LETTER

REPLY TO LYON ET AL.: Self-regulation and the *foraging* gene: From flies to humans

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Below we directly address Lyon et al.'s (1) critique of Struk et al. (2). We do not debate the utility of genome-wide vs. candidate gene studies of complex behavioral phenotypes (3).

The Struk et al. (2) paper uses a hypothesis-driven approach to test the association of the rs13499 single-nucleotide polymorphism (SNP) in the *PRKG1* gene with the locomotor/assessor self-regulation trait. The test is a straightforward single hypothesis-driven test of one SNP in one gene. Our hypothesis is derived from mechanistic studies of *PRKG1*'s ortholog (*foraging*) in *Drosophila* and other species (4).

From Struk et al.'s (2) analysis of CommonMind data: +SVA (synapse data) a P value of $P = 0.00232$ was observed for this one hypothesis that was tested, which also passed an adjusted false discovery rate (FDR) 0.1 (genome-wide adjustment for expression quantitative trait locus [eQTL] analysis). Lyon et al. (1) report CommonMind +SVA (synapse data) with FDR at 0.05 to 0.1, confirming the one reported in Struk et al. Lyon et al. also investigated the SNP genotype and gene expression correlation with –SVA data (unadjusted for hidden confounds), which yielded a larger P value (albeit still passing a standard single-hypothesis testing threshold). However, it is well known that technical and other artifacts drastically impact eQTL analysis, and hence SVA adjustment is now the standard in the field.

Lyon et al. (1) use BrainSeq (5) to suggest a lack of replication of the rs13499 SNP association with gene expression we reported from CommonMind. Expression levels of *PRKG1* are particularly low in brain tissue (e.g., as apparent from GTEx portal), making it difficult to detect associations. The sample from BrainSeq is also more heterogeneous than from CommonMind in terms of age ranges (6).

While Lyon et al. (1) are correct that A is the increasing allele, not C, this does not impact the conclusions of our study. *foraging* gene expression is complex, and the effect of higher or lower expression varies by isoform, phenotype, and species (4).

Lyon et al. (1) claim to test the validity of our rs13499 SNP (in the 3′ untranslated region) by investigating the rs1904701 SNP found in the 5′ untranslated region. However, it is erroneous to make assumptions about the effect of other SNPs in *PRKG1* based on associations found for rs13499. In general, effects of SNPs within a gene can be highly specific to the location of the SNP in the gene. For *PRKG1* specifically, different SNPs might affect different gene products (7–9).

Finally, Lyon et al. (1) attempt to compare our results, which use narrow, precisely defined phenotypes, to those from larger studies that use broader phenotypes, which clearly reveals a lack of understanding of the phenotype studied in Struk et al. (2). In Table 2 of ref. 1 Lyon et al. make use of metrics they suggest "correlate with goal pursuit." However, there is no evidence that these variables measure the same constructs assessed in Struk et al. Their measures are linked to emotional stability and well-being, constructs distinct from both self-regulatory variables (e.g., trait self-control) and the regulatory mode constructs we tested. Similarly, neuroticism connects to well-being but is not a personality trait directly assessing goal pursuit (10, 11).

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