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Provisional hypotheses for the molecular genetics of cognitive development: Imaging genetic pathways in the anterior cingulate cortex

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Abstract

Brain imaging genetic research involves a multitude of methods and spans many traditional levels of analysis. Given the vast permutations among several million common genetic variants with thousands of brain tissue voxels and a wide array of cognitive tasks that activate specific brain systems, we are prompted to develop specific hypotheses that synthesize converging evidence and state clear predictions about the anatomical sources, magnitude and direction (increases vs. decreases) of allele- and task-specific brain activity associations. To begin to develop a framework for shaping our imaging genetic hypotheses, we focus on previous results and the wider imaging genetic literature. Particular emphasis is placed on converging evidence that links system-level and biochemical studies with models of synaptic function. In shaping our own imaging genetic hypotheses on the development of Attention Networks, we review relevant literature on core models of synaptic physiology and development in the anterior cingulate cortex.

Introduction

Imaging genetic studies on the human brain involve a universe of permutations among several million common genetic variants with thousands of voxels in both white and gray matter and a wide array of cognitive tasks that activate specific brain systems. In order to avoid statistical limitations and expenditures inherent to unconstrained exploratory imaging-genetic analyses, we have adopted an hypothesis-driven investigative approach where predictions are synthesized from evidence obtained from structural and functional studies in humans, mice, and cell-based systems. We are focused on the developmental biology of Attention Networks and, most recently, on the role of the anterior cingulate cortex (ACC). Activity in this well-

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studied brain region has been implicated in cognitive monitoring of control (Botvinick et al., 2004), conflict resolution (Botvinick et al., 2001), effortful control and self regulation (Posner and Rothbart, 2007). Extensive projections from the ACC subgenual area 25 to the amygdala, parabrachial nucleus and periaqueductal grey are thought to underlie the role of this region in emotion (Vogt, 2005), somatosensory pain (Sikes & Vogt, 1992), social exclusion pain (Eisenberger et al., 2003) and placebo modulation of pain (Derbyshire et al., 2004; Raz et al., 2005). In each of these complex cognitive processes, the ACC participates in linking sensory inputs with top down rules or expectations in order to generate motor responses that guide behavior. Lesions to this area can have wide ranging effects from transient reduction of performance in specific tasks (Janer and Pardo, 1991) to an inability to make decisions in the real world (Eslinger & Damasio, 1985); whereas cingulotomies reduce the unpleasantness of pain (Zhuo 2002) and stimulation of specific cingulate subregions can relieve symptoms associated with negative mood and anxiety (Ressler & Mayberg, 2007).

In beginning to understand the biological basis for normal complex cognitive processes and abnormal processes related to neuropsychiatric illness we have undertaken a genetic approach. Although many complex disorders have a strong genetic component, we recognize that traditional behavioral-genetic studies often generate mixed results that can be difficult to replicate (Kendler, 2006). Interestingly, deficits in the structure and function of the ACC are well reported for many disorders. When such deficits are shown to co-segregate with disorders and also shown to be heritable, then the term ‘endophenotype’ can be used to indicate that the genetic basis for variation in such traits will likely inform the genetic risk for a more complex disorder. The cingulate region, in particular, appears well situated for genetic analysis. Healthy relatives of patients with schizophrenia show 11.4% less right cingulate gray matter volume, 8% reduction in surface area and bilateral reductions in thickness of up to 2.5% (Goghari et al., 2007). Variation in tasks that activate regions of the ACC, such as spatial working memory, divided attention and attentional set shifting typically show high heritabilities in twin studies (Cannon et al., 2000; Pardo et al., 2000). Also, twin studies reveal that genetic factors contribute about 60% of the variance in ERPs (event related potentials) that arise from activity in the ACC such as the N2 and P3 amplitudes (Anokhin et al., 2004). The seminal work of Pezawas and colleagues (Pezawas et al., 2005) has identified allele-specific grey matter volume associations and functional activations in this brain region with polymorphic expression states of the serotonin transporter (5HTT). Finally, a brief review of our own imaging genetic research on the development of normal attention shows that variation in several genes involved in dopaminergic regulation correlates with individual differences in brain activity in the ACC. Thus, imaging-genetic studies on the development of the ACC are, perhaps, an attractive endophenotype, or alternate strategy, for gaining access to details of the genetic risk of complex mental illness.

Imaging-genetic studies of attention link genotype to cingulate activation

Our efforts to understand how biochemical factors might relate to normal attention and abnormal behavior, have relied on The Attention Network Task (ANT), a task that has been shown to activate specific anatomical networks involved in orienting to sensory events, maintaining an alert state and resolving conflict between stimuli and responses (Corbetta and Shulman, 1998; Mesulam, 1990; Fan and Posner, 2004). We initially explored the reliability, validity and heritability of the ANT as an endophenotype for genetic studies. Test-retest studies on the ANT show the executive network is the most reliable (0.77) component. We also found executive attention deficits in schizophrenia (Wang et al., 2005). A small-scale twin study (n = 50 pairs) found that executive attention network efficiency has an heritability of (h^2 = 0.89) (Fan et al., 2001). Subsequent behavioral genetic investigations on a mixed population of 200 healthy adults showed modest genetic associations for common variants in genes including *monoamine oxidase a* (MAOA) and the *dopamine d4 receptor* (DRD4) (Fossella et al.,

2002). Subsequent imaging-genetic experiments on the *maoa* and *drd4* genes revealed significant genotype-dependent differences in the blood oxygen level dependent (BOLD) response, located in the ACC, when subjects were performing the executive attention component of the task (Fan et al., 2003). Later, a separate group replicated the *maoa* finding (Meyer-Lindenberg et al., 2006). In a follow-up study, we found individual differences in ACC activity that were associated with variation in a genetic marker linked to the *dopamine d2 receptor* (DRD2) (Fossella et al., 2006).

Bridging levels of analysis: from genes to BOLD response

A standard hypothesis for an imaging-genetic experiment would, naturally, suggest that a variant allele of a specific candidate gene is correlated with an increase (or decrease) in volume or BOLD response for a particular brain region, during a particular contrast of task conditions. For example, central hypotheses of studies on the Val108Met variant in the *catechol-O-methyl transferase* (COMT) gene predict that the less active *Methionine* protein isoform leads to slightly higher levels of extrasynaptic dopamine, which, then, is predicted to enhance activity-dependent synaptic processes (Egan et al., 2001). This prediction extends to task-related activity in regions, such as the prefrontal cortex, that are rich in dopaminergic innervation and where expression of the dopamine transporter is reduced (Sesack et al., 1998). Tests of this central hypothesis support this core synaptic model and find an inverted U-shaped response of BOLD vs. genotype that is consistent with the dose-response effects of neuromodulators on synaptic function (Mattay et al., 2003). In the case of COMT, an hypothesis based on the function of specific genes *at the level of the synapse*, constituted a natural midpoint or ‘conceptual bridge’ where evidence-based links between brain structure/function, on one side, and genetic variation, on the other side, could be linked together. Similarly, recent imaging genetic studies on the serotonin transporter that examine the BOLD response in brain regions that *share synaptic connectivity* are readily supported by converging evidence obtained from studies at the systems level, on one side, and biochemical pathway level, on the other (Heinz et al., 2005; Pezawas et al., 2005).

Despite a few robust and highly replicated findings in the imaging genetics literature, it is important to mention that there are still many gaps in the existing converging evidence and known limitations to the hypothesis shaping framework we are describing here. For one, the BOLD-response, which has an indirect relationship to synaptic activity, remains poorly understood in terms of biochemical pathways. Rapid presentation of visual stimuli, in a rat model, can give rise to a form of long-term potentiation that lasts up to 2 hours (Clapp et al., 2005a). Similar visual stimulation in humans induces a relative increase in BOLD activity in the primary visual areas (Clapp et al., 2005b). Using a whisker stimulation paradigm, Lu and colleagues (Lu et al., 2004) found that the hemodynamic response as measured by high resolution fMRI (3T, voxel size $156 \times 156 \times 2000\ \mu m^3$) in layers IV-VI of the rat whisker barrel cortex was tightly correlated with changes in cerebral blood volume (CBV) and neuronal activity as measured by *cfos* expression. Looking more closely at the biochemical level, however, it is clear that there are many overlapping signal transduction cascades that couple neural activity with vasodilation and vasoconstriction (Raichle & Mintun, 2006). For example, the *M5 muscarinic acetylcholine receptor* (M5R), when inactivated, gives rise to abnormal, long-lasting vasoconstriction of cerebral arteries, reduced blood flow, and atrophy of apical and basal dendritic arborizations in pyramidal neurons (Araya et al., 2006). Indeed, more genetic study directed to the BOLD response *per se*, will better inform future hypotheses. Also, the use of multiple imaging modalities has been suggested as a means to learn more about the physiological basis for fMRI-BOLD changes. In particular, fMRI in conjunction with EEG and deep electrodes has been successful at linking synaptic physiology with neurovascular coupling processes (Logothetis, 2007).

A core synaptic model for imaging genetic studies of the ACC

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 (Fan et al., 2007b). 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 (Fan et al., 2007a). Our utilization of several MRI- and non-MRI-based imaging modalities (such as EEG) 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. structure vs. functional vs. diffusion 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.

As noted earlier, we seek to construct hypotheses around synaptic processes as a point of convergence between systems-level and biochemical-level pathways. Among other processes, the synaptic changes associated with long lasting potentiation and depression are well studied at these levels of analysis. Our 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 (Zhao et al., 2005; (Zhao et al., 2006; Zhuo, 2007). 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 minutes (Wei et al., 2002b). 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 (Zhao et al., 2006). 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 (Toyoda et al., 2007). 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 (Wu et al., 2005b). 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 (Liauw et al., 2005). Activation of CREB was not observed in CaMKIV knock-out mice using theta-burst stimulation (Wei et al., 2002a; Wei et al., 2003). Lastly, it has been observed that LTP in the ACC is absent in mice lacking the FMRP synaptic protein (Zhao et al., 2005) and the transcription factor EGR1 (Ko et al., 2005).

To explore plasticity in the ACC 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 (Wei & Zhuo, 2001). Intracellular recordings showed rapid MK-801 (an NMDA antagonist) sensitive depolarization in response to injury followed by a prolonged state of depolarization (Wu et al., 2005c). 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 (Wei et al., 2002a; Wei et al., 2001). Mice that overexpress the NR2B subunit, for example, demonstrate increased sensitivity to peripheral injury (Wei & Zhuo, 2001) and these behavioral responses were reversed by administration of selective NR2B antagonists (Wu et al., 2005a). Similarly, mice lacking AC1 and/or AC8 show reduction of persistent pain which can be reversed via injection of AC activators such as forskolin (Wei et al., 2002a). Potentiation in response to injury may occur due to a loss of an auto-regulatory form of long-term depression that helps to normally quiet neuronal activity in the ACC, since, induction of LTD was only partially successful in injured animals and loss-of LTD was site-specific (Wei et al., 1999).

Provisional hypotheses in a developmental context

In seeking to develop testable imaging genetic hypotheses, we recognize that genetic programs contribute greatly to the early development of the brain, and, that long-range patterns of synaptic connectivity are under strong genetic control. Indeed, genetic influence on differences in behavior and brain activity in adults may well be the result of genetic processes that act quite early during brain and cognitive development (Scerif & Karmiloff-Smith, 2005). Developmental manipulations such as anoxia (Mehmet et al., 1994), maternal separation (Avishai-Eliner et al., 1999), amyloid protein expression (Dodart et al., 1999) and drug abuse (Ladenheim et al., 2000), all induce long-lasting changes such as hypometabolism, gliosis and programmed cell death in the ACC. Previously, we reported that maternal separation leads to changes in the frontal midline mRNA expression of *tgf-alpha*, a genetic mediator of post-natal maturation of dopamine neurons (Romeo et al., 2004). 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 (Shaw et al., 2007). 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 while those with high quality parenting did not (Sheese et al., 2007). These various developmental findings should, presumably, relate in some way to our adult imaging-genetic finding of *drd4*-dependent individual differences in ACC activation (Fan et al., 2003). The parenting study suggests an underlying rationale for the *long-lasting effects* of genes that influence the *early* stages of cognitive development because an organism like the human, born helpless, and with a complex culture, such heritable developmental influences may be very important targets for natural selection on survival and reproduction. Such gene-environment interactions also demonstrate that while heritable factors influence behavior, the developmental outcome of genetic variation can be heavily influenced by environmental context. Findings of gene-x-environment interaction are common in the behavioral literature (for review see (Rutter et al., 2006)).

To begin then, to better assess the role of genes in the *development* of the ACC, we focus on genetic pathways that act to establish and shape structures in the frontal midline. A role for genetics in early cognitive development is most well studied in hereditary developmental disorders such as Williams Syndrome (Karmiloff-Smith, 2007) and Fragile-X Mental Retardation (Bagni & Greenough, 2005) where abnormalities can be observed in young children, reflecting alterations in the patterning and the wiring of the fetal brain. The developing ACC is positioned dorsally, at the midline, where the cerebral hemispheres meet. 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 (Hebert et al., 2002; Monuki et al., 2001), whereas constitutive activation of BMP signaling causes dorsalization of the cortex (Panchision et al., 2001).

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 (Kinsman, 2004) reported abnormalities in the corpus callosum, corticospinal tract, medial lemniscus and cerebellar peduncles in less severe cases of holoprosencephaly. Takahashi and colleagues (Takahashi et al., 2003) used MRI to describe a series of 7 human brains with the less severe semi-lobular 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 (Cohen, 2003)). Cognitive deficits in humans have been reported in association with DHCR7 (Mueller et al., 2003) and ZIC2 hemizygous mice show deficits in sensorimotor gating (Ogura et al., 2001). We propose 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.

Looking deeper into the development of the ACC, Sugino and colleagues (Sugino et al., 2006) compared gene expression profiles for 3 types of interneurons and 2 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 (Lyuksyutova et al., 2003). 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 (Bilkei-Gorzo et al., 2002). TAC1 also emerged as a top candidate gene for depressive illness in a unique multi-stage analysis of animal model gene expression and human genetic linkage (Ogden et al., 2004). 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 (Beglopoulos et al., 2005).

Finally, several candidate pathways for ACC development emerge from developmental studies of the rostral forebrain. Frontal identity has been shown to be imparted by *fibroblast growth factor-8* (FGF8), which is expressed by the anterior neural ridge (ANR) within the fetal forebrain (Fukuchi-Shimogori & Grove, 2001). *Fgf8* gene expression is regulated by the homeobox transcription factor, *emx2*, and FGF8 protein forms a rostrocaudal gradient which

induces anterior cell-types at the expense of posterior cell-types (Fukuchi-Shimogori & Grove, 2003). FGF proteins signal primarily through MAP-kinase and PI-3-kinase pathways and mutations in the PI-3-kinase pathway are associated with autism (Greer & Wynshaw-Boris, 2006; Kwon et al., 2006) and schizophrenia (Bellon, 2007). 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 (Kaga et al., 2006). FGF14 gene targeted mouse models of spinocerebellar ataxia exhibit impaired spatial learning and defective theta burst induced LTP in hippocampal slices (Wozniak et al., 2007). Finally, the growth factor FGF20, which promotes dopaminergic cell survival has been implicated in psychiatric illness (Murase & McKay, 2006). Like hedgehog and BMP signaling, the FGF pathway is a promising source of converging evidence. It is important to note that candidate gene testing, even when focused on specific biochemical pathways, may still require caution in the area of statistical testing. Multiple testing of pathways and related families of candidate genes is expected to produce false positive results and require appropriate statistical corrections and adequate sample sizes.

Conclusion

As noted, we focus our imaging genetic strategy on Attention Networks, and, more deeply, on the ACC, in an effort to gain access to details of the genetic risk of complex psychiatric illness. Along these lines, it is important to caution that few of the candidates genes we have discussed have been associated with genetic risk for mental illness, even though deficits in attentional function and cingulate structure-function are well known in complex disorders such as depression, schizophrenia and autism. None of the genes in the *hedgehog* pathway have yet been shown to confer genetic risk, *per se*, for any of the major complex neuropsychiatric disorders. More typically, deficits in attention and cognition are present among individuals who carry mutations in the *hedgehog* pathway and present with minor forms of holoprosencephaly spectrum (Heussler et al., 2002). Careful analysis of gene expression in post-mortem tissue from the ACC is one research strategy that can more readily refine a core synaptic model for genes and cingulate function. Benes (Benes, 2000) shows that dopaminergic innervation of interneurons in layers II and V of the ACC are elevated in post mortem analyses of schizophrenia. The hyperinnervation of interneuronal DRD2 contacts is suspected to disable local inhibition of pyramidal neurons and leads to excess glutamatergic signalling and waves of excitotoxicity in downstream brain areas. Therefore, although it remains a possibility that the ACC is not affected by genetic risk factors, and is not a valid endophenotype for complex mental illness, we, nevertheless, also refine our hypothesis shaping process to prioritize genetic pathways that involve *known* genetic risk factors for such illnesses.

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