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A BRIEF INTRODUCTION TO THE NEUROGENETICS OF COGNITION-EMOTION INTERACTIONS

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Abstract

Neuroscience research has demonstrated that cognition, emotion, and their dynamic interactions emerge from complex and flexible patterns of activity across distributed neural circuits. A parallel branch of research in genetics has begun to identify common variation in the human DNA sequence (i.e., genome) that may shape individual differences in cognition-emotion interactions by altering molecular and cellular pathways that modulate the activity of these neural circuits. Here we provide a brief introduction to such neurogenetics research and how it may usefully inform our understanding of the biological mechanisms through which dynamic cognition-emotion interactions emerge and, subsequently, help shape normal and abnormal behavior.

Introduction

Emotions were once thought to be “lower order” constructs that resided primarily in subcortical circuits while cognition represented “higher order” functions primarily supported by the cortex (e.g. reviewed in: [1]). Emerging research, however, encourages the reconceptualization of both cognitive and emotional processing as arising from highly distributed and dynamic interactions across neural networks [2]. Although there are many possible ways to define a neural network (including structurally, based on cytoarchitecture), much of the cognitive and affective neuroscience literature has focused on fluctuations in fMRI signal across the brain, capturing an index of synchronization and functional communication between regions [3]. Such studies have demonstrated considerable overlap in the patterns of activity across brain regions during both cognitive and emotional tasks, with smaller, but important, reconfigurations used to address specific task demands [2,4–6]. Thus, a useful approach to studying cognition and emotion in the brain may be to investigate both shared and unique features of neural network function that contribute to cognition, emotion, and their interactions. It is these features that may serve as key target phenotypes in

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Conflict of Interest Declaration

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genetic association studies, which we next review. We conclude by considering how the development of neurogenetics within the context of cognition emotion interactions can help advance the search for biomarkers of risk for psychopathology.

Genetic Association Studies

Studies attempting to establish associations between specific genetic polymorphisms and either behavioral or biological phenotypes are positioned to inform our understanding of cognition-emotion interactions by identifying molecular, cellular, or network level processes contributing to either general or specific functions. The value of such studies is inherent in the observation that between 30–80% of the variability in general cognitive phenotypes reflects an individual's genomic architecture [7]. Similarly, the so-called heritability of mood and anxiety disorders is between 30–40% [8]. Moreover, recent analyses have estimated that 23–65% of the variability in the functional connectivity of neural networks and 25–42% of the variability in some between-network coherence is heritable [9]. The specific polymorphisms contributing to this broad heritability can be revealed through two complimentary approaches: hypothesis-free genome-wide association studies (GWAS) and hypothesis-bound candidate gene studies.

Candidate Genes

A useful way to gain insight into the neurogenetics of cognition-emotion interactions is through common polymorphisms in candidate genes that impact network function through modulatory effects on molecular or cellular signaling pathways. We now provide examples of several genetic variants and how they may impact particular cognitive and emotional phenotypes. The following are used as examples of this approach rather than as a comprehensive critical review of the literature, which is beyond the scope of the present article.

A number of studies have linked a common functional polymorphism (5-HTTLPR) in the human serotonin transporter gene [10] with individual differences in the functional connectivity of networks supporting both executive control [11] and emotion regulation [12,13] as well as connectivity within the default mode network [14] that is associated with self-referential processing. While the modulatory effects of such genetic variation on serotonin signaling is often discussed in relation to emotional processing, a growing literature identifies serotonin as important in modulating more generalized learning under conditions of uncertainty [15] where cognitive regulation of emotional drives is necessary to generate adaptive responses. Other studies have found that 5-HTTLPR genotype interacts with stress to bias attention towards negative emotional expressions [16], and have suggested that cognitive reappraisal may mediate the link between 5-HTTLPR genotype and risk for anxiety [17,18]. These studies of neural-network and broad behavioral phenotyping may yield more consistent results than prior studies of 5-HTTLPR phenotypes based on single brain regions and particular disorders [19,20], but given the novelty of these findings, it is possible that these approaches may similarly fail to replicate over time, and may also be dependent on gene-gene interactions [21], so an optimistic yet cautious outlook is warranted.

Common polymorphisms associated with variability in stress-related neurotransmitter signaling may also lead to specific enhancements or detriments of cognition, emotion, and their interactions (for an example of this approach, see Table 1). Common polymorphisms in the *FKBP5* gene, which plays an important regulatory function in HPA axis signaling, have been associated not only with depressive symptoms [22], but also differences in attention [23] and working memory performance [24], particularly as function of early life stress. Similar findings have emerged with polymorphisms affecting catecholamine signaling. For example, polymorphisms associated with noradrenergic function (*ADRA2B*) have been linked with emotional working memory and recognition of words read with affective intonation [25]. A functional polymorphism in *COMT*, which alters the stability of an enzyme regulating the degradation of catecholamines, has been linked with variability in executive control functions of the prefrontal cortex [26] as well as affective functions of corticolimbic networks [27]. Meta-analytic approaches have demonstrated neural and behavioral pleiotropy of *COMT*, where executive control paradigms favor one variant while emotional paradigms favor another, with opposite correlations on prefrontal activity across variants [28]. These results highlight both the utility of these approaches and the caution that needs to be taken in considering the range of ways in which these variants may influence brain function and behavior.

These are but a few of a growing number of findings from the neurogenetics literature, which collectively demonstrate the value of candidate gene studies in identifying shared molecular and cellular pathways (e.g., monoamines) supporting cognition, emotion, and their interactions with a particular emphasis on variability in underlying neural networks. An important caveat is that candidate gene studies may be biased towards false positive associations [29], in part due to a predominance of underpowered studies. The above examples are provided as a demonstration of an approach with specific associations requiring further replication and, ideally, meta-analytic synthesis as well as causal testing in preclinical model to establish the robustness and importance of these particular variants and pathways. Nevertheless, this approach may yield fruitful insights into the relationship between genetic variation with neural network signaling and cognitive and emotional phenotypes. More importantly, this approach represents the foundation from which we can identify the exact biological mechanisms through which effects of novel variants identified through genome-wide association studies shape cognition-emotion interactions.

Genome-Wide Association Studies

In addition to candidate gene studies, genome-wide association studies (GWAS) provide a hypothesis-free means of identifying common polymorphisms related to behavioral and neural phenotypes of interest. However, previously most GWAS lacked the statistical power to identify the very weak effects of individual common polymorphisms against overall genomic variation on complex phenotypes such as cognition and emotion. As the available data to power such analyses increases, in particular through multi-site consortia [30–32], novel discoveries are being reported. For example, various working groups have recently reported polymorphisms in pathways related to basic cellular functions across the brain that account for variability in cognition [30,31]. While not yet systematically mapped onto emotions (but see [33]), the location of these polymorphisms in mechanisms supporting

global functions suggest they will likely contribute to these processes as well as interactions between cognition and emotion, which exhibit shared network variance across tasks dependent on efficient neuronal activity [34] (Table 1).

Similarly, polymorphisms in genes that affect neuronal excitability may shape cognitive and emotional function through their impact on distributed brain network signaling [35–37], and have emerged as shared risk factors across psychiatric disorders [32,38]. Network strength has been linked with expression of genes that are related to synaptic function [39], and genes that impact neuronal differentiation and synaptogenesis have been shown to be related to cognitive function and mood as well as related brain structure and function [40]. Additionally, GWAS have revealed polymorphisms in genes involved in immune function that map onto emotion dysregulation [41] and default mode network connectivity [42], suggesting another avenue for future research.

While a genome-wide approach has many benefits, a limitation is that while some of the variants identified through GWAS have clear mechanisms of action, the majority are of unknown functional significance. Additionally, identified variants are often not directly involved in causal pathways but rather tag such variants through physical linkage disequilibrium. Thus, in many ways the output of GWAS represents but the first step in informing the genetic architecture of cognition-emotion interactions.

Looking Ahead

The combination of genetic association and neural network approaches have begun to illuminate mechanisms supporting cognition, emotion, and their interactions. Genetics influences on basic cellular processes and even immune functioning, highlight the broad nature of these constructs, while polymorphisms impacting established signaling pathways (e.g., monoamines, HPA axis) suggest both shared and unique influences on cognition and emotion (Figure 1). Future work will be needed to continue these cross-discipline investigations to further characterize mechanisms that support switching between global to specific networks that support cognitive and emotional processes. As consortia with ever-expanding sample sizes with shared measures of genes, cognition, emotion, and brain are developed, one future direction will be to match genome-wide approaches with network-based approaches to investigate global variability in cognitive and affective phenotypes [43]. Such efforts will also afford analyses across different temporal and spatial scales of processing [6,44,45]. For example, dynamic functional connectivity [46,47], which might better capture the momentary fluctuations in cognitive and emotional experience [46,48,49], may produce more informative phenotypes that can be targets in both candidate gene studies and GWAS. Studying the nature of neuronal network connections at the cellular level might also help to better understand the genetic influences on shaping cognitive and emotional processing [50].

Finally, it will be important to experimentally perturb identified networks to examine their necessity for cognitive and emotional function. Pharmacologic approaches in humans and transgenic animal models can be highly effective in parsing the importance of specific signaling pathways identified from neurogenetics (e.g., [51]). In parallel, the neural

networks onto which genetic polymorphisms are mapped can be manipulated in clinical populations using techniques such as transcranial magnetic stimulation [52]. All of these approaches will help lead to a more complete understanding of cognition-emotion processes and allow for more effective treatments for cognitive and emotional disorders.

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Highlights

- Cognition-emotion interactions can be mapped onto activity of neural networks
- DNA sequence variation in the genome may influence neural network activity
- Genetic variation associated with neural network structure supports shared and unique features of cognition and emotion
- Neurogenetics research can help parse mechanisms contributing to cognition, emotion, and their interactions

Figure 1. Neurogenetics of Shared and Unique Cognitive and Emotional Processes

An illustration of how certain genetic polymorphisms may impact (A) neural network structure accounting for shared variance across tasks, and (B) network reconfigurations accounting for unique variance in particular cognitive or emotional processes.

Table 1

Example of Neurogenetics of Cognition-Emotion Global and Specific Effects in the Brain

	Global	Specific
Genes	Sodium and calcium channel genes: SCN2A, SCN1B, SCN4B, CACNA1C, CACNB2	Catecholamine and glucocorticoid-related genes: COMT, FKBP5, ADRA2A
Physiology	Basic cellular function	Catecholamine signaling
Effects on Connectivity	Overall network strength [39]	Interactions between salience and executive control networks [27,43,44]
Outcome	General cognitive function [36] Transdiagnostic mental health [32]	Shift from working memory and positive mood to stimulus-response learning and anxiety/depression [22,24,26,45]

An example of common genetic polymorphisms impacting network connectivity and cognitive/emotional processing. Some polymorphisms are likely to contribute to shared variance across cognitive and emotional tasks (global column), while others are likely to impact the smaller degree of independent variance in network reconfigurations for particular processes (specific column).