Decoding biological asymmetry

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Strong left: while Rafael Nadal, who was leading the world ranking in tennis for many years, is right-handed, he predominantly holds the racket with his left hand. Researchers are investigating the differences in the brain of left- and right-handed people. Credit: Reuters / Issei Kato

Our bodies, our behaviour, but also our brains are anything other than symmetrical. And that 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 for this phenomenon. They want to decode the fundamental molecular biological mechanisms that contribute to asymmetry in the brain and identify possible causes for neurological disorder.

At first glance, the body looks completely symmetrical: two arms, two legs, two eyes, two ears. Even features like the nose and mouth also appear to be evenly positioned in both halves of the face in most people. Yet, on closer inspection, it can be seen that one leg is longer than the other, one hand is stronger or 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, gallbladder and spleen, on the other hand, are located in the right half of the body. The right kidney is usually located slightly lower than the left one, which is generally somewhat bigger and heavier.

The brain behaves in a very similar way: here too, its external appearance would lead us to believe that it is a completely symmetrical structure. The organ of thought is 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 strikingly unevenly distributed. The right and left hemispheres specialize in different cognitive functions. They essentially divide up the tasks between them - possibly to increase the overall range of tasks that can be achieved.

"Lateralization is clear in the brain's setup for language," says 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 dominantly in the left half of the brain in most people." In less than one percent of the population, the main centers of speech processing are in the right half – a phenomenon that occurs almost uniquely in left-handed people.

"Lateralization – both in the body structure and in the brain and behavior

– is a basic biological principle," explains Francks. He adds: "In the brain, however, it seems to develop largely independently of the body." The asymmetric structure of amino acids, which also determines how proteins are combined, is primarily responsible for the body anatomy. Even in the earliest embryonic development, the asymmetric structure of molecules determines how the various components are arranged in the newly-developing organism.

However, the cause and the mechanisms leading to the asymmetry in the brain and its function 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 apparent early in development. A case in point is handedness – an effect that is also related to lateralization in the organ of thought and at the same time is the most striking asymmetric behavioral principle. Even in a 10-week-old human fetus, an ultrasound scan will show that 85 percent of growing babies move their right arm more frequently than their left. Once the fetuses are 15 weeks old, the thumb that they prefer to suck is a good indicator of the hand that they will prefer to use as an adult.

Differences between men and women

Clyde Francks has been fascinated by the lateralization of the brain for many years now. Initially, as a doctoral student and subsequently as an academic staff member at the Wellcome Trust Centre for Human Genetics in Oxford, UK, the zoologist has since 2002 been searching for genes underlying handedness. In 2007, he published details of the discovery of a gene called LRRTM1 (leucine-rich repeat transmembrane neuronal 1), which may be linked to the tendency for left-handedness and be passed down through the paternal line.

In Oxford, Francks worked for a while with Simon Fisher, the current Director at the Max Planck Institute for Psycholinguistics. For Fisher, however, other topics were a priority. In 2001, he had discovered the widely known gene FOXP2, which plays a key role in speech and language. 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. And thus Clyde Francks and the subject of "asymmetry in the brain and behavior" arrived at the Max Planck Institute in Nijmegen.

The 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; however, they were no longer capable of expressing themselves verbally. Patients whose injuries affected the opposite side of the brain, namely the right hemisphere, did not display these deficits.

Tulya Kavaklioglu is member of the reserach group of Clyde Francks. For her doctoral work, she searches for genes that affect left-handedness. Both researchers are interested in the connections between handedness and the different functions of the two hemispheres.. Credit: MPI for Psycholinguistics

Speech is processed dominantly in the left half of the brain

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 but also in the processing of sentence structure and grammar. Another important center of language, Wernicke's area, was discovered by the 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.

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

Moreover: lateralization is expressed differently from person to person – not only in the few people whose brain is specialized the other way around. The brains of people whose center of language processing is located principally on the left also differ in terms of the degree of asymmetry. 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 came to the conclusion that although men are more frequently left-handed than women, they did not identify any differences between the sexes in the regions and the functions of the brain that the Dutch researchers had included in their study.

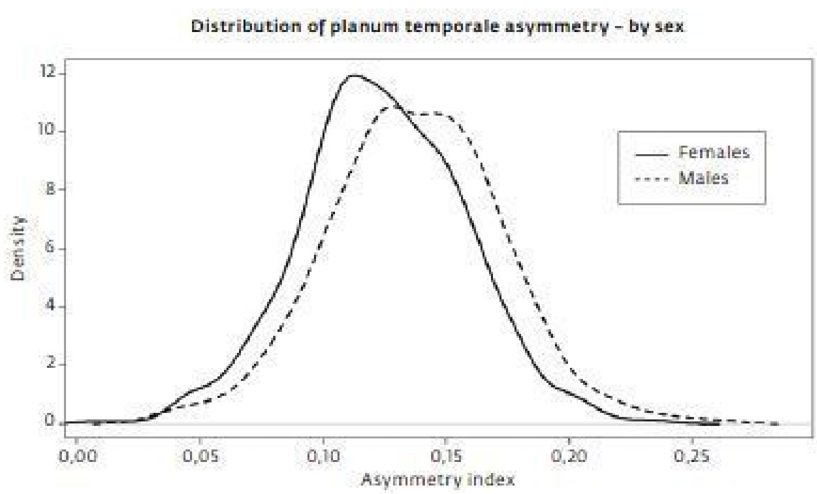
Francks was not convinced that subtle sex differences could be ruled out by these results. He and his graduate student Tulio Guadalupe therefore decided to investigate the question again themselves, and analyzed images of brain scans of more than 2,300 healthy men and women. In this study, they were able to access data that research groups in various institutions in the Netherlands had been collecting as part of the Brain Imaging Genetics Study since 2007, as well as data from a long-term study on health. It is only through such research collaborative endeavors that it is even possible to generate this type of large group of subjects – and thus arrive at a data quantity whose final analysis is statistically truly 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 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.

Francks and his colleagues 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. It cannot 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 yet satisfied with a pure survey – ultimately, his work is primarily concerned with decoding the mechanisms of lateralization. Therefore, in the next step, he and Guadalupe analyzed the genetic data that they had on the 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-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.



There are gender differences in the asymmetry of the planum temporale, an area which is found in both hemispheres of the brain. In women, the left asymmetry is less strong than in men on average. Men with a weakly developed left asymmetry often suffer from dyslexia. Credit: MPI for Psycholinguistics

Some 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 that straightforward. The search for genetic causes for 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 gyri, 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. Heschl's gyri are not only more strongly pronounced in the left cerebral hemisphere in most people. Their shape also varies considerably between individuals – anatomical peculiarities that are apparently inherited to an extent. Nevertheless, despite studying the data of more than 3,000 test subjects, the Max Planck researchers could not detect any gene variations that occur uniquely in conjunction with the manifestation of Heschl's gyri.

Equally sobering is the current search for other genes for handedness. Only last year the Nijmegen-based researchers analyzed the genetic material of 17 members of a Pakistani family that included a remarkably high number of left-handed individuals. "These are really the best conditions for detecting genetic material for this phenomenon," says Tulya Kavaklioglu, the doctoral student entrusted with this topic in Francks' team. "Despite this, we found absolutely nothing."

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

"We can be very sure that there is no individual gene variation that determines all people's handedness or brain asymmetry," emphasizes Clyde Francks. Instead, a large number of variations in the genome ultimately seem to lead to the anatomical manifestation that researchers see in their brain scans or simply in the preferred hand of their subjects. This is similar to body size, eye color or individual weight: here too, myriads of SNPs and other types of variation in the genome influence the observable physical characteristics. In addition, at least height and weight are shaped by environmental influences, as are also likely to play a part in the lateralization of the brain.

Disturbed asymmetry could cause diseases

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 an effect. 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, i.e., when it contains too few methyl groups compared to a "healthy" variant. This involves small chemical appendages on the DNA, which affect the activity of a gene, i.e., how frequently it is transcribed.

All of this clearly shows that anyone searching for genetic causes for asymmetry in the brain and behavior not only needs stamina but, most importantly, needs a high number of test subjects. This is the only way that subtle 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 really 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 to determine whether we prefer to use our right or left hand for certain activities?

Disorders including 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.

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