# Overdominance and Heterosis, when "*in medio* (may) *stat virtus*"

## A reply to Smucny

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*Aristotle (384–322 BC), in his Nicomachean Ethics, first conceptualized the widely known Latin phrase "In medio stat virtus" (virtue stands in the middle), defining a virtue as a balance point between a deficiency and an excess of a trait.*

In his informative review, Smucny (2018) describes our study as one of the first neuroimaging genetics investigations using large databases. Since such large-scale resources are becoming increasingly available, we are at the beginning of an exciting development, expecting a steep increase in the number of studies investigating the genetic contributions to brain function in the coming years. Several large-scale datasets in various age groups are available and currently being extended, including IMAGEN and PNC used in our study, the Adolescent Brain Cognitive Development (ABCD) project (https://abcdstudy.org/scientists-protocol.html ), the UK Biobank (http://www.ukbiobank.ac.uk), and the Human Connectome Project (HCP https://www.humanconnectome.org), among others. Large-scale data consortiums focusing on clinical populations, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI http://adni.loni.usc.edu/), are especially promising with regards to the clinical relevance emphasized in Smucny's review. Most of future functional neuroimaging genetics studies are likely to be performed on resting state functional MRI data. Task-free fMRI is included in most large-scale neuroimaging protocols, and is more readily comparable across different cohorts promoting replication across datasets. Resting state data lend themselves easily to exploratory approaches (Biswal et al., 2010), but by their very nature will focus efforts on intrinsic functional brain circuits. However, many datasets include fMRI from a few select cognitive tasks, permitting hypothesis-driven investigations into the genetics of neural activity underlying specific high-level cognitive processes as exemplified in our study.

The core message of Smucny's review revolves around our observation of an overdominant effect (aka heterozygote advantage) at the common *CHRNA4* rs1044396 single nucleotide polymorphism (SNP) (Sadaghiani et al., 2017). We emphatically agree with Smucny's focus on this aspect of our study. As progress in the neuroimaging genetics field clips along, we encourage researchers to include models of non-linear allele contributions in their investigations. It should be acknowledged that the search for overdominant loci has been largely overlooked by the scientific community leading to a constant bias towards additive and dominant

models in most of the genetic-association studies carried out so far. Indeed, it is typical to model genetic variation using an additive framework, but the architecture of complex traits is arguably more complex than the additive model allows (Hemani et al., 2013). Epistatic phenomena have been frequently neglected in complex trait studies, and only recently has the scientific community started to investigate gene-gene and gene-environment interactions using efficient tools able to overcome the computational burden linked to such analyses.

Epistasis has been often approached as a genetic phenomenon occurring between multiple loci, ideally located far apart on the genome, but linked by their functional role. However, epistasis may occur at a single locus, leading to overdominance, which is central to processes of heterosis and inbreeding depression (Hemani et al., 2013). Overdominance has been identified in molecular studies as well (molecular heterosis), both in humans and in animal models (Comings and MacMurray, 2010; Hemani et al., 2013). In humans, the best-known examples of overdominance have been described for *HBB* in relation to sickle-cell anemia (Aidoo et al., 2002), the *KLOTHO* gene (Arking et al., 2005; Dubal et al., 2014) and the *PRPN* gene (Palmer et al., 1991).

Evolutionary genetics and biology provide a strong basis for the existence of heterosis, as largely demonstrated in agricultural and animal genetics (Birchler et al., 2006; Draghi and Whitlock, 2015). However, the search for overdominant loci through genome-wide association studies (GWAS) presents several methodological drawbacks which limit its feasibility, especially when applied to a case-control study design (e.g. effective departures from Hardy-Weinberg equilibrium due the presence of selective pressures on heterozygotes; increased frequency of inbred subjects in one study group; subtle population stratification biases not captured through the adjustment by principal components).

The interpretation of overdominance at the molecular level can be very challenging, especially for genetic polymorphisms that do not change the coding sequence, such as synonymous, non-coding, intronic, 5'- and 3'-UTR SNPs. In this scenario, the SNP may alter gene-expression at the post-transcriptional level, by expanding (or reducing) the range of binding-sites for transcription factors, or by changing the splice-isoform ratios in a way that heterozygotes have a molecular advantage over homozygotes [e.g., splicingQTL (Monlong J et al. 2014)]. At the same time, heterozygotes may display a phenotypical advantage over homozygotes just because of their intermediate gene-expression level providing them a

functional, physiological optimum, as reported in our paper on *CHRNA4* rs1044396 and cingulo-opercular network activity (Sadaghiani et al., 2017)

Overall, we greatly encourage future efforts in the search of overdominant loci, both for quantitative and qualitative traits, especially because overdominance may occur at SNPs with very high minor allele frequency (MAF), thus affecting a large portion of the human population (as exemplified by *CHRNA4* rs1044396). This may help us to better understand the genetic architecture of common traits, the possible evolutionary pressures acting at a certain locus, and its underlying biology. The socio-demographic processes that occurred after World-War II have greatly affected the global population (Bittles and Black, 2010), both at the social and the biological level, by drastically reducing the level of inbreeding and, conversely, by increasing the level of ethnic admixture. Heterozygous effects can be profound and warrant substantial further investigation, especially at the behavioral/neurological level, where we expect most of the evolutionary pressures will be focused in the coming decades.

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