Autoimmunity in Left-Handers

Left-handedness may be associated with an increased risk of autoimmune disease. Is testosterone the link between the two?

"I think that there is very strong evidence that left-handers have a very high risk of developing certain diseases, some of which are very serious." With that provocative statement, Norman Geschwind of Harvard Medical School began his presentation at a recent symposium on "The Chemical Aspects of Brain, Behavior, and Neural Plasticity." *

Geschwind and his colleagues have linked left-handedness to language disorders, such as dyslexia, which is characterized by difficulty in learning to read. "This is not particularly new," Geschwind notes, "but we have also linked it to migraine and autoimmune diseases."

Autoimmunity occurs when the immune system begins attacking the body's own tissues, leading to such conditions as myasthenia gravis, which is caused by antibodies against the receptors that receive nerve signals, or inflammation of various tissues, including the joints, the thyroid gland, and the colon. An association between autoimmunity and left-handedness, a neurological variation, would be considered surprising, to say the least.

Geschwind first became interested in the possible existence of such a link in November 1980 at a meeting of the Orton Dyslexia Society. One of the speakers described a study of the incidence of dyslexia in relatives of patients with the learning disorder. In the discussion, Geschwind suggested that it might be a mistake to attempt to identify a genetic predisposition to a disease by looking only for that particular condition in a family because a susceptibility might manifest itself in different ways in different people. He cited a study in which John Simpson of the University of Glasgow, Scotland, found that patients with myasthenia gravis often had other autoimmune conditions as well. Their relatives also had a high incidence of autoimmune disease, although not of myasthenia gravis. Afterward, several members of the audience who were either dyslectics or relatives of dyslectics told Geschwind about their family histories, which often included additional language disorders such as stuttering, as well as migraine headaches and autoimmune diseases.

Studies by the late Samuel Orton, among others, had already shown that there is higher proportion of left-handers among individuals with dyslexia and related language disorders than among the general population. Both left-handedness and the language-related disabilities apparently result from the development of anomalous dominance in the brain.

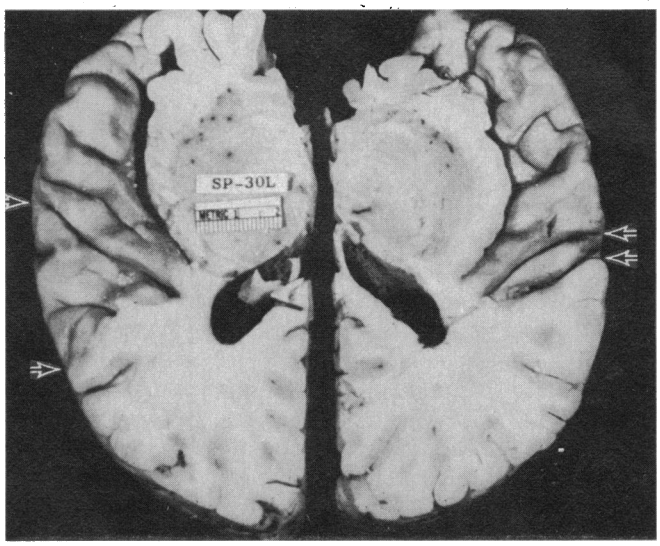
Over the past century, investigators have learned that, for most people, speech-related activities are primarily controlled by the left hemisphere and spatial abilities by the right. These individuals are usually right-handed. In a minority of people, the exact size of which is unknown, the right hemisphere has gained a greater or lesser degree of ascendancy over language abilities. This anomalous dominance carries with it an increased risk of learning problems for activities, such as reading and speaking, that are normally under the control of the left hemisphere. In addition, this group will include most, if not all, of the left-handers.

Most previous studies had looked at handedness in persons with learning disorders. Geschwind set out to do the reverse, to identify individuals of extreme left- or right-handedness and compare the incidences of learning disorders and autoimmunity in the individuals and their families.

Geschwind wanted to have a large number of subjects in his study so that even small effects could be detected. In addition, he wanted to have the data collected by people not familiar with the underlying ideas and to have the subjects recruited from outside the medical community. He turned for help to Peter Behan, a former student who is now at the University of Glasgow. "Although Behan was very skeptical, as I discovered later," Geschwind relates, "he agreed to participate."

They devised a questionnaire that included a test for laterality (hemispheric dominance), which was based on one formulated by the late Carolus Oldfield, plus questions about family histories of learning disorders, migraine, and autoimmunity. Only individuals who had scores on the laterality test of +100, which indicates extreme right-handedness, or −100, which denotes extreme left-handedness were to be included.

Ultimately, Geschwind and Behan conducted two independent studies† with subjects recruited in England and Scotland. The first included 253 left-handers and 253 right-handers. Learning disabilities were 12 times more frequent in the left-handers than in the right-



Asymmetry in a human brain

The planum temporale (marked by arrows) is much larger in the left hemisphere of this normal brain than in the right. [Source: Norman Geschwind of Harvard Medical School]

*Held in Philadelphia on 3 and 4 June under the auspices of the Institute for Child Development Research.

†Data in press in the August issue of the *Proceedings of the National Academy of Sciences U.S.A.*

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handers, and at least three times more frequent in the left-handers' relatives. This result agreed with what was already known about left-handedness and the learning disorders.

The results on autoimmunity were less predictable. About 11 percent of the left-handers reported suffering from autoimmune diseases, compared to 4 percent of the right-handers. The incidence of autoimmune diseases among the first- and second-degree relatives of the left-handers was about double what it was among relatives of the right-handers. The data on migraine were not usable in this study.

The first study could be criticized because of the way the left-handers were recruited, with questionnaires placed in a London shop that specializes in items for left-handers. Those who chose to respond may have included a disproportionate number with the learning disorders or autoimmune problems. Geschwind says, however, "We collected our left-handers for the second study in a very different way, from the general population of Glasgow, but got the same results. Again, the percentage of left-handers with autoimmune disease was about 2½ times the percentage of right-handers." For an autoimmune disease to be counted, it had to be diagnosed in a hospital. The diseases that turned up most often were Hashimoto's thyroiditis and conditions, such as celiac disease and ulcerative colitis, which affect the intestines. In a third study, left-handedness was found to be more frequent in patients who suffered from severe migraine headaches than in controls taken from the general population.

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"We are looking at an association of autoimmune disease with learning disorders and left-handedness," Geschwind says. "The obvious question is why this association. You could say that this effect is all psychological, due to stress caused by the learning disorders. I think that this is untenable because it then becomes extremely difficult to account for the high frequency of autoimmune disease in the relatives who do not have learning disabilities."

According to Geschwind, both the autoimmunity and the neurological ef-

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Superclouds

During the last several years, Patrick Thaddeus and his colleagues at Columbia University have been mapping out our galaxy's molecular clouds, those great cold masses of interstellar gas and dust that are the birthplaces of stars. These clouds are invisible to the human eye, and were utterly unknown until the 1970's. Now the Columbia survey has shown that they are far bigger than anyone realized. They are, in fact, the largest objects in the galaxy.

Strung out along the spiral arms like so many beads on a string, these superclouds are hundreds of parsecs long and more than a million times as massive as the sun. Columbia's Bruce Elmegreen told the AAS* that the great star-forming regions of our galaxy—the "giant" molecular clouds such as we see in Orion, Perseus, and Centaurus—have turned out to be nothing more than denser knots within the larger structures. In fact, these particular regions, which lie far apart in the skies of Earth, are associated with a large band of active star formation long known as the Gould Belt; Elmegreen argues that the belt outlines the supercloud that happens to encompass the solar system.

The clouds themselves consist almost entirely of molecular hydrogen, which for technical reasons is very difficult to observe. Far easier is a tracer molecule, carbon monoxide. (It was the detection of interstellar carbon monoxide in 1970 that led to the discovery of molecular clouds.) The molecule's signals are so strong that the Columbia group has been able to map the galaxy with a four-foot microwave dish on a rooftop in Manhattan.

The carbon monoxide maps that Elmegreen showed to the AAS (they are largely due to the thesis work of Thaddeus' student, T. M. Dame) covered the first quadrant of the galactic disk interior to the sun—that is, the quadrant visible from upper Broadway. The clouds clearly traced out the Sagittarius spiral arm, the next one inwards from the sun. After a gap, there were hints of another arm even further in. Some 30 separate clouds were visible, with an average spacing of 2 kiloparsecs. Elmegreen told *Science* that in separate work, he and Debra Meloy Elmegreen of IBM's Watson Research Laboratory have recently identified similar structures, with similar spacings, in the arms of other spiral galaxies.

According to the popular, but still-unproven, density wave theory of spiral structure, the stars and gas clouds of the galaxy slowly rotate through a set of standing waves—the spiral arms. It seems reasonable that gas might collect there into superclouds, says Elmegreen. (In fact, the size, density, and temperature of the superclouds are such that they might well be gravitationally bound.) Shock waves from supernovas and the like could then cause them to collapse further into star-forming regions like Orion—which explains why the arms of distant galaxies and the arms of our own galaxy are strewn with blue-white clumps of hot young stars.

*The 160th Meeting of the American Astronomical Society, Troy, New York, 6 to 9 June 1982.

Stellar Hurricanes

Only within the last 2 years have astronomers begun to realize what a violent process star formation really is. Newborn stars seem to spend their early years in astrophysical turmoil, emitting great quantities of high-velocity gas back into the interstellar medium that spawned them. These outflows are like the solar wind, except that they are more like stellar hurricanes: mass losses of 0.1 solar masses per year are not uncommon, while velocities reach hundreds of kilometers per second. The causes are unknown, but the phenomenon may well be universal. Outflows have been observed around virtually every kind of star, ranging from the hot, blue-white giants to dim yellow dwarfs like our own sun.

The field was reviewed for the AAS meeting by Charles Lada of the University of Arizona. Observations have accumulated rapidly, he said, most importantly from the millimeter-wave observations of carbon monoxide, which serves as a tracer for the cold, dark molecular clouds where stars form.

Motion within such a cloud can be determined by the broadening of the carbon monoxide emission lines as seen from Earth, Lada explained.

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fects may result from excess production of, or sensitivity to, testosterone in the fetus. This may be caused in most cases by a genetic predisposition, although environmental effects may also be involved.

Fetal testes secrete large amounts of the hormone. Moreover, several investigators, including Roger Gorski of the University of California School of Medicine at Los Angeles, and Fernando Nottebohm of Rockefeller University, have shown that testosterone affects the development of brain structures. For example, its classic action on the preoptic nucleus leads to noncyclic release of the gonad-stimulating hormones, which is characteristic of the male, rather than the cyclic release pattern seen in the female.

Beginning some 15 years ago, at the Boston University School of Medicine, Geschwind and Walter Levitsky noted anatomic differences between the hemispheres of the brain that could underlie the usual language dominance of the left over the right. In particular, the planum temporale, an area of the brain cortex that is involved in speech, is markedly larger in the left hemispheres of most people.

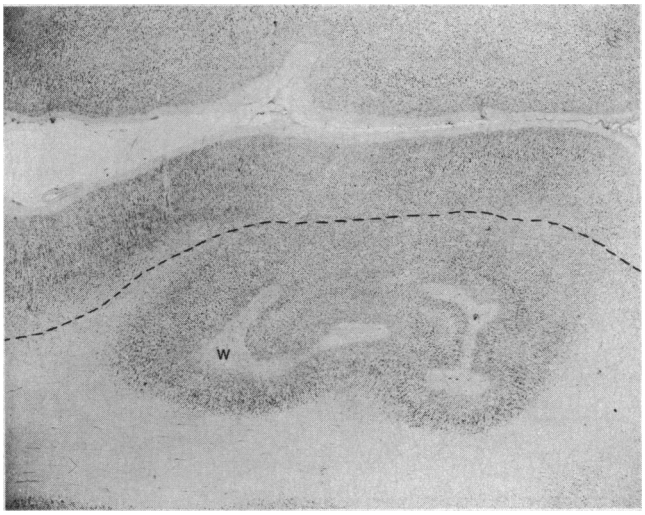
More recently, Geschwind and Marian Diamond, who is now at the University of California at Berkeley, observed sex-related anatomic differences in the brains of rats. Part of the cortex of the right hemisphere in male rats is thicker than the same region in female rats. The analogous area of the left hemisphere is larger in female rats. These patterns can be changed by hormonal manipulations, such as early castration of the males, which causes their brain anatomy to become more like that of females.

Geschwind thinks that testosterone slows the growth of the left hemisphere, in effect favoring greater development of the right. "Consequently," he says, "males end up right-handed less often than females, as was shown by Oldfield and others."

Geschwind, Albert Galaburda, also of Harvard Medical School, and Thomas Kemper of Boston University School of Medicine have found evidence of slowed development in the brain of a male dyslectic patient who died in an accident. The normal hemispheric size discrepancy in the planum temporale was much reduced. In addition, there was a large island of cortex in an abnormal location below the left planum. This, plus other changes in the architecture of the brain, suggested that the normal migration of neurons to the left cortex had been slowed during development.

Abnormal structure in a dyslectic brain

The left planum temporale in this brain from a dyslectic patient contains an island of cortex in an abnormal location below the usual cortical boundary (marked by the dashed line). The abnormal island contains both white (W) and grey matter. [Source: Albert Galaburda of Harvard Medical School and Thomas Kemper of Boston University School of Medicine]



This does not necessarily rule out additional effects of testosterone on the right hemisphere. "There may be a multiplicity of effects, depending on when you have an excess of testosterone," Geschwind says.

"The interesting thing," he continues, "is that the pathology of these disorders is a pathology of superiority as well as inferiority, since you often find remarkable talents in the learning disabled." Although the affected individuals may stutter, have trouble reading, or have other speech-related deficits, their spatial talents may be much better than average. As shown by Marian Annett of the Lanchester Polytechnic in Coventry, England, a disproportionate number of artists, musicians, mathematicians, and engineers are left-handed. "In principle, you might be able to prevent the learning disorders, but if you did, you would want to find a way that wouldn't reduce the superior talents," Geschwind explains.

He postulates that excess testosterone, or increased sensitivity to the hormone, in addition to slowing the development of the left half of the brain, leads to a higher incidence of autoimmunity in left-handers by suppressing the development of the thymus gland in the fetus. Because the thymus gland is the site of maturation of the T lymphocytes, which have among their functions the distinction of self from nonself, the result might be the inappropriate attack of the immune system on the body.

However, there is a possible problem with this idea. In contrast to learning disorders and left-handedness, many autoimmune diseases are more prevalent in females than in males. Geschwind does not think this is an insurmountable obstacle to his theory, however. He points out that after birth, at least from puberty until testosterone production begins to decline later in life, males may be protected against the onset of autoimmune symptoms by the hormone. In certain mouse models, the autoimmune disease systemic lupus erythematosus is usually more severe in females, and develops in them at an earlier age than in males. Testosterone suppresses the development of the disorder in females.

"The final point I want to make is that this powerful association between testosterone and immunity is no accident," Geschwind said as he concluded his presentation. The major histocompatibility complex (MHC) is a large genetic region that controls many of the activities of immune cells. According to P. Ivanyi of the Netherlands Red Cross Blood Transfusion Service Center Laboratory in Amsterdam, the MHC also affects the weight of the testes, the serum level of testosterone, the sensitivity of organs to testosterone, and other parameters related to the hormone and its actions. Conceivably, genes that influence the development of autoimmunity may be linked, or identical to, genes specifying high testosterone production or sensitivity, which in turn influences the development of the brain, leading to anomalous dominance.

If borne out by further investigation, Geschwind's findings would seem to have sinister implications for left-handers. But this is not necessarily so. As already mentioned, their spatial talents are often very high. And Geschwind adds, "My own belief is that the same population at high risk for the diseases I am talking about is probably going to be found to be at lower risk for other diseases. I doubt that the left-hand population is declining."—JEAN L. MARX