Neuroscience 164 (2009) 72–87

REVIEW

GENES, COGNITION AND BRAIN THROUGH A COMT LENS

D. DICKINSON[a,b]* AND B. ELVEVÅG[a]*

[a]*Clinical Brain Disorders Branch, National Institute of Mental Health, National Institutes of Health, Building 10, 3C104, MSC 1379, Bethesda, MD 20892, USA*

[b]*Department of Psychiatry, University of Maryland School of Medicine, VISN–MIRECC, Suite 6A (BT/MIRECC), 10 North Greene Street, Baltimore, MD 21201, USA*

Abstract—Various genes are known to modulate the delicate balance of dopamine in prefrontal cortex and influence cortical information processing. Catechol-O-methyltransferase (COMT) on chromosome 22q11 is the most widely studied of these genes. Val158Met, a common, functional variant in the coding sequence that increases or decreases the enzymatic activity of the gene has been shown to impact the efficiency of prefrontally-mediated cognition, specifically executive functioning, working memory, fluid intelligence and attentional control. We review the rapidly evolving literature exploring the association between COMT genotype and cognitive performance, and illustrate how this polymorphism has served a pivotal role in characterizing various interacting dimensions of complexity in the relationship between genes and cognition. We review how Val158Met has been used to help develop and validate behavioral and neurophysiological phenotypes, as a critical tool in dissecting overlapping neural functional systems and exploring interactions within and between genes, and in exploring how gene effects on cognition are modulated by environmental, demographic and developmental factors. Despite the impressive range of findings, the COMT story is also a bracing reminder of how much work remains to translate this knowledge into practical clinical applications. Published by Elsevier Ltd on behalf of IBRO.

Key words: prefrontal cortex, executive function, working memory.

Contents

Substantial experimental work involving both humans and non-human primates illustrates the central role of the prefrontal cortex in various aspects of higher-order information processing (Bachevalier and Mishkin, 1986; Fuster, 1997; Goldman-Rakic, 1998; Mishkin and Manning, 1978; Passingham, 1975; Smith and Jonides, 1999; Ungerleider et al., 1998). Dopamine extensively modulates this information processing (Goldman-Rakic, 1998; Levy and Goldman-Rakic, 2000; Robbins, 2000) and a rich literature establishes that genetic factors affect dopamine flux in prefrontal cortex (Harrison and Weinberger, 2005). Recent work suggests complementary processing states in the prefrontal cortex and complementary roles for D1 and D2 dopamine receptors in modulating these states. In particular, tonic stimulation of D1 receptors stabilizes and sustains mental representations in active memory and protects them against distracters. Phasic D2 receptor binding supports flexible adjustment of processing, marking salient new information and permitting manipulation and rapid updating of the contents of active memory through a network that includes posterior cortex and striatum, along with prefrontal cortex (Durstewitz and Seamans, 2002; Seamans et al., 2001; Seamans and Yang, 2004). The balance of dopamine modulation in this system is delicate. An inverted "U"-shaped curve describes the relationship between dopamine levels and cognitive performance, with both suboptimal and supraoptimal dopamine activity impairing cognitive performance (Mattay et al., 2003; Vijayraghavan et al., 2007). Thus, genes affecting the dopamine system in prefrontal cortex are of great interest in attempting to unravel higher order cognitive processes.

The catechol-O-methyltransferase (COMT) gene on chromosome 22q11 is the most widely studied gene of this description and its actions in regard to dopamine and prefrontal cortex have been frequently discussed. Briefly, COMT is an enzyme that degrades cortical dopamine. Because other regulators of synaptic dopamine (e.g. dopamine transporters) are rare in prefrontal cortex synapses, COMT plays a central role in regulating prefrontal dopamine levels (Meyer-Lindenberg and Weinberger, 2006; Tunbridge et al., 2004). In rats and mice, COMT accounts for more than 60% of prefrontal cortex dopamine degradation (Karoum et al., 1994; Yavich et al., 2007). The COMT gene in humans contains a highly functional and

*Correspondence to: D. Dickinson or B. Elvevåg.
E-mail address: Dwight.Dickinson@nih.gov (D. Dickinson), brita@elvevaag.net (B. Elvevåg).

Abbreviations: COMT, catechol-O-methyltransferase; GRM3, glutamate receptor 3; Met, methionine; SNP, single nucleotide polymorphism; Val, valine; WCST, Wisconsin Card Sorting Test.

0306-4522/09 $ - see front matter. Published by Elsevier Ltd on behalf of IBRO.
doi:10.1016/j.neuroscience.2009.05.014

common variation in its coding sequence in exon 4: a substitution of valine (Val) by methionine (Met) in the peptide sequence (commonly referred to as Val158Met). The Val158Met substitution impacts the thermostability of the COMT protein and may reduce enzymatic activity by more than one-half in human brain (Chen et al., 2004; Weinshilboum et al., 1999). These findings suggest that the more stable Val allele will be associated with greater dopamine degradation and less synaptic dopamine than the less stable Met allele, that this difference will have a greater effect on regulation of dopamine and cortical physiology in the prefrontal cortex than elsewhere and, consequently, that COMT genotype will impact prefrontally-mediated cognition (Meyer-Lindenberg and Weinberger, 2006). Thus, many investigations have explored the effects of this single nucleotide polymorphism (SNP) on "executive functioning" and "working memory" associated with dopamine modulation in the dorsolateral prefrontal cortex (Aguilera et al., 2008; Bruder et al., 2005; Diaz-Asper et al., 2008; Egan et al., 2001; Mattay et al., 2003), while others have explored COMT association with "attentional control" and the functioning of the anterior cingulate cortex (Blasi et al., 2005; Krabbendam et al., 2006; Winterer et al., 2006c). A number of studies have addressed other cognitive processes with more complex associations to prefrontal cortex (Bertolino et al., 2006; Bilder et al., 2002; de Frias et al., 2004; Strauss et al., 2004).

The hypothesis of a modest association between COMT genotype and cognitive performance in healthy humans has growing support in the literature, some of which we will review hereafter. However, it seems likely that the importance of COMT in understanding the genetics of cognition lies not in the appreciation of a small, direct association of the gene to behavior but, rather, in the seminal role this gene has played as a platform for exploration of various dimensions of complexity in the relationship between genes and cognition. After stating more specifically what aspects of "cognition" are covered in this review, we go on to discuss how research using COMT as a probe has provided insights into (1) the specification of phenotypes, both (a) behavioral and (b) neurophysiological, (2) the characterization of intra- and inter-regional neural systems underpinning cognitive behavior, (3) haplotype, gene-gene interaction, and gene-environment interaction effects on cognition, (4) demographic and developmental effects on gene-cognition associations, and (5) the role of genes in the interplay between cognition and emotion.

PREFRONTAL COGNITION

The current review is concerned with the genetics of what we will call "prefrontal cognition," most simply, the set of cognitive abilities subserved by the prefrontal cortex. This is a narrower focus than the broadest conceptions of cognitive ability, including "g" or "general cognitive ability" or "general intelligence," which are addressed by other contributors to this special issue. Yet, as is readily apparent from the literature, this narrower focus still encompasses a frustratingly diverse and overlapping set of cognitive constructs—"executive functioning," "working memory," "fluid intelligence," "attentional control"—that are often invoked without a careful delineation of the specific cognitive processes involved, the underlying neurobiology, or the precise manner in which the construct is operationalized by a given cognitive task. Table 1 provides a hierarchy and definitions of these cognitive constructs, and connects them to brain regions, specific cognitive processes and cognitive measures. Not all readers will accept the schema (Sabb et al., 2008), but it highlights the need for precision in attempting to synthesize research findings. Terminology used to describe prefrontal cortex-related cognitive constructs has been a moving target. The term "executive functioning" is a case in point. Although widely used for many years by neuropsychologists, "executive functioning" is an underspecified umbrella term usually defined with reference to a very loosely connected set of problem-solving processes (e.g. "concept formation," "mental flexibility," "planning") and specific cognitive measures (e.g. the Wisconsin Card Sorting Test [WCST], the Tower of Hanoi Test) (Miyake et al., 2000). Newer formulations—"executive functioning/working memory" (Diaz-Asper et al., 2008; Ho et al., 2005)—do not eliminate confusion. First, working memory is generally conceptualized as a subcomponent of executive functioning; the latter term is understood to encompass additional capacities, such as abstract concept formation. Second, working memory itself comprises many distinct processes such as encoding and short-term information storage, on-line manipulation, and integration and updating of new information (Awh et al., 1998; Baddeley, 1992; Jonides et al., 1998). It is not readily apparent how to avoid these cognitive constructs in a review of this sort. However, we will try to be consistent and clear about how we are using specific cognitive constructs as we proceed. Table 1 serves as a guide to and partial glossary of the terminology that will be used.

COMT and the specification of behavioral and neurophysiological phenotypes

Behavioral phenotypes. The first significant wave of work on the relationship between COMT and cognition focused on individuals with schizophrenia and made use of the WCST (Berg, 1948), a complex measure of concept formation, mental flexibility, and ongoing task monitoring and strategy adjustment (Bilder et al., 2002; Egan et al., 2001; Ho et al., 2005) (see Fig. 1). Because of concerns about medication, symptom and other chronic disease effects in patients, this early work also included unaffected relatives of patients and healthy controls. Schizophrenia and the WCST were natural choices to test the COMT hypothesis for several reasons: schizophrenia patients have shown consistent impairments on the measure; beginning in the 1980s, functional neuroimaging studies showed dorsolateral prefrontal cortex activation during performance on the task (Carter et al., 1998; Weinberger et al., 1986); and dopamimetic drugs were shown to enhance the prefrontal physiological response on this task