

# Left-handedness: Association with immune disease, migraine, and developmental learning disorder

(cerebral dominance/autoimmunity/laterality/dyslexia)

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**ABSTRACT** We report an experimental study designed to test the following hypothesis derived from clinical observations: There is an elevated frequency in left-handed individuals and in their families of immune disease, migraine, and developmental learning disorders. In two separate investigations the frequency of these conditions was compared in strongly left-handed subjects and in strongly right-handed controls. In each of the investigations we found markedly higher frequencies of immune disease in the left-handers than in the right-handers. The rate of learning disabilities was also much higher in the left-handers than in the right-handers in both investigations. In a second study the frequency of left-handedness was compared in patients with migraine or immune disease and in general population control subjects free of these disorders. There was a higher frequency of left-handedness in patients with migraine and myasthenia gravis than in controls. We present a brief outline of a hypothesis that may account for an increased frequency of immune disease in left-handers and in their families.

Cerebral dominance—i.e., greater proficiency of each cerebral hemisphere in acquisition and performance of certain specific functions—has been recognized as a biological characteristic of humans for over 100 years. In most people there is dominance of the left hemisphere for language and of the right side for certain spatial functions. The older literature dealt predominantly with humans, with major stress on the laterality of lesions producing certain cognitive deficits. Since World War II there have been many studies that demonstrate dominance in normals.

By contrast, few studies on laterality deal with the kinds of data that are often found in studies of other biological traits, such as eye color. Examples of such data include the anatomical structures involved, biochemical and immunological properties, genetics, ontogeny, evolution, and comparative features in other species. In older publications one finds a few discussions of associations of handedness, such as asymmetries in fingerprints (1). More recent studies deal with anatomical asymmetries in the human brain, especially in language areas (2–6), asymmetries of function and structure in other species (7–11), the genetics of handedness (10, 12, 13), and the relationship of sinistrality to learning disabilities and to artistic, athletic, and other talents (12, 14). Anatomical maldevelopment has been demonstrated in the left side of the cortex (15) and in the thalamus (16) of a left-handed childhood dyslexic. These studies reflect growing interest in the biological associations of dominance.

Since the autumn of 1980, one of us (N.G.) has been impressed by observations on both patients and normals with an apparently elevated frequency of certain disorders in left-hand-

ers and in their families, including immune disorders (e.g., ulcerative colitis, celiac disease, and Hashimoto's thyroiditis) and migraine. Developmental learning disorders (e.g., dyslexia and stuttering) were also present in elevated frequency, as described by others (12, 17). Several family trees of left-handers included, over several generations, many left-handers and individuals with immune disorders, migraine, or learning disorders, either alone or in combination. The decision was made to test these clinical impressions in studies on left-handers and controls. We also studied the frequency of left-handedness in groups of patients with migraine and immune disorders.

## FIRST STUDY

**Methods.** For use in our investigation, we developed a questionnaire containing a series of questions concerning personal and family history as well as a modification of the Oldfield Handedness Inventory (18). The score on this inventory is expressed as a laterality quotient (LQ) which ranges in value from +100 (right-handedness in all tasks) to -100 (complete left-handedness). The  $\chi^2$  test was used in all statistical comparisons.

The first study consisted of two separate investigations. In the first, we distributed 500 questionnaires in a shop in London that supplies items for use by left-handers, and we received 253 responses from individuals who had a LQ of -100. Questionnaires were also filled out by unselected individuals from the general population of Glasgow, including civil service applicants, attendants at conferences of teachers and nurses and their spouses, and individuals coming to a shop in Glasgow in which one of our assistants was employed. We selected from this group the questionnaires of 253 individuals, all of whom had a LQ of +100 and who were matched for age and sex to the 253 left-handers.

In the second part of the first study we administered questionnaires to additional individuals gathered in the same manner as the general population group described in the preceding paragraph. Of this group we selected 247 individuals with a LQ of -100 and 647 individuals with a LQ of +100. In the first part of the study we had calculated the frequencies of immune disease entirely on the basis of the subjects' responses to the questionnaire. In the second part we scored a subject as suffering from immune disease only if the diagnosis had been made in a hospital.

**Results.** In part 1 of this study, the frequency of immune disease reported by the left-handed subjects was 2.7 times greater than in the control right-handers ( $P < 0.005$ ). The left-handers also reported significantly larger numbers of first- and second-degree relatives with immune disease (Table 1). Al-

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Abbreviation: LQ, laterality quotient.

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Table 1. First study, part 1

	Immune disorders			Learning disorders		
	LH	RH	<i>P</i>	LH	RH	<i>P</i>
Subjects*	27 (10.7)	10 (4.0)	<0.005	24 (9.5)	2 (0.8)	<0.005
First-degree relatives†	48	25	<0.01	21	7	<0.01
Second-degree relatives†	45	23	<0.01	11	1	<0.001

LH, left-handers ( $n = 253$ ); RH, right-handers, ( $n = 253$ ).

\* The number and percentage (in parentheses) of subjects suffering from one of the indicated disorders.

† The number of relatives suffering from these disorders.

though several types of immune disorders were reported, the frequency of thyroid and bowel disorders was notable. [The following immune disorders were reported: celiac disease, dermatomyositis, diabetes, Hashimoto's thyroiditis, myxedema, regional ileitis (Crohn's disease), rheumatoid arthritis, thyrotoxicosis, ulcerative colitis, and uveitis.]

We also found a much higher frequency of developmental learning disorders (dyslexia and stuttering) reported by the left-handers than by the right-handers ( $P < 0.005$ ). The left-handers also reported significantly larger numbers of relatives with learning disorders (Table 1).

In part 2 of the first study, the absolute rates of immune disorder in both the left- and right-handers were lower than those in part I because we accepted only those with diagnoses established in a hospital. However, the relative rates were comparable to those found in part 1, with the rate for left-handers 2.3 times as high as that in the right-handers ( $P < 0.025$ ) (Table 2). Again the left-handers reported significantly higher rates of immune disorders in relatives. The left-handers reported a much higher rate of learning disorders than the right-handers ( $P < 0.001$ ), as well as higher rates in their relatives (Table 2).

We could not study the frequency of migraine in the two groups because we found that the answers to questions concerning headache were too vague for proper distinction between migraine and other forms of headache.

## SECOND STUDY

**Introduction.** In the second study we compared the frequency of left-handedness among patients with migraine or immune disorders seen in the neurological clinics in Glasgow and in a group of general population controls.

We expected the study of the patient groups to give results less clearcut than those of the first study. We did not have available groups of patients with those immune disorders (i.e., involving thyroid or bowel) that our first study had found most often in the left-handers. Second, even the patient groups available to us were much smaller than those of the groups in the two parts of the first study.

**Methods.** The patient groups consisted of carefully diagnosed patients with severe migraine or with immune disorders. The

control group consisted of 1,142 individuals from the general population of Glasgow, selected by the same methods as those described in the first study. The questionnaire and statistical methods were the same as those used in the first study. We compared the frequencies of individuals with different degrees of left-handedness among the patients and the controls. In the 1,142 controls there were 82 individuals with a LQ < 0 (i.e., with all degrees of left-handedness)—i.e., 7.2%, a figure comparable to that found by Oldfield (18) in a Scottish population.

**Results.** Table 3 summarizes the findings from the comparisons of patient groups and controls. There was a higher percentage of left-handedness among the severe migraine patients. The difference in the frequency of left-handedness was marginally significant ( $P < 0.1$ ) at LQ < 0 and significant at LQ < -30 ( $P < 0.02$ ) and < -50 ( $P < 0.02$ ).

In 98 patients with myasthenia gravis there was an elevated frequency of left-handedness at all three cutoff points, although the difference was significant only at LQ < 0 ( $P < 0.05$ ).

The differences in the frequency of left-handedness found in comparisons of other patient groups (102 patients with rheumatoid arthritis, 168 with mixed-collagen vascular diseases, and 118 with multiple sclerosis) and the general population controls were not statistically significant.

## DISCUSSION

The findings of the first study were in conformity with the hypothesis that immune disorders would be present more often in left-handers and their families than in right-handers. However, the data from this study suggest that the elevated rate is the result of preferential increases in certain forms of immune disorder, especially those involving bowel and gut. The first study is also concordant with the hypothesis of a higher rate of learning disabilities in left-handers and their relatives—a result in conformity with many, although not all, earlier studies (12, 17).

Although we believe that the data on immune disorders and learning disabilities reflect large differences between left-handers and right-handers, the reported frequency differences in relatives may be less reliable. An individual with a learning disability or an immune disorder may be more aware of the

Table 2. First study, part 2

	Immune disorders			Learning disorders		
	LH	RH	<i>P</i>	LH	RH	<i>P</i>
Subjects*	13 (5.3)	15 (2.3)	<0.025	27 (10.9)	8 (1.2)	<0.001
First-degree relatives†	58	102	<0.025	19	24	<0.025
Second-degree relatives†	19	18	<0.005	2	4	‡

LH, left-handers ( $n = 247$ ); RH, right-handers ( $n = 647$ ). Footnotes (\*, †) as in Table 1.

‡ Numbers too small for calculation of *P*.

Table 3. Left-handedness in patient and control groups

LQ	C	M	P*	MG	P*
<0	82 (7.2)	17 (11.6)	<0.1	13 (13.3)	<0.05
<-30	71 (6.2)	17 (11.6)	<0.02	9 (9.2)	<0.3
<-50	59 (5.2)	15 (10.3)	<0.02	7 (7.1)	<0.5

C, controls ( $n = 1,142$ ); M, migraine patients ( $n = 146$ ); MG, myasthenia gravis patients ( $n = 98$ ). Each entry indicates the number and percentage (in parentheses) of controls or patients with a LQ below the level indicated on the left.

\*P, probability of difference between the patient group and the controls.

presence of these conditions in relatives than would individuals free of these disorders.

As we have already pointed out, we could not carry out an adequate study of the frequency of migraine in sinistrals because the answers to the questionnaire did not permit reliable distinction between migraine and other forms of headache. However, in the second study, we did find a significantly higher number of left-handers among carefully diagnosed patients with migraine.

We found an elevated frequency of left-handedness among patients with myasthenia gravis that was statistically significant only at LQ <0, although it was of the same order of magnitude as the elevation in migraine. We did not find significantly elevated frequencies of left-handedness in the other immune disease groups studied. However, we did not have available large groups of cases with the forms of immune disorder found in greatest numbers in the first study. Furthermore, because the frequency of left-handedness in any one form of immune disease is probably lower than is the frequency of all such diseases among left-handers, much larger patient groups will be required than those which were available to us.

The increased rate of learning disorders among left-handers is not difficult to understand because impairments of the left hemisphere that disturb language functions may also cause a shift of handedness to the right hemisphere (19).

The association of sinistrality, learning disorders, and immune disorders suggests the possibility of a common origin that may help in accounting for certain findings in childhood autism, one of the forms of developmental cognitive disorder. Coleman *et al.* (20) report that 10% of a group of autistic children suffered from well-diagnosed celiac disease, confirming other studies. A common interpretation is that celiac disease may be one cause of autism. An alternative hypothesis is that celiac disease, linked to HLA-B8 (21), is another manifestation of immune disorder in a group with elevated left-handedness. This interpretation is consistent with an elevated rate of hypothyroidism in parents of autistic children and with an elevated number of relatives with Down's syndrome (22), another condition often accompanied by immune alterations in both the patients and their relatives (23).

The most surprising finding in this study is the markedly elevated frequency of immune disorders in left-handers and in their relatives as compared to the rates in right-handers and their families. One possible explanation is that immune disorders are the result of stress in patients with learning disorders. This explanation is difficult to accept because immune disorders may be found in elevated frequency among relatives without learning disorders.

Another possible explanation for the association of immune disorders and sinistrality is that of separate genes on the same chromosome, with incomplete penetrance, for left-handedness and immune disease. The association would only indicate joint chromosomal localization and not causal connection. However,

there is an alternative explanation based on a hypothesis formulated by one of us (N.G.) on the biological foundations of laterality, of which only a very brief summary can now be given.

The neurons that will occupy the cerebral cortex are formed before 20 weeks of gestation in the central core of the developing brain and then migrate to their future locations (24). The study of fetal brains shows that the hemispheres are asymmetrical during gestation (3, 25). We have found that the gyri and sulci of the cortical convexity usually appear earlier on the right side. Chi *et al.* (4) have found a larger left planum temporale, part of the language area of Wernicke (2), at 31 weeks of gestation, but the homologous region on the right side develops earlier. Ounsted and Taylor (26) hypothesized that the left hemisphere matures later—especially in males—on the basis of the finding that febrile convulsions were most likely to damage the left temporal lobe in boys in the first year of life.

It is proposed that a major influence that slows growth of the convexity of the left hemisphere *in utero* is testosterone. This effect will usually be greater in males because the fetal testes secrete testosterone. The effect of testosterone on neuronal development has been documented in such structures as the preoptic nucleus in which it has been shown to cause dimorphism in male and female rats (27–29). Diamond *et al.* (11) have found the right posterior cortex to be thicker in male rats, and it has been found in our laboratory that the cytoarchitectonic areas in the same region are larger in male rats (unpublished observation). The findings of Goldman and Brown (30) are also consistent with differential cortical maturation in males and females.

Delayed growth in the left hemisphere as a result of testosterone would account for the greater frequency of left-handedness in males. When testosterone effects are more marked and neuronal migration is interfered with to a greater extent, abnormalities in the formation of the left hemisphere will result—especially in males—such as those described by Galaburda and Kemper (15) in the left temporal speech area of a severe childhood dyslexic. This type of effect would account for the much greater incidence of learning disorders in boys.

During fetal life the immune system is also maturing. Testosterone has important suppressive effects on the thymus both *in utero* and after birth (31, 32). Thus, during periods of increased testosterone effects on left brain development, maturation of the immune system is also likely to be affected. There are studies that support the hypothesis that the fetal thymus controls development of lymphocytes which are responsible for recognition of self-antigens and thus for prevention of autoimmunity (33, 34). Suppression of thymic growth during fetal life might therefore favor the development of autoimmunity in later life.

One might expect that this hypothesis would imply earlier development and higher frequency of immune disease in males. However, testosterone continues in postnatal life to exert a suppressive effect on the thymus. Thus, certain immune disorders such as myasthenia gravis and lupus erythematosus have a higher incidence in young women and older men (35)—i.e., groups in which testosterone effects are lowest. In the genetically autoimmune New Zealand black mouse (36) the disease develops later in the male. Castration accelerates autoimmunity in the male and testosterone administration slows it in the female.

The hypothesis that testosterone has a major role in the development of immunity is in conformity with several experimental studies. Iványi (37) has shown that several loci on the major histocompatibility complex in the mouse control not only the immune system but also various aspects of male differentiation, including mass of testis and thymus, blood testosterone

and testosterone-binding globulin levels, sensitivity to testosterone, and expression of H-Y antigen on thymus. Androgens also control the serum level of the fourth component of complement in mice (38). The minor histocompatibility complex controls  $\beta$ -2-microglobulin which is essential for immune responses; Ohno (39) has proposed that it also controls expression of H-Y antigen which is necessary for development of testes. There is thus an intimate bond between the control of male development and many aspects of the immune system.

One must raise the question as to participation of genetic factors in the familial clustering of left-handedness, immune disorders, and learning disabilities. The hereditary patterns can be explained at least in part by the gene complexes mentioned in the preceding paragraph. We presume that other genes also participate in the joint control of anatomical asymmetry and immunity.

The hypothesis summarized here thus proposes that testosterone slows neuronal development in the left hemisphere, while simultaneously affecting immune development, and thus favoring later immune disorder. Conversely, genes controlling immune responsiveness also regulate testosterone effects.

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