Biological Psychiatry

Lack of Meta-Analytic Evidence for an Impact of *COMT* Val158Met Genotype on Brain Activation During Working Memory Tasks

To the Editor:

Imaging genetics, that is, the investigation of neuroimaging correlates for genetic variation, have been highly popular over the last decade. Within this framework, schizophrenia risk genes and, in particular, the effect of the Val158Met (rs4680) single nucleotide polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene on activations related to working memory have been studied extensively. *COMT* mediates the degradation of dopamine in the synaptic cleft, and its Val allele is associated with lower working memory performance (1). It is assumed that these effects are due to increased enzymatic activity in Val allele carriers leading to decreased prefrontal dopamine concentration, causing changes in regional activity during working memory tasks. However, is there reliable evidence to support this conclusion?

To investigate whether there is converging evidence from imaging genetics studies for *COMT* genotype effects on working memory-related activation, we performed a quantitative coordinate-based meta-analysis using the activation likelihood estimation (ALE) approach (2). Relevant studies were retrieved through PubMed and Google Scholar, review articles, and reference tracing. Inclusion criteria are reported in the legend to Table 1. In total, 14 studies published between 2004 and 2014 met inclusion criteria (Table 1). Together, these studies enrolled a total of 995 subjects (920 healthy subjects and 75 schizophrenia patients). Although most studies tested for linear effects of increasing or decreasing Val alleles, not all publications used this contrast (cf. Table 1). To establish a standardized classification for assessing the convergence of results despite methodical heterogeneity of the original studies, we summarized different contrasts by focusing on the number of Val alleles. In the following, we thus refer to hyper- or hypoactivation associated with a higher number of Val alleles in the original contrast (e.g., Met/Met > Val/Met > Val/Val, but also, e.g., Met allele carriers > Val/Val). Among the included studies, eight studies reported only hyperactivations, whereas three studies reported only hypoactivation, and four studies reported both hyper- and hypoactivation with higher numbers of Val alleles. To determine whether genotype effects showed convergent results regardless of diagnosis, both the healthy controls and the schizophrenia patients were included in a first analysis. We also conducted a subanalysis that included only the healthy controls.

ALE meta-analysis across all reported findings was conducted (3), and ensuing statistical parametric maps were thresholded at $p < .05$ [cluster-level family-wise error (FWE), corrected for multiple comparisons, cluster-forming threshold at voxel level $p < .001$ (2)]. We first tested whether there were convergent results (aberrant activations) across hyper- or hypoactivation associated with a higher number of Val alleles in the original contrast. We conducted additional analyses in all contrasts testing for convergence only among those studies reporting increased and decreased activation associated with a higher number of Val alleles in the original contrast, respectively. Because diagnostic status, age, and also paradigm might lead to a heterogeneity within the data that might obscure otherwise significant results, we also realized several supplementary analyses of homogeneous subgroups with regard to these parameters. As in our main analysis, all of these exploratory meta-analyses were analyzed for a significant convergence of both hyper- and hypoactivation separately, as well as aberrant activations (joint analysis of hyper- and hypoactivation).

We did not retrieve any significant results for any of these meta-analyses. Subthreshold analyses revealed that the highest likelihoods for activation differences due to the Val158Met polymorphism across both healthy controls and schizophrenia patients were located (Figure 1) in the right inferior parietal lobe and the right dorsolateral prefrontal cortex. These findings are thus in line with the current hypotheses in the field, but it must be reiterated that they did not reach whole-brain corrected significance.

To the best of our knowledge, this is the first observer-independent coordinate-based meta-analysis of imaging genetics studies. Importantly, multiple subanalyses of more homogeneous samples with regard to diagnostic status, age, and paradigm all failed to yield significant results (minimal p value across all analyses of .2414). These findings strongly corroborate the negative finding of the main analysis and argue against study inhomogeneity as an explanation of that null result. However, more detailed subanalyses may be warranted, once a higher number of original studies becomes available.

The lack of convergent evidence for aberrant activations associated with increasing Val alleles in the original contrasts implies three conclusions. First, our results emphasize the need for whole-brain-based approaches in imaging genetics to avoid self-fulfilling prophecies [i.e., analyses limited to the frontal lobe reporting significant changes due to *COMT* genotype (cf (4)]. Although region of interest-based approaches are more sensitive, this advantage comes with a potential bias toward brain regions defined by (potentially subjective) expectations. The frequent use of a priori restricted inference spaces, therefore, may suggest stronger convergence than actually present when considering whole-brain findings, as shown by our analysis. Second, our findings question the common notion of a greater penetrance of risk gene effects on an imaging endophenotype than on a behavioral phenotype level (5). Although our method certainly does not allow inference about effect sizes, the lack of significant spatial convergence urges caution in that respect. Third, the pivotal role of sufficient sample sizes becomes obvious due to these considerations.

There are several limitations that need to be acknowledged. Although ALE is a well-validated and widely used coordinate-based meta-analytic approach (2), it stands to reason that an image-based data pooling may have provided a greater sensitivity. There was also a considerable heterogeneity of comparisons between genotypes that needed to be categorized by standardized labels to achieve comparability. This is

http://dx.doi.org/10.1016/j.biopsych.2015.02.030
ISSN: 0006-3223

Table 1. Overview of Studies Enrolled in This Meta-Analysis

Study, year (ref)	No. of Healthy Subjects	No. of Schizophrenia Patients	No. of Smallest Genotype Group	Populations Enrolled	Task Used by Each Study	First-Level Contrast	Group Level Contrast	Covariates
Bertolino *et al.*, 2004 (8)	-	20	3	Adult patients suffering from an acute psychotic episode	n-back	2-back, 1-back - 0-back	Val/Val – Val/Met – Met/Met	Performance, gender
Bertolino *et al.*, 2006 (9)	62	-	14	Healthy adults	n-back	2 back - 0-back	Val/Val – Val/Met – Met/Met	NA
Bertolino *et al.*, 2008 (10)	72	-	16	Healthy adults	n-back	2-back, 1-back – 0-back	Val/Val – Val/Met – Met/Met	NA
Caldu *et al.*, 2007[a] (11)	75	-	17	Healthy adults	n-back	2-back – 0-back	Val/Val – Val/Met – Met/Met	NA
de Frias *et al.*, 2010 (12)	22	-	11	Healthy aging adults (50-65 years)	n-back	2-back vs. baseline	Val/Val – Met/Met	NA
Dumontheil *et al.*, 2011 (13)	81	-	31	Healthy participants in nine different age groups (6, 8, 10, 12, 14, 16, 18, 20, and 25 years of age)	Grid task (dot matrix)	Visuospatial WM task > visual control condition	Val/Val - Val/Met - Met/Met Met carriers, Val dominance model, Met dominance model	Age, sex
El-Hage *et al.*, 2013 (14)	90	-	40	Healthy adults	n-back	3-back, 2-back, 1-back – 0-back	Val/Val – Met carriers	NA
Ho *et al.*, 2005[b] (15)	-	13	6	Adult schizophrenia patients and healthy adults	n-back	Visuospatial 1-back – visual control condition	Val/Val – Met/Met	Gender, education, IQ
Meyer-Lindenberg *et al.*, 2006 (16)	126	-	28	Healthy adults	n-back	2-back – 0-back	Val/Val – Val/Met – Met/Met	Gender, age, task performance
Nyberg *et al.*, 2014 (17)	197	-	43	Healthy subjects	Modified Sternberg (LTR/PLUS)	Manipulation - Maintenance	Val/Val – Val/Met – Met/Met	NA
Pomarol-Clotelet *et al.*, 2010 (18)	31	42	8	Schizophrenia patients and healthy adults	n-back	2-back, 1-back - baseline	Val/Val – Met carriers	Performance
Qin *et al.*, 2012 (19)	39	-	7	Healthy adults	n-back	2-back – 0-back	Met/Met vs. Val-carriers	NA
Sambatero *et al.*, 2009 (20)	75	-	20	Healthy adults (broad age range)	n-back	1-back – 0-back	Val/Val – Val/Met – Met/Met	Handedness
Stokes *et al.*, 2011 (21)	50	-	13	Healthy adults	n-back	2-back – 0-back, 2-back – rest (deactivation)	Val/Val – Val/Met – Met/Met	Gender
Total *N*	920	75	NA					

Overview of the studies enrolled in this meta-analysis, with the total number of subjects enrolled and the smallest genotype groups. Inclusion criteria were: 1) functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies published until July 2014; 2) original peer-reviewed studies; 3) whole-brain assessment not restricting analysis or inference to a priori regions of interest; 4) studies reporting comparison of only *COMT* genotypes, not exclusively comparisons with other genotypes or multi-gene interactions or comparison between *COMT* genotypes between diagnostic groups (e.g., between Met/Met carriers in a patient population and healthy controls); 5) if inclusion of patient populations with diagnoses according to ICD-10 or DSM-IV by original studies: studies reporting activations that are assigned either to the patient population or to healthy controls, not activations of a diagnostically mixed group of a given *COMT* genotype (e.g., both the schizophrenia patients and the healthy controls included in one genotype group); 6) complete reporting of peak coordinates of all clusters in stereotactic space (Talairach/MNI); 7) bidirectional analysis of contrasts (i.e., analysis of both hyper- and hypoactivations for a given contrast).

NA, not applicable; WM, working memory.

[a]Caldu *et al.* (11) did not report any significant effects for *COMT* Val158Met genotype inference and, thus, did not contribute to the meta-analysis.

[b]Ho *et al.* (15) reported Val158Met genotype effects on cerebral blood flow, determined by [^{15}O]$H_2$0 PET, whereas all other studies used fMRI.

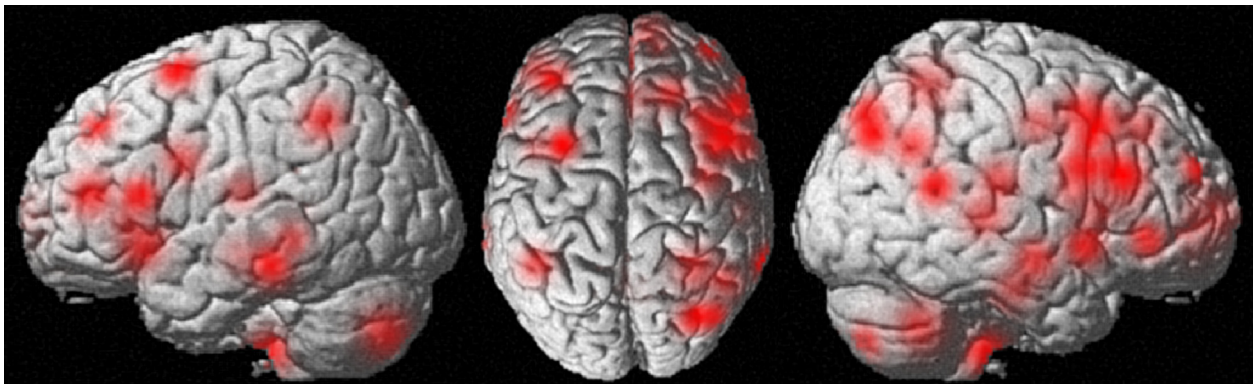

Figure 1. Subthreshold analysis of aberrant activations due to *COMT* Val158Met genotype including both healthy subjects and schizophrenic patients. Shown are the subthreshold results of an analysis of all activations that met inclusion criteria. In addition to increasing statistical power, we applied this approach to investigate, whether there were common effects of *COMT* genotype on working memory across diagnoses. Both of the meta-contrasts of our meta-analysis, that is, both the hyper- and the hypoactivation associated with a higher number of Val alleles in the original contrasts ("aberrant activations") were jointly analyzed for spatial convergence. Highest likelihoods for convergent results were located in the right inferior parietal lobe and the right dorsolateral prefrontal cortex. However, it deserves to be emphasized that we did not retrieve any significant results for any contrast, regardless of the mode of inference.

worth revisiting once a sufficient number of homogeneous experiments (reporting, e.g., linear contrasts between all three genotypes) becomes available. Finally, a higher number of original studies would also increase power in future meta-analyses, although similarly powered meta-analyses repeatedly found significant convergence (6,7).

We would thus conclude that contrary to common perception, there is presently no (significant) spatial convergence of imaging genetics findings on the most frequently studied association, that is, that between *COMT* Val158Met genotype and working memory-related activations. We would thus argue that more caution needs to be exercised in this field.

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Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Nov 4, 2014; revised Feb 20, 2015; accepted Feb 23, 2015.

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