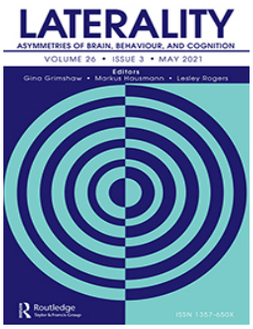

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Is any but a tiny fraction of handedness variance likely to be due to the external environment?

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ABSTRACT

Non-shared environmental variance (NSEV) accounts for 76% of variance in genetic modelling of handedness. However, it is very misleading to suggest that NSEV, "highlights the importance of non-genetic factors for the ontogenesis of hemispheric asymmetries". NSEV is poorly named, is calculated only by subtraction, and provides no direct evidence for environmental effects in the sense of the external environment. Miller suggested that it would be better named as "residual effect". Mitchell has suggested that much or indeed most of NSEV is "developmental variance" and should be included under the heading of nature rather than nurture, and in handedness, "largely reflect[s] the outcome of randomness in brain development". Overall only a very small proportion of NSEV in handedness is likely to be related to external environmental factors in the usual sense of the term.

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KEYWORDS Handedness; non-shared environmental variance (NSEV); developmental variance; environmental influences

In 2019, I reviewed half century of research on lateralization, (McManus, 2019), and had my title been, "Emerging from the previous five decades", it would have perfectly complemented, "Entering the next decade" by Ocklenburg et al. My sub-title did though imply many false leads—"Myths, Truths; Fictions, Facts; Backwards but mostly Forwards". Perhaps it is always thus in research.

OBP&F's masterly overview considers mostly the past decade, with 121/186 (65%) references from 2010 onwards, 44 (24%) from the 2000s, 13 (7%) from the 1990s, 6 (3%) from the 1980s and just 2 (1%) from the 1970s. The 65% drop per decade, with a half-life for scientific awareness of about

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seven years, is a salutary reminder to scientists in early, mid and late career. A future *Laterality* review in 2040 may have only 20 of these 186 citations, but picking those winners is a difficult game.

My comments concentrate on, "one of the core questions in laterality research", the question of, "how genetic and non-genetic factors interact during the ontogenesis of hemispheric asymmetries" (p. 11).

OBP&F start with Medland et al.'s study of 54,000 twins and singleton siblings (Medland et al., 2009), whose polygenic model found 23.64% additive genetic variance (similar to single-gene models), with the remainder being "non-shared environmental variance" (NSEV), a problematic and misleading term in genetics.

Medland et al. concluded only that, "additive genetic effects … accounted for about a quarter of the variation in [handedness]" (p. 336). OBP&F however jumped deeper in, emphasizing that NSEV "accounted for the remaining 76.36% [of the variance]", which is technically correct, but then potentially it is very misleading to continue, "*This highlights the importance of non-genetic factors for the ontogenesis of hemispheric asymmetries*" (my emphasis). Non-genetic factors they say were searched for in the half million UK Biobank participants (de Kovel, Carrión-Castillo, & Francks, 2019), but measures had, "only minimal predictive value for handedness". Hardly any of that 76% of variance is therefore explained, but OBP&F suggest, "other factors … might also be relevant and need to be investigated in the coming decade … [perhaps with] a more in-depth look at stress experiences in early and later life". Is it therefore plausible that much of that 76% NSEV can be found? Surprisingly OBP&F don't mention left-handedness being scarcer in breast-fed children (Denny, 2012; Hujoel, 2019), although gene-environment correlation may be part of its explanation.

NSEV is a very problematic term in genetics, as it is not calculated by modelling causal processes but by subtraction, just as are "residual variances" in ANOVA and regression. Much NSEV, or even most or all, could simply be noise. In biology such noise, which in effect is randomness, is well known and goes under the name of "fluctuating asymmetry". The probable role of randomness in determining lateralization has been argued recently (Bishop & Bates, 2020; de Kovel et al., 2019), but also back to the 1970s (Annett, 1972; McManus, 1979).

To see the problem posed by NSEV, do a thought-experiment. Large numbers of twin pairs toss coins, and genetic statistics model the proportion of heads thrown. Almost all the variance will be NSEV. Researchers might then be tempted to search for environmental factors, maybe temperature or humidity or muscular dynamics to find the elusive environmental variance, particularly as physicists make clear the, "dynamics of coin tossing is predictable" (Strzalko, Grabski, Stefanki, Perlikowski, & Kapitaniak, 2008). The latter should be read with care though, as outcomes are so sensitive to miniscule differences in initial conditions, that coin tossing is random for all practical

purposes. It is therefore plausible that NSEV for other behaviours is also effectively randomness.

Plomin reviewed thirty years of searches for NSEV in behaviour genetics. A few small effects are identified, but "much of what appears to be differential effects of experience on outcomes turns out to be due to genotype–environment correlation" (Plomin, 2011). Most NSEV remains unexplained therefore.

A problem for NSEV is its deceptive name, with the comforting suggestion of a real phenomenon. Deriving it by subtraction is though rather like referring to debts as "negative assets", potentially misleading the unwary to search out their hidden assets to make them wealthy again. The term NSEV has inevitably been criticized.

Miller suggests that most NSEV is actually randomness (Miller, 1997), and cites a laterality example from Bulmer (Bulmer, 1980). *Drosophila* sometimes shows non-heritable variation in asymmetry of left and right sided bristle number (Reeve, 1960). Something must affect the sides independently, but as Miller emphasizes, "this seems to be a case where what geneticists call environmental is true randomness, not merely an effect from the environs". Miller then concludes, "To avoid implying that evidence for an environmental effect (i.e., an effect from the environs of the organism) has been found *when there is no direct evidence of such an effect*, the phrase nonshared environmental effect *should be replaced with residual effect*" (my emphases).

Kevin Mitchell's recent book *Innate* takes issue with NSEV implying effects of environment *qua* external events, instead regarding it as, "caused not by any factors outside the organism, but by *inherent variation in the processes of development themselves*" (Mitchell, 2018, p. 30, my emphasis). Much NSEV is therefore *developmental variance* unique to the person. Using Waddington's concept of an epigenetic landscape, genes influence ontogenesis via the environment they themselves create, the developing organism itself. In terms of *nature versus nurture*, Mitchell includes developmental variance and genetics as *nature*—i.e., variance which is unique to the individual—rather than as *nurture* in the sense of the external environment. Therefore, "many traits are *even more innate* than heritability estimates alone would suggest" (p. 264, emphasis in original). Mitchell specifically considers handedness which he describes as, "highly innate, despite being only partly genetic, largely reflecting the outcome of randomness in brain development" (p. 73). Randomness occurs for Mitchell due to, "genetic differences in the program specifying brain development and function, *and random variation in how that program plays out in an actual individual*—they both contribute to the differences in a person at birth, the everyday sense of 'innate'" (p. 264, my emphasis). Almost all handedness variance is therefore genetic in the strict sense or is developmental variance, with only a tiny proportion due to variation in the external environment.

Taken overall, my prediction is that the next decade or two will find few environmental factors accounting for more than a percent or two of variance

in handedness. In contrast, it is highly likely that further genes will be found to add to the 41 recently found which relate to left-handedness (Cuellar-Partida et al., 2021), and had been predicted in 2013 (McManus, Davison, & Armour, 2013, p. 8).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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