CORRESPONDENCE

The Role of COMT Val158Met i

To the Editor:

Does the meta-analysis of Barnett *et al.* (1), "Meta-Analysis of the Cognitive Effects of the Catechol-*O*-Methyltransferase Gene Val158/108Met Polymorphism," justify their conclusion that "Despite initial promising results, the *COMT* Val158/108Met polymorphism appears to have little if any association with cognitive function"? We submit that this statement illustrates the potential shortcomings of a purely statistical evaluation of a domain of inquiry that has penetrated to the deeper level of biological mechanisms. Initial association studies of *COMT* with cognition and other behaviors (stress sensitivity and pain response) were themselves supplemented with convergent brain-imaging data on the basis of predicted effects of cortical dopamine (DA) on the tuning of intrinsic circuitry that manages cognitive and emotional information, drug challenges based on animal literature about how modifying DA or COMT activity affects cognition and cortical tuning (e.g., tolcapone, amphetamine), and predicted epistatic effects with other genes that perturb the same cortical tuning mechanisms (e.g., *GRM3*, *GAD1*, *RGS4*, *AKT1*). Recent work in transgenic and knockout mice establishes conclusively and unequivocally that genetic variation in *COMT* dramatically alters the very cognitive functions that have been linked to it in human studies—specifically working memory, attentional control, and episodic memory (2). Does the failure of the meta-analysis by Barnett *et al.* to confirm this effect in humans, based on their statistical approach, mean that despite the conclusive effects of *COMT* on cognition in the mouse, it does not have such effects in humans? This is not likely, in our view. What is much more likely is that their approach to meta-analysis of the association of *COMT* with cognition has missed issues critical to understanding how a gene such as *COMT* might affect human cognition.

In their meta-analysis, but contrary to their conclusion, Barnett *et al.* did find a robust association between Val158Met and IQ, for which there were the most data available, with no evidence of study heterogeneity nor ascertainment bias, nor an effect of patient–nonpatient status, sex, or ethnicity. IQ measurement assessment tools are likely to be the most comparable across studies and least confounded. Notably, several of the other neurocognitive phenotypes studied by Barnett and colleagues demonstrated substantial between-study heterogeneity. Perhaps their meta-analysis would have benefited from a more refined appreciation of the psychometric properties of assessment tools used in individual studies. *COMT* is widely expressed in the brain and has various functions, but in the frontal cortex, it is not a (gene for) N-back or Wisconsin Card Sorting task performance. COMT plays an important role in frontal cortex DA function, critical for the stabilization and excitability profile of intrinsic microcircuits that handle certain types of information. The role of *COMT* functional variation in cognition is supported by imaging and cognitive studies showing that the *COMT* genotype more strongly predicts measures related to the manipulation of information rather than to its storage. This, we also believe, explains some of the discrepancies in the clinical genetic association data. For example, some N-back tests are storage loaded and require only yes-no responses to a match (3), whereas others require a precise response to each stimulus (4), resulting in higher updating and interference management demands. Cognition is not a singular construct, nor is working memory, and tests labeled "the N-back task" can be non-equivalent. It appears that the closer one gets to frontal cortical neurobiology tuned by dopamine, the stronger the effect of *COMT* functional genetic variation (5). It is interesting to note, and not mentioned in the Barnett *et al.* report, that in the same sample of Greek recruits, a more refined analysis using RT variability in the Continuous Performance Test—Identical Pairs Version resulted in a positive *COMT* genotype finding. Val alleles were associated with a less stable response profile, even though overall error rates did not differ. This finding is in fact consistent with the basic science evidence that prefrontal DA is critical for response variability and stability and perhaps reflects the role of DA in stabilizing a target representation among competing distracters—that is, tuning it (6). These results also nicely illustrate the point that it is not the name of the cognitive test that counts; rather, what matters is the cognitive demand of the paradigm and how that demand is measured.

It is also important to appreciate differences in the genetic and experiential background of the populations analyzed and differences in the genetic technologies used. These distinctions may be important in the context of the complex genetics of *COMT*, which contains functional loci in addition to Val158Met that have been shown to modulate the val/met effect (7). Nothing is known about the genetics of *COMT* Val158Met in Greeks or the southeastern European populations studied by Stefanis *et al.* (8) vis-à-vis other functional loci in the *COMT* region. For example, Nackley *et al.* (7) described a set of linked *COMT* alleles (haplotype) altering translatability of *COMT* mRNA. When the higher-activity Val allele is found on the high-expression genetic background, it behaves as a high-activity allele, but it does not do so otherwise, and the frequency of that higher-activity Val allele is only approximately 10%. The frequency of the two varieties of Val alleles has not been reported in Greeks. As the Stefanis group has pointed out, it would be important to genotype other *COMT* markers in this population. Many issues could also be considered in the evaluation of the Stefanis report, and indeed some of those same issues could be identified for other reports analyzed by Barnett *et al.* For the Stefanis report, these included genotype failure rate (10%), the frequency of completion of the neuropsychological task (16% noncompleters for the N-back), and the potential that young conscripts may be differentially affected by the stress of cognitive testing or illicit or licit substance use, which influences dopaminergic tone.

As shown by the foregoing discussion of a single study (8) that strongly drove the conclusions of Barnett *et al.*, identifying sources of heterogeneity and error is not an easy task. However, it was the responsibility of Barnett *et al.* to ascertain whether phenotypes and data sets were suitable for their meta-analysis, and, if they were, to proceed to contend with the problems of heterogeneity. In their conclusion, and despite their finding a significant relationship of *COMT* to IQ, they attempted to overturn a compelling body of data from many levels of biological analysis that low-activity *COMT* genotypes have more efficient frontal cognitive function. They had the primary responsibility to explain the dissonance between statistical findings and biology, or to parse conclusions more modestly.

We close by emphasizing that this letter is not meant to be purely critical or to suggest that the problems we have pointed out are unique to the Barnett *et al.* study. We also think that the points we raised in the context of this study suggest a

difference in approach to understanding genetic effects on behavior. One is primarily statistical and based on *p* values and power analyses; the other is based on convergent neurobiological evidence and prior probabilities derived from an understanding of the basic science of the gene and of brain function related to human behavior.

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Some of the authors (DG, TEG, DRW) have a patent pending, filed on behalf of the U.S. government. This patent is on the role of COMT Val158Met in cognition and other human phenotypes. Dr. Goldberg has received consulting fees from Merck, Wyeth, Pfizer, and Organon. He receives royalties for use of the Brief Assessment of Cognition in Schizophrenia (BACS) in clinical trials. Dr. Malhotra is a consultant to Vanda Pharmaceuticals, Wyeth, Janssen, and Bristol Meyers Squibb.

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