

A Cinch for the Brain

Our bodies, our behavior and even our brains are anything but symmetrical. And this seems to be an important factor in the seamless functioning of our thought, speech and motor faculties. Researchers at the **Max Planck Institute for Psycholinguistics** in Nijmegen are currently searching for genetic clues to this phenomenon. They want to decode the fundamental molecular biological mechanisms that contribute to asymmetry in the brain, and to identify possible causes for neurological disorders.

TEXT **STEFANIE REINBERGER**

At first glance, the human body appears to be completely symmetrical: two arms, two legs, two eyes, two ears. Even features like the nose and mouth appear to be evenly positioned in both halves of the face in most people. On closer inspection, though, we see that one leg is longer than the other, one hand is stronger, or maybe the left ear is positioned lower than the right one. This becomes even clearer when we take a look inside the body: the heart beats on the left-hand side; the liver and gallbladder, in contrast, are located in the right half of the body. The right kidney usually sits slightly lower than the left one, which is generally somewhat bigger and heavier.

The external appearance of the brain would also lead us to believe that it is a completely symmetrical struc-

ture. It's divided into two halves, both of which are equal in size and whose furrows and bulges follow a similar pattern. But the functional centers are extremely unevenly distributed. The right and left hemispheres specialize in different cognitive functions. They essentially divide up the work between them, possibly to expand the total range of tasks performed.

"Lateralization is a very distinct phenomenon in language," explains Clyde Francks, Research Group Leader in the Language and Genetics Department at the Max Planck Institute for Psycholinguistics in Nijmegen, in the Netherlands. "Speech is processed predominantly in the left half of the brain in most people." Only in less than 1 percent of the population are the main centers of speech processing in the right half – a phenomenon that occurs almost exclusively in left-handed people. >

A strong left: Rafael Nadal, for many years the world's number one men's tennis player, is right-handed but holds the racket in his left hand most of the time. Researchers are studying how the brains of left- and right-handed people differ.





Photo: Issei Kato/Reuters



» Lateralization is expressed differently from person to person – and not only in the few people whose brain is specialized mirror-inversely to the majority of people.

“Lateralization – both in the body structure and in the brain and behavior – is a basic biological principle,” says Francks. “In the brain, however, it seems to develop largely independently of the body,” he points out. The asymmetric structure of amino acids, which also determines how proteins are combined, is primarily responsible for the anatomy. Even in the earliest stages of embryonic development, the asymmetric structure of the molecules determines how the individual components are arranged in the newly developing organism.

The cause and the mechanisms that lead to the asymmetry in the brain and in its function, in contrast, are still largely unclear. It is very likely that genetics play an important role here. This is suggested by the fact that the differences between the two halves of the brain are already very apparent

early in development. A case in point is handedness – an effect that is also related to lateralization in the brain, and that simultaneously constitutes the most striking asymmetric behavioral principle. Even in ten-week-old human fetuses, an ultrasound scan shows that 85 percent of the growing babies move the right arm more frequently than the left. Once the fetuses are 15 weeks old, the thumb that they prefer to suck is a highly accurate indicator of which hand they will favor as an adult.

DISCOVERY OF AN INITIAL LEFT-HANDEDNESS GENE

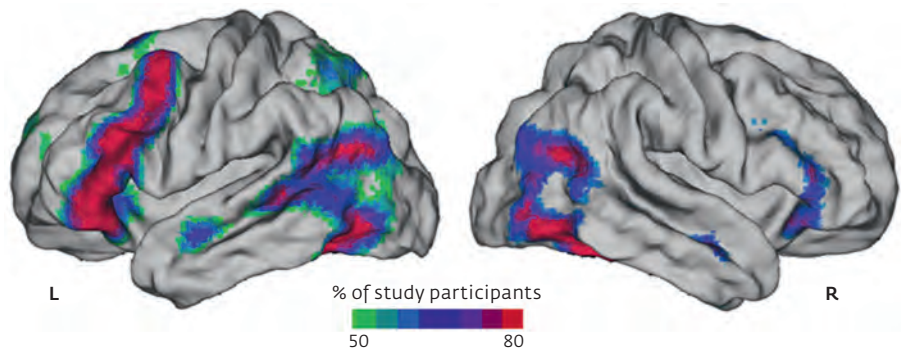
Clyde Francks has been fascinated by the lateralization of the brain for many years now. A zoologist, he has been searching for genes underlying handedness at the Wellcome Trust Centre

for Human Genetics in Oxford, UK, since 2002, initially as a doctoral student and later as an academic staff member. In 2007, he published details of the discovery of a gene called LR-RTM1 (leucine-rich repeat transmembrane neuronal 1), which may be linked to the tendency toward left-handedness and is passed down through the paternal line.

In Oxford, Francks worked for a while with Simon E. Fisher, who is currently a Director at the Max Planck Institute for Psycholinguistics. Fisher, however, was focused on other topics. He had discovered the widely known gene FOXP2, which plays a key role in speech and language, in 2001. When Fisher joined the Max Planck Institute for Psycholinguistics in 2010 to set up the new Language and Genetics Department, he recruited his former colleague. The subject of “asymmetry in the brain

Left Tulya Kavaklioglu is a member of Clyde Francks' research group. As part of her doctorate, she is looking for genes that influence left-handedness. Researchers are interested in the links between handedness and the various functionalities of the two cerebral hemispheres.

Right Studies using magnetic resonance imaging (MRI) show that more than 90 percent of right-handed people process language more in the left cerebral hemisphere than in the right one. The same applies to around 80 percent of left-handed people. The rare phenomenon of increased language processing in the right cerebral hemisphere manifests itself almost exclusively in left-handed people.



and behavior” thus arrived at the Max Planck Institute in Nijmegen together with Clyde Francks.

French physician Paul Broca had already discovered in the early 1860s that the important functional centers for language and speech are distributed asymmetrically across the brain. He had stumbled across a strange phenomenon: if a particular area in the left half of the brain was destroyed, those affected were still able to understand what was being said to them, but they were no longer capable of expressing themselves verbally. Patients whose injuries were located on the opposite side of the brain, however, thus affecting the right hemisphere, did not display these deficits.

The Frenchman had discovered one of the main centers of speech, named Broca's area after him, which is now considered to play an important role in speech production as well as in the processing of sentence structure and grammar. Another important center of language, Wernicke's area, was discovered by German neurologist Carl Wernicke (1848–1905) just a few years later, in

1874. This region of the brain plays an important role in language comprehension – and just like Broca's area, the Wernicke region is located on the left in most people.

DIFFERENCES BETWEEN MEN AND WOMEN

More recent scientific studies based on functional imaging, which can be used to depict the active regions of the brain based on blood circulation or sugar metabolism, have shown that the relevant areas for language and language processing are distributed across the brain, often even in regions that are far apart from one another. Researchers thus also report language and speech activity in the right hemisphere – albeit less than in the left hemisphere.

Moreover, lateralization is expressed differently from person to person – and not only in the few people whose brain is specialized mirror-inversely to the majority of people. The brains of people whose center of language processing is located principally on the left also differ in terms of how pro-

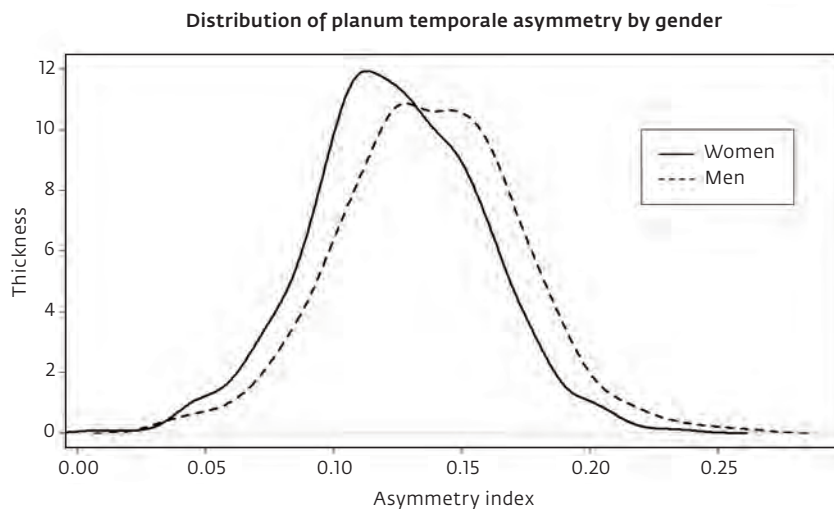
nounced the asymmetry is. This may even affect just individual areas of the brain. But how does this affect an individual's cognitive functions? And how does it affect the differences between men and women?

Previous research findings provided very different answers to the gender question. In 2008, for example, a team of researchers from the University Medical Center Utrecht in the Netherlands carried out a meta-analysis. The scientists analyzed data from 13 studies on handedness and the lateralization of certain regions and functions of the brain. They concluded that, although men are more frequently left-handed than women, they did not identify any differences whatsoever between the sexes in the regions and the functions of the brain that the Dutch researchers had included in their study.

Francks wasn't convinced. As in the past, he suspected that there were slight differences between the sexes. Together with doctoral student Tulio Guadalupe, he therefore decided to investigate it again himself. The two scientists analyzed images of brain scans of more

Below Gender-specific differences are found in the asymmetry of the planum temporale, an area that is located in both cerebral hemispheres: left-right asymmetry is generally less pronounced in women than in men. Men with less-pronounced left-right asymmetry often experience reading difficulties.

Right The molecular biology lab at the Max Planck Institute for Psycholinguistics offers researchers the opportunity to study at cellular level the effect of certain genes on the development of the brain.



than 2,300 healthy men and women. In this study, they were able to access data that research groups in various institutions in the Netherlands had been collecting since 2007 as part of the Brain Imaging Genetics Study, as well as data from a long-term German study on health. It is only through collaborative research endeavors like this that it is even possible to generate such a large group of subjects – and thus obtain a data quantity whose final analysis is truly statistically meaningful.

In their study, Francks and Guadalupe concentrated on the planum temporale, a region of the brain that their colleagues in Utrecht already had in their sights. The planum temporale sits on both sides of the brain in the temporal lobe and plays a role in the processing of language and music, but it also has an influence on absolute pitch. In around 90 percent of the population, it is more pronounced on the left side

of the brain and can be up to five times bigger there than its equivalent on the right-hand side. Researchers also see a connection between a lack of left-right asymmetry in the planum temporale and dyslexia. Those affected by this disorder have difficulty reading and understanding words even though their intelligence, eyesight and hearing have developed normally.

SURPRISING LINK TO SEX HORMONES

Francks and his colleague measured the planum temporale using very exact methods to determine the volume of areas of the brain. When the researchers had finally analyzed the available data, it was clear that there is indeed a difference between men and women – at least in the planum temporale. Francks' studies showed that this region in the female brain is less

lateralized than in men. Now, it can't be concluded from this result that women are therefore the weaker readers. "That is not the case," emphasizes Francks. "But men in whom the left-right asymmetry of the planum temporale is less pronounced have a greater tendency to be dyslexic."

Francks was not satisfied with a pure survey – ultimately, his work is concerned primarily with decoding the mechanisms of lateralization. Therefore, in the next step, he and Guadalupe analyzed the genetic data that he had on his subjects. The researchers concentrated on searching for so-called single nucleotide polymorphisms (SNPs). These are not mutations, but rather gene variations that occur with a certain frequency in the population and in which only a single base pair is modified in the DNA strand.

The results were interesting: in conjunction with the manifestation of left-



Graphic: Max Planck Institute for Psycholinguistics



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right asymmetry in the planum temporale, the researchers found a particularly high number of SNPs in genes that are involved in the metabolism of steroid hormones, namely, among other things, in the synthesis of male and female sex hormones. And the functioning of the steroid hormones actually appears to have an effect on the lateralization of the planum temporale in both men and women. However, it is still unclear what role steroid hormones ultimately play in reading and linguistic ability. Francks wants to solve this puzzle in future research projects.

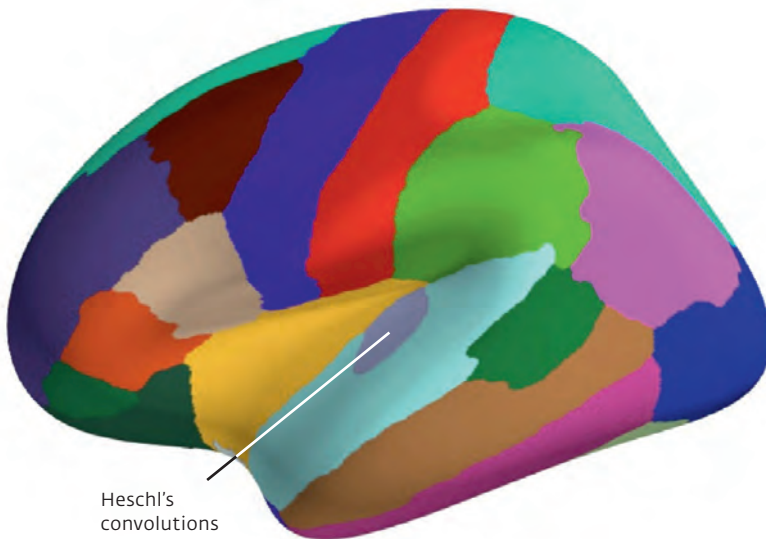
Much of the work done by Clyde Francks and his team in Nijmegen seems, at first glance, almost simple:

they choose a prominent, asymmetric region in the brain and check whether gene variations exist that can explain this asymmetry. But it's not quite that straightforward. The search for genetic causes of the lateralization is akin to the proverbial search for a needle in a haystack. This was revealed, for example, when the researchers examined Heschl's convolutions, as they are known. This region of the brain is located in the temporal lobe in both cerebral hemispheres; it houses the primary auditory cortex and is important for language comprehension. Not only are Heschl's convolutions more strongly pronounced in the left cerebral hemisphere in most people, but their shape

also varies considerably between individuals – anatomical peculiarities that, to a certain extent, must be inherited. Nevertheless, despite studying the data of more than 3,000 test subjects, the Max Planck researchers couldn't detect any gene variations that occur uniquely in conjunction with the manifestation of Heschl's convolutions.

GENETIC INFLUENCES ARE COMPLEX AND MULTIFACETED

Equally sobering is the current search for other genes for handedness. Just last year, the Nijmegen-based researchers analyzed the genetic material of 17 members of a Pakistani family that in-



Left For scientists, the brain is much more than simply gray matter. The folds and indentations in the cerebral cortex form a specific pattern. Individual functions can be allocated to specific sections: the primary auditory cortex, for instance, is located in the Heschl's convolutions.

Right Handedness manifests itself at a very early stage. Based on the preferred thumb, hand preference can be clearly determined, not only in babies, but even in 15-week-old embryos.

cluded a remarkably high number of left-handed individuals. “These are really the best conditions for detecting genetic material for the phenomenon,” says Tulya Kavaklioglu, the doctoral student entrusted with this topic in Francks’ team. “Still, we found absolutely nothing.”

Frustrating for the doctoral student, yet an important finding for this area of research. The apparent failure underscores how complex and multifaceted the genetic influences must be that ultimately lead to a certain region of the brain being more strongly lateralized in some people than in others, or to certain individuals preferring the left hand over the right hand.

“We can be very sure that there is no single gene variation that determines handedness or brain asymmetry,” emphasizes Francks. Instead, a number of variations in the genome seem to ultimately lead to the anatomical manifestation that researchers see in their brain scans or simply in their subjects’ preferred hand. This is similar to body size, eye color and individ-

ual weight: here, too, a myriad of SNPs and other forms of modifications in the genome influence the phenotype – the observable physical characteristics. In addition, at least height and weight are also shaped by environmental influences, a phenomenon that could also play a part in the lateralization of the brain.

DISRUPTED ASYMMETRY COULD CAUSE DISORDERS

Added to this are so-called epigenetic mechanisms, DNA modifications that affect whether and to what extent a certain gene or a certain variation even has any impact. In 2014, Francks’ team detected such an effect in the LRRTM1 gene. This is the gene that Francks associated with the propensity for left-handedness during his time in Oxford – at least when there is hypermethylation of LRRTM1, that is, when it contains too few methyl groups compared to a “healthy” variant. This involves small chemical appendages on the DNA that affect the activity of a

gene, in other words how frequently it is transcribed.

All of this clearly shows that anyone searching for genetic causes for asymmetry in the brain and behavior needs not only stamina but, most importantly, a large number of test subjects. This is the only way that slight effects can be detected. To this end, large research networks have been established in recent years. These include the international consortium ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis), whose objective is to pool data from imaging procedures and genetic studies in order to gain a better understanding of the brain and its functioning in very large groups of subjects. Clyde Francks heads up the Lateralization group in this network.

At this point, the question may well be asked: Why are the Nijmegen researchers even making such a major effort to detect a few fine genetic traces that make tiny contributions to the individual brain anatomy? Is it important to know why Heschl’s convolutions are manifested in a particular way in one

person and slightly differently in another? And what is the use of knowing about genes that help determine whether we prefer to use our right or left hand for certain activities?

“We are interested in understanding the fundamental genetic and molecular biological principles that lead to lateralization of the brain,” says Francks. Disorders such as schizophrenia also appear to be linked to insufficient cerebral lateralization. And deviations in the asymmetry of certain structures deep inside the cerebrum evidently play a role in hyperactivity in children. “If we understand the mechanisms of how the asymmetry occurs, we can then move on to investigating at what point something goes wrong if the lateralization is damaged,” says Francks. And that would be an important first step in one day helping people affected by the phenomenon. ◀

TO THE POINT

- The two halves of the human brain perform different tasks, but the asymmetry varies in each individual.
- There is no clear link between right- and left-handedness and the distribution of other functions in the human brain. Thus, in terms of language processing, the brain structure of left-handed people is, in most cases, similar to that of right-handed people.
- Certain brain asymmetries manifest themselves differently in men and women.
- The search for the genetic causes of right- and left-handedness and of deviations in brain symmetry has proved to be difficult.

GLOSSARY

Lateralization: A basic biological principle whereby the human body, despite its symmetrical appearance, exhibits anatomical and functional differences between the right and left halves. Lateralization of the brain is most apparent in language processing.

Single Nucleotide Polymorphism (SNP): A variation of an individual base pair in a DNA strand. SNPs are inherited and hereditary genetic variants – in contrast to mutations, which generally indicate a new modification.

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