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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.

Keywords: Genetic; Imaging; Brain; Cingulate; Development

1. 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 a 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-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 and 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 and Damasio, 1985); whereas cingulotomies reduce the unpleasantness of pain (Zhuo, 2005) and stimulation of specific

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cingulate subregions can relieve symptoms associated with negative mood and anxiety (Ressler and 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.

1.1. 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, 1981; 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 a 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).

1.2. 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 versus genotype that is consistent with the dose–response effects of neuromodulators on synaptic function (Mattay et al., 2003). In the case of COMT, a 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 h (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