induce a form of potentiation that can last from 40 to 120 min.[203] Not surprisingly, these forms of potentiation are dependent, to different extents, on presynaptic and postsynaptic enhancement mechanisms as well as structural changes at the synaptic cleft. Presynaptic mechanisms are supported by increased input–output curves and decreased paired pulse facilitation in ACC slice recordings from animals suffering from chronic pain.[202] Pharmacological manipulations reveal that *GluR1*, but not *GluR2* subunits of AMPA receptors modulate an early induction phase while both NR2A and NR2B subunits are necessary for the maintenance of LTP.[204] Characterization of plasticity using various gene-targeted mouse models reveals specific roles for NMDA receptors, adenylyl cyclase subunits (AC1 and AC8), and calcium calmodulin dependent kinase type-IV (CaMKIV) in long-lasting plasticity in the ACC. For example, in mice lacking either the GluR5 or GluR6 subunit, kainate EPSP's were reduced in single knockout and absent entirely in double 5/6 targeted animals.[205] Gene deletion of adenylate cyclase subunits AC8 and AC1 reduced forskolin-induced plasticity and abolished LTP in the ACC using both theta-burst and EPSP-paring.[206] Activation of CREB was not observed in CaMKIV knock-out mice using theta-burst stimulation.[207,208] Finally, it has been observed that LTP in the ACC is absent in mice lacking the FMRP synaptic protein[209] and the transcription factor EGR1.[210] Explorations of genetic polymorphisms in the human GRIN2B glutamate subunit gene have not yet revealed associations with executive attention in our population of healthy 5- to 13-year-old children.

To explore a more natural form of plasticity in the ACC, that is, without the use of artificial stimulation, Zhuo and colleagues have developed paradigms involving peripheral hindlimb injury. Following amputation of a central digit of the hindpaw, rapid and longlasting enhancements of sensory responses are observed to peripheral stimulation.[211] Intracellular recordings showed rapid MK-801 (an NMDA antagonist) sensitive depolarization in response to injury followed by a prolonged state of depolarization.[212] This extended period of depolarization was accompanied by a well-known set of immediate

early genes such as C-FOS, EGR1, and CREB, which, via transcriptional activation, may help sustain periods of potentiation lasting for several days. Thus, the core model suggests that LTP in the ACC occurs after peripheral injury and may mediate persistent pain. Again, NR2B as well as AC1 and AC8 were implicated in this in-vivo form of plasticity using gene targeted mouse models.[207,213] Mice that overexpress the NR2B subunit, for example, demonstrate increased sensitivity to peripheral injury[213] and these behavioral responses were reversed by administration of selective NR2B antagonists.[214] Similarly, mice lacking AC1 and/or AC8 show reduction of persistent pain which can be reversed via injection of AC activators such as forskolin.[207] Potentiation in response to injury may occur because of a loss of an autoregulatory form of long-term depression that helps to normally quiet neuronal activity in the ACC, because, induction of LTD was only partially successful in injured animals and loss-of LTD was site-specific.[215]

Concluding remarks on the inextricable role of the environment

As explored above, there is a great deal of information to consider when designing cognitive-neurogenetic and imaging-genetic studies. When seeking, as we have been, to identify separable components of neural network structure and dynamics related to attention and to understand the basis of individual differences in attentional function, it is useful to understand the many biochemical pathways that lead to the development of candidate structures and also to be aware of the anatomical limits of gene expression and the timing of gene expression. Perhaps more importantly, however, it is of the utmost importance to understand that the environment is an especially potent driver of gene expression throughout brain development. For example, anoxia,[216] maternal separation,[217] amyloid protein expression,[218] and drug abuse,[219] all induce hypometabolism, gliosis, and programmed cell death in the ACC, a central node in the executive attention network. Exposure to environmental and social stress can induce the expression of glucocorticoid receptor (GR), a transcription factor which mediates the cellular response to stress and influences functional coupling in the amygdala.[220] Our group has reported that other genes as well can be influenced by environmental forces. We found that the expression of TGF-alpha, a factor in the postnatal maturation of dopamine neurons, was found to be downregulated by neonatal separation stress in male pups.[221] Additional evidence that stress may influence dopaminergic function can be found in the work of Benes and colleagues, who show that dopaminergic innervation of interneurons in layers II and V of the ACC are elevated in postmortem analyses of schizophrenia. The hyperinnervation of interneuronal DRD2 contacts is suspected to disable local inhibition of pyramidal cells and lead to excess glutamatergic signaling and waves of excitotoxicity in downstream brain areas.[222]

Current genetic and imaging genetic work has begun to explore the way that the genome and the environment may interact to influence cognition. Epidemiological findings by Caspi and colleagues show that interactions of genotype together with certain aspects of stress or neglect can influence the onset of depression and aggression.[54,136] Imaging genetic studies on the genetic loci involved in these gene-x-environment phenomena reveal gene-associated brain activity in regions of affective and cognitive control, in particular, the ACC.[68] Such environmental interactions pose an experimental challenge to imaging-genetic research because it is often difficult to ascertain an experimental volunteer's past experience with stress and or neglect. Similarly, it is difficult to determine the current state of stress for a subject who may or may-not experience anxiety in the local laboratory or scanner environment. Canli and colleagues have evaluated this issue in more detail via the introduction of baseline brain activity conditions to begin to explore 5HTT-LPR-related individual differences in the response of subjects to the scanner environment.[5]

Thus, we acknowledge that the genetic material is not determinative, but rather exerts limited effects on the development of neural networks via complex interactions with the environment. Further work in the genetics area will likely seek to capture early and concomitant environmental factors as a means to better account for such interactions. Finally, we wish to acknowledge that our work, like all cognitive-genetic work, has an ethical dimension that bears on the current rise of medical- and consumer-based genetic testing, especially regarding children. Although we do not address these issues here, we wish to recognize the importance of

the ethical and privacy issues revolving around the new genetic research.[223,224]

Conflicts of interest

The authors declare no conflicts of interest.

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