

LEFT-HANDEDNESS AND MYASTHENIA GRAVIS

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Abstract—In two separate studies comparing the handedness of patients suffering from myasthenia gravis with matched controls, no evidence was found to support the Geschwind–Behan hypothesis of an association between autoimmune disease and left-handedness. Counter to prediction both studies found marginally lower incidences of left-handedness in myasthenics, and when combined with the similar result of Costi *et al.* (*Cortex* 24, 573–577, 1988) the difference was highly statistically significant. The personality of myasthenics, as assessed by the Eysenck Personality Questionnaire (EPQ), and in particular the psychoticism scale, which has been postulated to be related to androgen levels, was not significantly different from controls. However, assessment of sex-roles using the Bem Sex Role Inventory suggested that female myasthenics were more masculine than controls.

INTRODUCTION

GESCHWIND and BEHAN in a series of influential papers [12, 13, 14] have proposed a novel theory of cerebral dominance and handedness which in principle can account for a wide range of disparate data (henceforward the Geschwind–Behan hypothesis). The theory is essentially a “pathological” theory, taking one particular pattern of cerebral dominance (“standard dominance” [14]; i.e. right-handedness, left hemisphere language dominance and right hemisphere visual–spatial dominance) as normal, and arguing that deviations from this pattern (“anomalous dominance”) are a result of hormonal effects early in development. It is suggested that a masculinising hormone, probably testosterone, slows the development of the left hemisphere with the result that the normally less well-developed right hemisphere can become dominant. This influence will result in an increased incidence of left-handedness and right hemisphere language dominance, in a diminished degree of handedness in right-handers, and in a greater degree of anatomical symmetry of the cerebral hemispheres, especially in the planum temporale. Disequilibrium in the normal growth rates of right and left hemispheres is also claimed to cause an imbalance in their normal interaction, resulting in a suggested increased incidence of dyslexia and stuttering.

The Geschwind–Behan hypothesis also proposes that testosterone has a broader range of effects than merely acting upon left cerebral maturation, with other physiological systems also being affected. In particular it is also suggested that the immune system is affected by high levels of testosterone: *in utero* this results in a retardation of immune development, which causes an increase in immune disorders in young males; post-pubertally testosterone is supposed to cause thymic suppression which results in a higher incidence of auto-immune disorders in females.

The Geschwind–Behan hypothesis requires a long chain of causal reasoning, many steps of which are not as well supported as they might be by evidence, not least because of the

empirical difficulty of obtaining such evidence. However that problem was brilliantly finessed by Geschwind and Behan when they argued that since testosterone (a) results in an increased incidence of left-handedness and (b) results in subsequent development of auto-immune disorder, then auto-immune disorders should be associated with left-handedness. Such a hypothesis is highly counter-intuitive, and prior to the 1982 paper of GESCHWIND and BEHAN [12] the literature contained almost nothing that might suggest a link between left-handedness and vulnerability to physical disease. If this "most surprising finding" [12: p. 5099] is true then it is of the greatest importance for understanding left-handedness, and it would almost certainly initiate what Lakatos called a major research programme because of its ability to "predict novel facts . . . (previously) undreamt of" [17; p. 5]. Because of the emphasis made by Geschwind and Behan upon their data, and the straightforward method of testing, it is not surprising that the association of auto-immune disease with left-handedness has been the central focus for tests of the Geschwind–Behan hypothesis.

In Study 1 of their 1982 paper Geschwind and Behan reported a study in which left-handers self-reported a higher incidence of "immune disorders", including coeliac disease, dermatomyositis, diabetes, Hashimoto's thyroiditis, myxoedema, regional ileitis (Crohn's disease), rheumatoid arthritis, thyrotoxicosis, ulcerative colitis and uveitis, although numbers were too small for detailed figures to be given for each condition. Although interesting, the methodological problems with this study (self-diagnosis, small numbers, heterogenous conditions, uncontrolled samples) make its interpretation difficult (see also SATZ and SOPER's criticisms [30]). We also note that in another study relying on self-report of auto-immune disorders by right- and left-handers, that van Strien *et al.* [35] found no association between left-handedness and self-reported auto-immune disease, allergies or migraine.

In their Study 2 Geschwind and Behan looked at two neurological conditions, migraine and myasthenia gravis, the latter of which is almost certainly an auto-immune disorder. Amongst 98 myasthenic patients 13 (13.3%) were left-handed using a criterion of a laterality quotient (LQ) less than zero, compared with 7.2% of controls ($P < 0.05$). There was also a raised incidence of left-handedness in patients with migraine, although this was only significant using the unusual criterion of a laterality quotient of less than -30 .

In their 1984 chapter [13] Geschwind and Behan describe a further 304 patients with proven auto-immune disorders and in the case of Crohn's disease, ulcerative colitis, coeliac disease, "thyroid disorders" and myasthenia gravis they reported significantly raised incidences both of left-handedness and of individuals with left-handed first degree relatives. In particular 19% of 36 myasthenic patients were left-handed compared with a rate of 10.6% in controls ($P < 0.05$). Three other putative auto-immune disorders, diabetes mellitus, rheumatoid arthritis and polymyositis showed no increased incidence of left-handedness. In a less well controlled study comparing self-diagnosis in random populations of right and left-handers, migraine, "allergies", "skeletal malformations", and "thyroid disorders" were more frequent in left-handers than right-handers.

Various investigators have tried to replicate the findings of Geschwind and Behan, with varying degrees of success. In the largest and best controlled of the studies BISHOP [3] found no association between left-handedness and allergies, eczema, psoriasis or asthma in a longitudinal study of 12 000 16 year-olds with data available also at ages of 7 and 11. Likewise neither SALCEDO *et al.* [28, 29] nor SCHUR [31] could find an association between left-handedness and systemic lupus erythematosus, a disease which is undoubtedly auto-immune in origin (although as GALABURDA [1] has pointed out, the Geschwind–Behan

hypothesis does not say that *all* auto-immune disorders are necessarily associated with sinistrality). In contrast, in a large study, SMITH [34] found a high rate of left-handedness in patients attending an allergy clinic, particularly in those with IgE-mediated syndromes (although Bishop [3] had found no such association in children). SEARLEMAN and FUGAGLI [32] investigated patients with Crohn's disease, ulcerative colitis and diabetes, and found evidence (notwithstanding the criticisms of PERSSON and AHLBOM [23, 33]) that left-handedness was more common in both Crohn's disease and ulcerative colitis, although no convincing association with diabetes was found. MEYERS and JANOWITZ [21] however could find no association between inflammatory bowel disease and left-handedness. Migraine is not conventionally regarded as an auto-immune disease, although some evidence has been cited for such an aetiology [14: p. 91]. Although a controlled study by BLAU [14] has failed to find an association with left-handedness, and BISHOP [3] also found no evidence of a link, a study by GUIDETTI *et al.* [15] has found an association with left-handedness.

Myasthenia gravis is a severe chronic disease in which destruction of the motor end-plates results in a progressive paralysis of voluntary muscle [36]. The aetiology is generally accepted as auto-immune, and many patients are helped by thymectomy. Although cited by Geschwind and Behan as a disease in which there is an increased incidence of left-handedness, we know of only one other attempt to replicate their findings, which was published after the data had been collected for the present study. COSI *et al.* [7] compared a group of 102 myasthenics with 178 unmatched controls. Of the controls 6.2% were left-handed compared with 1.0% of those with myasthenia ($\chi^2 = 4.27$, 1 d.f., $P < 0.05$, Yates' correction not applied), a significant difference in the opposite direction to that reported by Geschwind and Behan. Analysis of variance of a laterality index showed no significant difference between patients and controls.

In this paper we report the results of two separate studies of handedness in subjects with myasthenia gravis. In each study the subjects are compared with an individually matched control, the spouse in Study 1 and an age- and sex-matched control in Study 2, and in each study we assess not only direction of handedness but also degree of handedness. In Study 2 we also assess the incidence of left-handed relatives, and examine several other measures of lateralization and also look at the broader question of whether the personality of myasthenics differs significantly from that in controls. The personality dimension of psychoticism has been proposed by EYSENCK [10] to be related to androgen levels. Similarly sex-role related behaviours might be modified by fetal androgens having a masculinising effect upon behaviour.

STUDY 1

Method

Subjects with myasthenia gravis were contacted by J.N. through a national support group, the British Association of Myasthenics, either being met directly at chapter meetings of the Association, or contacted by post or telephone via chapter secretaries and presidents. No subjects were approached without some form of personal contact, in order to minimize the risk of response bias. No precise estimate of response rate is, however, possible, because not all subjects were asked to take part by J.N. Nevertheless considering reports from chapter secretaries and presidents we believe the response rate was probably very high. Subjects came from most areas of England and Wales.

Subjects were sent individually a questionnaire which included a handedness inventory which had been specially designed to provide a straightforward screening for several aspects of handedness and lateralization which might be of possible interest in a study such as this. Nine questions asked about the hand typically used for different tasks. The first item asked about writing hand. Another three questions asked about items which previously have not been shown to have any strong cultural influence [19], two asked about items with strong cultural influences, and three were reversed items, in order to detect response sets. The questionnaire therefore allows the calculation of

four separate laterality indices, of non-culturally determined hand preference, culturally determined hand preference, preference on reversed items, and total scores of direction and degree of handedness. The questionnaire also included items about a range of other diseases which may, or may not, be associated with myaesthesia or left-handedness. Diagnosis of myasthenia was by self-report in a group of patients all of whom had had the disease for a number of years. Subjects were asked also to provide details of medication (specifically anti-cholinesterases) and other specific treatments for myasthenia (specifically thymectomy). Each subject was also asked, if married, to ask their spouse to complete a similar questionnaire which asked about handedness and other diseases, although it omitted the specific questions about myasthenia. Owing to occasional missing variables not all measures could be calculated for all subjects and controls.

Results

One hundred myasthenic subjects completed the questionnaire, and of these 81 were married and their spouse also completed the questionnaire, providing the control data for the matched pair analysis. For all respondents the median age of their first symptom was 29, at diagnosis was 33, and their current age was 51. Sixty-four per cent had undergone thymectomy, and all but one were currently receiving anti-cholinesterase medication. Seventy-three per cent of subjects were female.

Four of the 112 myasthenics (3.6%) used the left hand for writing, compared with 9 of 81 controls (11.1%) ($\chi^2 = 2.06$, 1 d.f., ns).

Considering the overall laterality score, calculated from all nine of the handedness items after reversal of the reversed items, which can take values in the range -100 (fully left-handed) to $+100$ (fully right-handed), myasthenics were significantly more lateralized (mean = 84.9) than controls (mean = 72.2) (paired $t = 2.19$, 73 d.f., $P = 0.031$). However this difference was secondary to the different incidence of overall left-handedness (which was significant for the writing hand, 2 of 81 myasthenics using the left hand compared with 9 of 81 controls (McNemar's test, $P < 0.05$) although it did not reach significance on a criterion of a $LQ \leq 0$ —Table 1). Calculation of absolute laterality scores (which take values in the range 0 to $+100$), and assess degree of lateralization independently of direction, showed no overall differences between patients and controls.

Discussion

Although Study 1 provides no support for the hypothesis that left-handedness is more common in patients with myasthenia gravis than in controls, there are some minor differences in handedness between the two groups. A defect in the design of Study 1 is that although the matched control is of similar age and social class to the patient, they are necessarily of the opposite sex (being the spouse), and since myasthenia is more common in females than males, the sex-ratios in our subjects and our controls are not the same. Study 2 avoided this problem by using a sex and age-matched control for each subject.

STUDY 2

Method

Fifty subjects with myasthenia gravis were contacted via the British Association of Myasthenics by B.L.B., who is herself myasthenic and a member of the BAM. None of these subjects had taken part in Study 1. Each subject, who was contacted personally, was asked to find a non-myasthenic friend of the same sex and within 5 years of the subject's age, to act as a control matched for age, sex and (approximately) social class. Both subject and control were given their own response booklets which not only asked about disease history and severity (for the subjects), and about handedness, using the questionnaire described above, but also included other measures of dominance such as hand-clasping and arm-folding (which have on occasions been seen as measures of latent left-handedness—see Refs [6, 20, 27]), eye-dominance, and familial left-handedness. In addition the Eysenck Personality Questionnaire (EPQ) [9] and the Bem Sex Role Inventory (BSRI) [1, 5] were included as measures of personality and sex-roles. The

rationale for including these instruments was two-fold; firstly, we had been unable to find any other studies in the literature of the personality of myasthenics, and wished therefore to include a broadly-based instrument such as the EPQ; and secondly we reasoned that if the early sex hormone environment was atypical in myasthenics then that might result in atypical sexual behaviour, which could be assessed by an instrument such as the BSRI (and might also manifest as higher scores on the psychoticism (P) scale of the EPQ). A majority of myasthenics are female and therefore in this study an explicit attempt was made to encourage male myasthenics to respond, and thereby to balance the sex-ratio. As in Study 1 we have no precise estimate of the response rate, but it is of the order of 60-70%. Subjects were randomly selected within the BAM and in so far as members of the BAM are representative of myasthenics then our subjects are also representative of myasthenics; certainly it seems most unlikely that they are systematically biased with respect to their lateralization.

Results

Fifty subjects and 50 matched controls responded to the questionnaire. For myasthenic subjects the median age of first symptom was 36, at diagnosis was 38, and their current age was 52. Sixty-four per cent has undergone thymectomy, and all were currently receiving anti-cholinesterase medication. Fifty-four per cent of subjects were female.

Table 1.

	Study 1*			Study 2*		
	Myasthenics	Controls	Sig.	Myasthenics	Controls	Sig.
Writing hand: Left (%)	2/81 (2.5%)	9/81 (11.1%)	<0.05	2/50 (4.0%)	5/50 (10.0%)	NS
LQ—Overall mean (SD)	84.9 (32.9)	72.2 (51.2)	<0.05	80.8 (34.1)	69.3 (69.3)	NS
LQ—Non-cultural	84.1 (37.7)	71.8 (59.1)	<0.1	81.0 (40.5)	64.3 (62.2)	<0.1
LQ—Cultural	93.6 (27.2)	82.1 (44.8)	<0.05	88.5 (27.8)	81.0 (48.1)	NS
LQ—Reversed	79.6 (45.6)	65.8 (60.5)	<0.05	71.7 (48.9)	63.0 (51.3)	NS
LQ ≤ 0 (%)	2/74 (2.7%)	7/74 (9.5%)	NS	2/50 (4.0%)	4/50 (8.0%)	
LQ —Overall	89.2 (18.5)	85.1 (23.7)	NS	85.2 (20.2)	78.7 (24.3)	NS
LQ —Non-cultural	90.1 (22.6)	89.1 (26.0)	NS	87.7 (22.3)	85.0 (26.8)	NS
LQ —Cultural	96.2 (15.6)	87.2 (33.6)	<0.05	89.5 (24.3)	90.0 (27.2)	NS
LQ —Reversed	88.3 (24.6)	84.8 (27.3)	NS	83.0 (24.6)	75.0 (30.7)	NS
Hand-clasping (% left)	—	—	—	53.1%	59.2%	NS
Arm-folding (% left)	—	—	—	56.0%	54.0%	NS
Eye-dominance (% left)	—	—	—	32.0%	46.0%	NS
Mother left-handed (%)	—	—	—	4.0%	2.0%	NS
Father left-handed (%)	—	—	—	12.0%	2.0%	NS
One or more left-handed siblings (%)	—	—	—	22.0%	14.0%	NS

*Matched pairs only.

Table 1 summarizes the results of the laterality inventory. 2/50 (4.0%) subjects and 5/50 (10.0%) subjects were left-handed (ns: McNemar's test). None of the measures derived from the laterality inventory showed any significant differences between patients and controls. Similarly there were no significant differences in the incidence of left hand-clasping, left arm-folding, left eye-dominance or familial sinistrality.

Table 2. Mean (SD) of personality measures in myasthenics and controls

	Myasthenics	Controls	Sig.
EPQ extraversion	11.62 (5.62)	12.82 (9.58)	ns
EPQ neuroticism	10.86 (5.25)	11.20 (5.72)	ns
EPQ psychoticism	2.08 (1.51)	1.98 (1.59)	ns
EPQ lie scale	9.94 (4.61)	9.94 (4.26)	ns
<i>BSRI: all subjects</i>			
Masculinity	4.61 (0.99)	4.19 (1.12)	<0.025
Femininity	4.70 (0.59)	4.66 (0.63)	ns
Social desirability	5.23 (0.54)	5.30 (0.69)	ns
<i>BSRI: males only</i>			
Masculinity	5.05 (0.76)	4.89 (0.82)	ns
Femininity	4.63 (0.57)	4.52 (0.53)	ns
Social desirability	5.02 (0.62)	5.36 (0.44)	<0.05
<i>BSRI: females only</i>			
Masculinity	4.24 (1.02)	3.58 (0.99)	<0.01
Femininity	4.75 (0.60)	4.79 (0.69)	ns
Social desirability	5.42 (0.40)	5.25 (0.85)	ns

Table 2 summarizes the results for the personality inventories; significance was assessed by paired *t*-tests between members of each pair, and by a three-way regression approach ANOVA with sex, group (i.e. myasthenics vs controls) and handedness as the independent variables. The EPQ showed no significant differences between patients and controls. However on the BSRI, the myasthenic subjects were significantly more masculine than the controls ($P < 0.025$). Analyses were subsequently carried out separately for male and female subjects. The difference in patients and controls on the masculinity sub-scale was significant only for the female subjects, and not for the male subjects. ANOVA with masculinity as the dependent variable found a significant main effect of group [$F(1, 93) = 6.33, P = 0.014$], a highly significant main effect of sex [$F(1, 93) = 29.1, P < 0.001$] and an almost significant main effect of handedness [$F(1, 93) = 3.42, P = 0.068$]. The interaction between group and sex showed a trend towards significance [$F(1, 93) = 2.209, P = 0.141$], and none of the other

interactions approached significance. The femininity scale showed no significant differences between groups, and the analysis of variance showed neither significant main effects nor interactions. The social desirability scale showed a significant difference between the myasthenics and controls in the males ($P < 0.05$) but not in the females. ANOVA showed no main effects of group, sex or handedness, but an almost significant interaction of group and sex [$F(1, 93) = 3.902, P = 0.051$]. It is not possible to compare our scores with those of the norms described by BEM [1] since those apply only to student and school populations who are substantially younger than our group, and who represent different birth cohorts.

Discussion

The two studies reported in this paper have failed to replicate the observation of GESCHWIND AND BEHAN [13] of a raised incidence of left-handedness in patients with myasthenia gravis. GESCHWIND and BEHAN [13] found a significant effect in a study with only 36 myasthenics, and in their 1982 paper [12] they found a significant effect with a sample of 98 myasthenics. Our studies contained 50 and 81 myasthenics, and therefore are of comparable size to those of Geschwind and Behan (131 myasthenics compared with Geschwind and Behan's 134 myasthenics): on that basis they should therefore have equivalent power for finding a significant difference, although in addition our study used matched controls for each patient.

Taken together our two studies show a trend towards a *decreased* incidence of left-handedness in myasthenics. It is therefore of particular interest that COST *et al.* [7] also found a reduced incidence of left-handedness in myasthenics. Taking the three studies together, 5/233 (2.1%) of myasthenics were left-handed compared with 25/309 (8.1%) of controls, the latter value being typical of those found in adult populations. The difference is highly significant ($\chi^2 = 8.97, 1 \text{ d.f.}, P < 0.01$, Yates' correction not applied). The interpretation of this result is not at all obvious given that it is in the opposite direction to that reported by Geschwind and Behan: certainly therefore it can provide no support for the Geschwind–Behan hypothesis. Whether it is indeed a meaningful result must await further confirmation and exploration. At present we have no convincing theoretical explanation for it.

Our data studying degree of handedness consistently finds no difference between myasthenics and controls, and similarly we find little evidence for an increased incidence of familial sinistrality in myasthenics. We therefore conclude that these results cannot support the additional predictions of the Geschwind–Behan hypothesis.

Taking these findings together we conclude that Geschwind and Behan's original finding is not replicated. Given the number of repeated statistical tests carried out in Geschwind and Behan's Table 14.3 [13: p. 218], and the *post hoc* criterion of left-handedness used in Study 2 of their 1982 paper [12]—commented on also by Bishop [3]—it is possible that a type I statistical error might have occurred.

Taken in context with other attempts to find evidence supporting the Geschwind–Behan hypothesis we must be circumspect. Table 3 summarizes published disease associations with left-handedness, found using a systematic computer search of Index Medicus for the years 1985 to 1987 and the first two quarters of 1988, and looking at all publications which included the term "handedness" in the title, key-words, or abstract, and which referred specifically to a physical disease without any component which potentially might be seen as functional in origin (so that, for instance we excluded papers showing an increased incidence of left-handedness in essential tremor [2], and squint [18], the latter being in a long line of papers reporting such an association e.g. [25]). We have divided the disorders into those

Table 3. Summary of disease associations with left-handedness, including studies only if the diagnosis is principally made by medical personnel, directly or indirectly, rather than relying merely on self-diagnosis.
 Key: blank: not studied; 0: no association; +: excess of left-handers; -: deficit of left-handers

	G&B (1982) [1] Study 2	G&B (1984) [2] Table 14.3	Other
<i>Auto-immune disorders</i>			
Rheumatoid arthritis		0	
Polymyositis		0	
Systemic lupus erythematosus			0, 0 [28, 31]
Myasthenia gravis	+	+	-, - [7, this study]
Crohn's disease		+	+, 0 [21, 32]
Ulcerative colitis		+	+, 0 [21, 32]
Coeliac disease		+	
Thyroid disorders		+	
Diabetes mellitus		0	0, 0 [3, 21]
Allergic disorder			0, + [3, 34]
Asthma			0 [3]
Eczema			0 [3]
Psoriasis			0 [3]
Sub-total (+/0, -)	1/0/0	5/3/0	3/10/2
<i>Other diseases</i>			
Migraine	+		0, 0, + [3, 4, 15]
Carcinoma of the breast			+
Congenital adrenal hyperplasia			+
Cleft palate			+
Sub-total (+/0/-)	1/0/0	0/0/0	4/2/0
Total (+/0/-)	2/0/0	5/3/0	7/12/2

which are conventionally accepted as possibly auto-immune and those which are not. Excluding Geschwind and Behan's own data, amongst the putative auto-immune disorders there is evidence that allergies (in adults), ulcerative colitis and Crohn's disease are indeed associated with left-handedness, whereas systemic lupus erythematosus, diabetes mellitus, childhood allergies, asthma, eczema, psoriasis, and myasthenia gravis are not associated with left-handedness. Nevertheless out of a total of 15 tested associations between left-handedness and disease since the original papers were published only 3 out of 15 (20%) have been statistically significant. Allowing for the "file-drawer effect" [26], whereby researchers are more likely to submit papers and have them accepted for publication if they show statistically convincing results, then these data are not convincing evidence for an association between auto-immune disease and left-handedness.

Our finding in Study 2 that myasthenics, particularly female myasthenics, are more masculine than controls on the Bem Sex Role Inventory can at best be seen as only indirect support for the idea that early hormonal environment of myasthenics contains more androgens than normal, especially as it must be accepted that the association between fetal androgenization and masculine behaviour is still far from proven [8]. It might also be the case that the more masculine behaviour of myasthenic females reflects an adaptive response to their illness rather than evidence of an early hormonal cause, or may be a selective bias in that those joining self-groups are more self-reliant and assertive (and hence score more highly on a masculinity scale).

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