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Discussions

Polygenicity and GxE Interactions Do Not Imply Biological Arbitrariness: Response to Commentaries by Deary et al. and Matzel & Sauce

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We respond to two commentaries about our recent paper on molecular biology and human intelligence. They rightly point out the complexities involved, especially from polygenicity and gene X environmental interactions. Our view is that these factors do not negate an underlying biology of intelligence that can be accessible by advances in genetic and neuroscience technologies and analytic methods. We see the complexities as inspiring challenges that can be addressed rather than permanent roadblocks that discourage research.

We appreciate the thoughtful commentaries by Deary et al. (Deary et al., 2026) and Matzel and Sauce (Matzel & Sauce, 2026) on our article Toward a Molecular Biology of Human Intelligence (Gargus & Haier, 2025). Both responses highlight the formidable difficulty of linking genomic variation, neural systems, and cognitive phenotypes. Our aim was not to reduce intelligence to a small set of genes or deterministic pathways. Rather, we proposed a biologically constrained framework intended to organize the rapidly expanding empirical literature connecting genomics, neurobiology, and psychometrics. Intelligence must ultimately be implemented by physical neural systems operating under metabolic and developmental constraints. Our goal was, therefore, heuristic and integrative: to identify plausible biological bottlenecks through which the large number of small genetic effects identified by genome-wide studies might converge. This perspective is consistent with the observation that the modern human genome is ~99.8–99.9% identical to that of Neanderthals, indicating that relatively small genetic differences can produce substantial phenotypic consequences.

A central theme raised by both commentaries concerns the extreme polygenicity of intelligence and the difficulty of inferring mechanism from genetic associations with very small individual effect sizes. We fully agree that intelligence differences arise from the cumulative influence of many variants and that GWAS signals alone cannot provide direct mechanistic explanations. However, polygenicity does not imply biological arbitrariness. Many complex traits characterized by thousands of variants nonetheless converge on identifiable biological pathways or system-level constraints. Moreover, the high heritability estimates observed in classical twin studies are increasingly approached as GWAS sample sizes expand, suggesting that the polygenic architecture identified by modern genomics is converging toward the same upper bound inferred decades ago from behavioral genetics; see (Wolfram et al., 2026).

The interpretation of these twin studies is not fully explored in Matzel and Sauce's comments – which depends critically on comparisons between monozygotic (MZ) and dizygotic (DZ) twins raised in the same family environment. Across decades of research, MZ twins raised together correlate approximately r ≈ 0.85–0.88 in IQ, whereas DZ twins raised together correlate about r ≈ 0.55–0.60. Because both types of twins share the same household environment, this difference directly reflects genetic influence. Using the classical Falconer estimator $h^2 = 2(r_{MZ} - r_{DZ})$, these values yield heritability estimates near 0.50–0.60. Additional evidence comes from twins raised apart. Monozygotic twins raised apart still correlate around r ≈ 0.70–0.75, indicating that removing the shared family environment reduces similarity only modestly. Indeed, the reduction in similarity from MZ twins raised together (~0.86) to those raised apart (~0.70) is substantially smaller than the difference between MZ and DZ twins raised in the same environment (~0.26). These comparisons demonstrate that genetic influences substantially exceed the effects attributable to shared family environment. Adoption studies provide convergent evidence: correlations between adoptive parents and adopted children decline toward zero in adulthood, while correlations with biological parents increase; see reviews (Haier, 2023; Haier et al., 2024) . These findings underscore that gene–environment correlations amplify genetic effects rather than replace them.

Within this context, our paper emphasizes that polygenic signals may converge on specific biological systems. Despite thousands of loci identified across major GWAS of educational attainment, general intelligence, and cognitive performance (Davies et al., 2018; Lee et al., 2018; Savage

et al., 2018) only two genes - the two we explicitly discuss - *CADM2* and *SLC39A8* - reach genome-wide significance across all three datasets. These genes were not selectively chosen; there are not thousands of others we or others could have chosen; they emerge as the only overlapping signals across the full set of loci. Both converge on core neuronal biology. *CADM2* encodes a synaptic adhesion molecule involved in organizing excitatory synaptic connectivity, while *SLC39A8* encodes a metal transporter that regulates manganese homeostasis required for enzymatic cofactors involved in glycosylation and oxidative stress defense. The fact that only two genes replicate across studies involving thousands of loci illustrates both the extreme polygenicity of cognitive traits and the possibility of convergence on fundamental neuronal mechanisms.

An important implication of this convergence is that the biological pathways highlighted by genomic studies align closely with the energetic constraints imposed by cortical evolution. Association cortex - and particularly hubs of the default mode network such as the precuneus - represents some of the most metabolically demanding neural tissue in the human brain. These regions maintain the highest baseline glucose utilization observed in resting-state imaging studies and support long-range integrative processing across distributed cortical networks. Sustaining such energetically expensive computation requires highly stable synaptic signaling and tightly regulated neuronal metabolism. The genes that reproducibly emerge across large-scale GWAS of cognitive traits converge precisely on these requirements. *CADM2* contributes to the organization and stabilization of excitatory synaptic contacts that support long-range cortical integration, while *SLC39A8* regulates manganese-dependent enzymatic processes essential for glycosylation, mitochondrial function, and oxidative stress defense. These processes are critical for maintaining neuronal energetics and protecting high-activity cortical networks from metabolic instability. In this sense, the extreme polygenicity observed in genomic studies may reflect numerous small perturbations affecting the efficiency and stability of neural systems that support energetically costly integrative cognition. Polygenicity therefore does not imply biological arbitrariness; rather, it may reflect many small perturbations acting on a limited set of neural systems whose metabolic stability is required to sustain large-scale cortical integration.

Matzel and Sauce emphasize that the pathway from genotype to cognitive phenotype is long and mediated by environmental experience. We agree with this characterization and regard gene–environment interplay as central to cognitive development. However, the existence of gene–environment correlations does not negate biological constraints. Developmental amplification requires underlying biological variation upon which environmental processes act. Evidence from model organisms is instructive. In yeast, where simplicity of the organism allows GxE experiments to approach saturation, Smith and Kruglyak demonstrated that roughly 20–50% of genetic variance is environment-dependent (Smith & Kruglyak, 2008), meaning that the majority of variance remains attributable to genomic architecture. Similar patterns are observed in more complex organisms: studies in Drosophila and mice show that environmental context can modulate 30–60% of genetic effects, yet these interactions still converge on core biological pathways including metabolism, stress responses, and synaptic function. In humans, by contrast, only a tiny number of well-established gene-by-environment interactions have been identified at the molecular level - on the order of a few dozen. The classical example is phenylketonuria, in which mutations in the *PAH* gene interact with dietary phenylalanine exposure to determine neurodevelopmental outcome. Such examples demonstrate that environmental modulation typically operates on underlying biological constraints rather than replacing them. Waiting for a complete enumeration of human gene–environment interactions would render mechanistic inquiry effectively impossible.

Deary et al. also question our emphasis on particular neural regions and evolutionary considerations. These elements were intended not as definitive explanations but as empirically grounded starting points. The precuneus, for example, was highlighted as a region where multiple independent lines of evidence converge. Comparative neuroanatomical studies indicate that one of the most pronounced morphological differences between humans and chimpanzees involves expansion of the precuneus (Bruner & Iriki, 2016); see also(Bruner et al., 2014, 2015). Functional imaging studies consistently show that the posterior precuneus/posterior cingulate exhibits the highest resting glucose metabolism within the default mode network (Gusnard et al., 2001; Utevsky et al., 2014), making it among the most energetically demanding cortical regions. In addition, human-accelerated regions (HARs) - rapidly evolved regulatory elements, many primarily active during fetal brain development - are enriched in enhancers regulating genes expressed in cortical radial glia and layer II/III pyramidal neurons (Won et al., 2019), precisely the neuronal populations supporting long-range associative connectivity in the precuneus and other default-mode hubs. These convergent observations illustrate the type of biological constraint our framework seeks to identify.

We did not place a focus on the evolutionary timeline of brain expansion, but pointed to one critical period as modern brains emerged. Major increases in hominin brain volume began roughly two million years ago with the emergence of early Homo, accelerated during the Middle Pleistocene, and approached near-modern volumes by approximately 200–100 thousand years ago. Subsequent evolution, occurring in the 80-60 ka period, appear to involve reorganization of cortical architecture, including the globularization of the modern human brain, rather than a large overall increase in volume (Neubauer et al., 2018). These late changes coincide with expansions of association cortex and the neural networks that support integrative cognition. Thus, evolutionary genomic innovations, developmental neurobiology, and contemporary genetic variation may intersect through shared neural substrates; see also (Geary, 2026).

Ultimately, the perspectives offered in these commentaries underscore the central challenge of intelligence research: connecting levels of analysis that span genes, neural systems, development, and experience. Our framework attempts to contribute to this effort by emphasizing biologically grounded constraints—particularly those related to neural metabolism, synaptic integration, and large-scale network organization—that may help explain how thousands of small genetic effects combine to influence cognitive function. These proposals should be viewed as provisional and testable rather than definitive. Progress will likely require continued integration of large-scale genomics, multi-omic approaches, neuroimaging, as well as cognitive and developmental neuroscience.

We hope that discussions initiated by these constructive commentaries stimulate precisely the interdisciplinary collaborations required to advance a biologically informed understanding of human intelligence. In our paper, we tried to look beyond the current complexities to a future of new technologies and methods. In our optimistic view, complexity is not a permanent roadblock. Rather, complexity is the motivating challenge for a new molecular science of intelligence.

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