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Response to Comment on “Genetically Determined Differences in Learning from Errors”

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Since the publication of our findings, further genetic and pharmacological studies have bolstered our conclusion that dopamine D2 receptors are essential for performance monitoring and learning. Although the functionally complex dopamine D2 receptor gene polymorphism DRD2-TAQ-IA may also affect cellular signaling components, the accumulated evidence supports the notion that our findings were mediated by differential D2 receptor density.

We thank Lucht and Roskopf (1) for pointing out the inherent complexity of the genetic locus under investigation in our recent report (2). In fact, the way by which the DRD2-TAQ-IA polymorphism exerts its functional impact is not completely understood. Nevertheless, the main conclusion of our study—that dopamine plays a major role in learning from errors—remains robust.

The vast majority of studies have shown a reduction of dopamine D2 receptors for subjects carrying the A1 allele (3–8). Contradictory findings (9) may be explained by the particular populations used (e.g., schizophrenia patients, in which pathological changes in receptor densities may mask genetic effects) and different, potentially less sensitive, imaging techniques (such as single-photon computerized tomography instead of positron emission tomography or autoradiography).

The question remains, however, how a mutation located less than 10 kilobases downstream

of DRD2 within a protein-coding region of the adjacent ankyrin repeat and protein kinase domain-containing protein 1 (ANKK1) gene (10) can affect receptor expression. A recent study by Zhang *et al.* (11) investigated 23 polymorphisms within the D2 gene. The authors report that expression of the short splice variant of the D2 receptor was less than that of the long splice variant; the difference was related to two intronic single-nucleotide polymorphisms (SNPs), rs2283265 and rs1076560. Both SNPs were associated with an increased functional magnetic resonance imaging signal in the striatum and the prefrontal cortex during a working memory task. At the same time, these SNPs were associated with reduced performance in the working memory task. The minor allele of the two SNPs shows strong linkage disequilibrium with the A1 allele of the DRD2-TAQ-IA polymorphism [$D' = 0.855$ (11)]. It may be this linkage that causes DRD2-TAQ-IA to be a marker for dopamine receptor density, as indicated by numerous studies (3–8). As we discussed in (2), the finding of a higher 3,4-dihydroxyphenylalanine uptake of A1 allele carriers (12) adds evidence supporting a functional role of this polymorphism for dopaminergic transmission.

At the behavioral level, converging evidence supporting our findings showing genetic influences on preference and avoidance learning in humans comes from a recent study (13). It shows an influence of the C957T polymorphism (rs6277 located in exon 7) of the DRD2 gene on preference/avoidance learning in human volunteers. Subjects carrying at least one C allele (C/C homozygous or C/T heterozygous, associated with lower D2 receptor availability) showed impairments on avoidance learning, consistent with our findings in the A1+ subjects. These correlative findings are bolstered by a study in which pharmacological challenge with a D2 receptor agonist impaired reinforcement learning (14).

Taking these converging findings into account, our study yields strong evidence for the role of dopamine in feedback-based reinforcement learning. Hence, although the genetic regulation of D2 receptor density is highly complex and requires further investigation, the DRD2-TAQ-IA polymorphism in our opinion provides a useful marker for dopamine activity, enabling hypotheses testing of dopaminergic transmission in cognitive functions.

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