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Commentary

Precisely wrong? The problems with the Jones and Martin genetic model of sex differences in handedness and language lateralisation

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John Maynard Keynes, the economist, "preferred to be vaguely right to being precisely wrong" (Bhatt, 2001). For the theory of Jones and Martin (2010), its strength, which is undoubtedly its precision, is also its weakness, for the theory allows precise calculations that undermine not only its application to sex differences in language lateralisation, but also its predecessor theory of sex differences in handedness (Jones and Martin, 2000). To my eye, and perhaps also the two other (anonymous) reviewers of the paper, Jones and Martin's theory is precisely wrong. Having said that, science functions best in the public domain, rather than behind an editor's closed doors, and others may disagree with my perceptions.

In this commentary, I will briefly set out the theory, and then look at its problems, firstly in explaining handedness, and secondly in explaining language dominance. It should be noted in particular that if the model fails for handedness then it fails *a fortiori* for language dominance, since the model for language dominance is built upon that of handedness.

1. *The Jones and Martin sex-linked theory of handedness.* Jones and Martin (2010) (henceforth J&M) proposed that the gene for left-handedness is on the X chromosome, and that it is recessive and partially penetrant. Although J&M refer to the alleles as D and C, I will here refer to them as D^+ and C^+, so as not to confuse them with the D and C of McManus (1985) and the D* and C* of McManus (1999). The D^+ allele has an estimated frequency *d* of .38, and hence *c*, the frequency of the C^+ allele, is .62. D^+ is dominant to C^+ and always results in right-handedness. C^+ is recessive and only partially penetrant, so that a proportion *a* of C^+C^+ homozygotes are left-handed, *a* being estimated as .21. The proportion of left-handers in females is therefore $a.c^2 = .21 \times .62 \times .62 = 8.07\%$. Males are hemizygous, having only one X chromosome, so that the genotype is either D^+ (and hence right-handed) or C^+ (of whom .21 are left-handed). As a result, the proportion of left-handers in males is $a.c = .21 \times .62 = 13.02\%$. The odds ratio for a male being left-handed, relative to a female, is therefore $.1302 \times (1 - .0807)/(1 - .1302)/.0807 = 1.70\times$. As is typically the case for sex-linked genes the rate in males is substantially higher than in females, although the ratio is nothing like as extreme as in colour-blindness or haemophilia, primarily because in those conditions, the rate of the mutant allele, *c*, is far lower, being less than 10% for colour-blindness and much lower for haemophilia.
2. *Empirical data on sex differences in the rate of handedness.* There are few fundamental constants in psychology, but it could well be argued that the sex ratio in handedness is one of them. Almost all of the various studies find about five left-handed males for every four left-handed females, with male to female odds ratios of 1.281, 1.242, 1.238 and 1.378 being found in the very large studies (five to seven digit sample size) of Gilbert and Wysocki (1992), Halpern et al. (1998), Peters et al. (2006) and Carrothers (1947), and 1.25, 1.23 and 1.299 in the meta-analyses of

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Sommer et al. (2008), Papadatou-Pastou et al. (2008) and Seddon and McManus (1991) [see http://www.ucl.ac.uk/medical-education/publications/unpublished-manuscripts/meta-analysis-of-handedness and McManus (1991)]. The sex ratio also appears to be historically invariant over the past 100 years (McManus, 2009).

3. *The fit of the J&M model to the handedness data*. Papadatou-Pastou et al. make clear that, "the male to female odds ratio [of] 1.23 (95% confidence interval – CI = 1.19–1.27)… places an important constraint on current theories of handedness". (Papadatou-Pastou et al., 2008). That is indeed the case, and it is only with much wriggling and prestidigitation that J&M suggest that 1.23 is compatible with their prediction of 1.70. J&M suggest that when, "… grouping studies by location, the ratio of male to female left- to right-handedness odds for studies in East Asia (including Japan and China) was 1.60". That value of 1.60 is still short of 1.70 (although it is included in the wide 95% CI of 1.36–1.87). With a median sample size of about 1300, and a maximum of 4282, almost none of these East Asian studies would individually have had adequate power for detecting sex differences, making them problematic. J&M also invoke method differences, saying that, "the observed odds ratio ranged from 1.16 for studies that simply utilised writing hand to 2.28 for studies that used the Annett Hand Preference Questionnaire (AHPQ)…". In fact of the seven methods described, six had odds ratios of 1.16, 1.28, 1.28, 1.19 1.17 and 1.20, the only apparent exception being the 2.28 for the AHPQ, and that perhaps should not be taken too seriously as it has a 95% CI from 1.07 to 4.86, which of course includes 1.23. At this point I can do no better than to quote one of the other reviewers of this paper:

> "The answers involve a lot of special pleading, even to the extent of undermining the findings of [J&M's] own meta-analysis of sex differences for handedness… I do not find the arguments convincing but I believe they could be offered for wider scientific scrutiny."

I presume that J&M would not wish to suggest that their sex-linked genetic theory only adequately explains studies in East Asia or studies using the AHPQ. Certainly it does not seem to explain the vast amount of data collected in the West using other standard methods.

4. *The J&M sex-linked theory of language dominance*. The J&M theory of language dominance follows on from that of McManus (1984) and Annett (1985) in suggesting that a single gene controls both handedness and language lateralisation. The novelty is that the gene is on the X chromosome, and hence sex differences are an integral part of the model. The predictions of the theory are fairly straightforward. As J&M's table 1 shows, there is complete equivalence of minority handedness (left) and minority language hemisphere (right). Minority hemisphere, in the population overall, therefore has the same odds ratio for sex as does minority handedness, i.e., 1.70. In right-handers, though, as J&M's formula 1 shows, the odds ratio is somewhat higher at 1.80, whereas in left-handers an identical proportion of males and females have minority language, giving an odds ratio of exactly 1.
5. *The fit of the J&M model to the language dominance data of Knecht et al*. Knecht et al. (2000a, 2000b) reported that 28/113 (24.8%) of left-handers showed right language dominance compared with 14/188 (7.5%) right-handers, a large difference which is compatible with other studies. J&M's predictions fit well with those data (21.0% and 9.3%), but then so do most other theories.[1] Knecht et al. did not report their left-handed data by sex, and hence J&M's prediction of no sex difference cannot be tested. However in male right-handers, 8/77 (10.4%) showed right language dominance compared with 6/111 (5.4%) females. Although the odds ratio is 2.029, that difference is not statistically significant ($p = .201$), and a bootstrap calculation suggests that the 95% confidence interval is from .24 to 3.16, the wide range being expected as there were only 14 individuals in total with right language dominance. Such data are compatible with almost any model that can be proposed, and in particular they are compatible with a null model suggesting *no* sex differences. Perhaps the most curious feature of the J&M study is testing a model that predicts sex differences against a dataset without significant sex differences, and then claiming that the data support the model. That sort of test is no test at all, and it is hardly fair to suggest that "ultrasonography makes it possible to test this new theory rigorously, and its parameter-free pattern of predictions is found to be supported."
6. *The fit of the J&M model to other data on sex differences in language dominance*. Sex differences in language lateralisation have been controversial for many years, not least since the high profile paper by Shaywitz et al. (1995). Meta-analyses have been rare, although Voyer (1996) did suggest that there might be modest sex differences. The systematic meta-analysis of Sommer et al. (2008) reviewed the available data on sex differences in dichotic listening (DL; 12 datasets, $n = 3822$) and functional imaging (FI; 26 datasets, $n = 2151$), as well as in asymmetries of the planum temporale (PT; 12 datasets, $n = 807$), which some suggest underpins language dominance. Together those studies have the statistical power that J&M suggest when they say, "the detection of [the sex difference] is expected to need of the order of a thousand participants". In Sommer et al's meta-analyses, Hedge's *g* (which is very similar to Cohen's *d*), was .09 ($p = .18$), .01 ($p = .73$)[2] and −.11 ($p = .68$), for DL, FI and PT, respectively. In contrast, the recessive model's predictions of 6.9% and 11.8% in right-handers would be equivalent to a Cohen's *d* of .326. Even if there are minor doubts about

[1] Care should be taken in interpreting J&M's statement that, "Furthermore, the large number of observations [in Knecht's studies] meant that the failure to reject the theory could not be attributed to any lack of power in the test. Instead, power analysis showed that the actual power of detecting a medium-sized discrepancy from the theory was, according to Cohen (1988), greater than 99.5%". They are describing here only the theory's prediction of a greater rate of right language localisation in left-handers than right-handers, a finding well-known for a century or more.

[2] I have used the values in their figure 4, rather than in the text, which are presumably a typo.

particular studies included in the meta-analysis, the picture overall is clear. There is currently no evidence for significant sex differences in language lateralisation, and the values are far removed from J&M's predictions. The values for FI (but not DL) are also significantly lower than the *d* of .114 that would be expected from the 1.23× odds ratio found in handedness.

Taken overall, it is difficult to see that the J&M model succeeds in any of its objectives. It does not adequately explain the vast majority of data on sex differences in handedness (which undoubtedly exist but are much smaller than J&M suggest), and it attempts to explain sex differences in language lateralisation (which are not convincingly present in the data in the literature). At this point a comment of the third reviewer of the paper is perhaps apposite: ''My overall conclusion is that support for the X-linked recessive theory rests on a very slender foundation. Other theories in the field are able to explain Knecht's findings at least as well.'' To me, the attempts by J&M to explain away problems in terms of the data rather than the theory are unconvincing, and reminded me of the ironic comment by Bertolt Brecht, after the 1953 popular uprising in East Berlin, that, the government should dissolve the people, and elect another.

Despite my relentless criticism of the J&M model, it should be said that it is not alone in failing to explain sex differences. No current genetic model of handedness is entirely satisfactory, each having some strengths, and most explaining the patterns of handedness in families and in twins, and how language dominance relates to handedness. For me, what is most surprising – and it is a reason for studying the J&M model seriously – is the possibility that sex differences are heterogenous, for while there is undoubtedly an excess of male left-handers, it is also probable that there are *no* sex differences in language lateralisation. Most genetic models have assumed that any pleomorphic effects of the genes would behave similarly for handedness and language dominance. If that is not the case then there is a lot of explaining to do.

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