REPLY TO FRIEDRICH ET AL.:

Both genetic and environmental factors may contribute to laterality in mesencephalic connectivity and bias

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We thank Friedrich et al. (1) for their keen interest in our study (2) and for highlighting additional examples of asymmetries in visually guided behavior and brain connectivity across several vertebrate classes.

The superior colliculus (SC), or its nonmammalian homolog, the optic tectum (OT), is, indeed, an evolutionarily conserved vertebrate midbrain structure (3, 4). The SC/OT is spatiotopically organized and multilayered and exhibits strong anatomical and functional homology across vertebrates (3, 5). Superficial layers of the SC/OT receive visual inputs, whereas intermediate layers receive multisensory inputs (3, 5). SC/OT intermediate layers also receive inputs from the forebrain (3). For example, in nonhuman primates, SC/OT intermediate layers receive inputs from frontal and parietal cortex, including the frontal eye field and lateral intraparietal area (5). Similarly, in birds, gaze-related forebrain areas project to the intermediate layers of the SC/OT (3). The SC/OT intermediate and deep layers, in turn, project to premotor circuitry in the brainstem for controlling gaze and orienting the body (3, 5).

It is increasingly clear that the SC/OT also plays a causal role in the selection of behaviorally relevant stimuli for attention, both in monkeys (e.g., ref. 6) and in birds (7). Forebrain projections to the SC/OT intermediate layers, observed in both of these vertebrate classes (3, 5), may serve a common purpose in mediating this function. Our study quantifies asymmetries in corticotectal connections in humans with diffusion MRI tractography and shows that these asymmetries are correlated with lateralization in a specific attention metric: spatial choice bias. Whether the asymmetries in choice bias and SC–cortex connectivity arise from environmental factors, genetic factors, or a combination of both remains an important open question.

Given the homology in SC/OT anatomy and function over evolutionary timescales, it is tempting to hypothesize that hemispheric asymmetries in SC–cortex connectivity, and hemifield asymmetries in choice bias, have a genetic basis. Emerging evidence suggests that physiological signatures and structural features in the human brain are heritable. For example, physiological signatures (peak frequencies) of visually induced cortical gamma band oscillations are highly correlated across monozygotic twins (8). Moreover, a recent, genome-wide association study (GWAS) showed that white-matter phenotypes, as measured with diffusion MRI and tractography, are heritable (9). Behavioral and diffusion MRI measurements in twin subjects, or in conjunction with GWAS studies, may provide important evidence regarding the heritability of choice bias or SC–cortex connectivity asymmetries in humans.

On the other hand, environmental factors over comparatively shorter timescales are likely to also contribute to these asymmetries. Plastic changes in brain connectivity induced by skill learning occur over various timescales, from weeks to years (10), and can be reliably quantified with diffusion MRI. Moreover, rapid, learning-induced changes in white-matter microstructure can occur within the timescale of just a few hours (e.g., ref. 11). In this context, it is instructive to ask whether training attention, over each of these timescales, can induce, or reverse, asymmetries in SC–cortex connectivity or choice bias. The answer may have critical implications for understanding the mechanistic relationship between white-matter connectivity and human selective attention.

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Author contributions: V.S. and D.S. wrote the paper.
The authors declare no competing interest.

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First published January 24, 2020.

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