Interactions between the genome and the environment

Parental neglect appears to lead to epigenetic changes in children, which result in behavioural problems in later years. This is one issue amongst the many that were addressed at the colloquium "Gene und Umwelt – Wie wir werden, was wir sind" (Genes and the environment – how we become what we are) recently organized by the Daimler and Benz Foundation in Berlin.

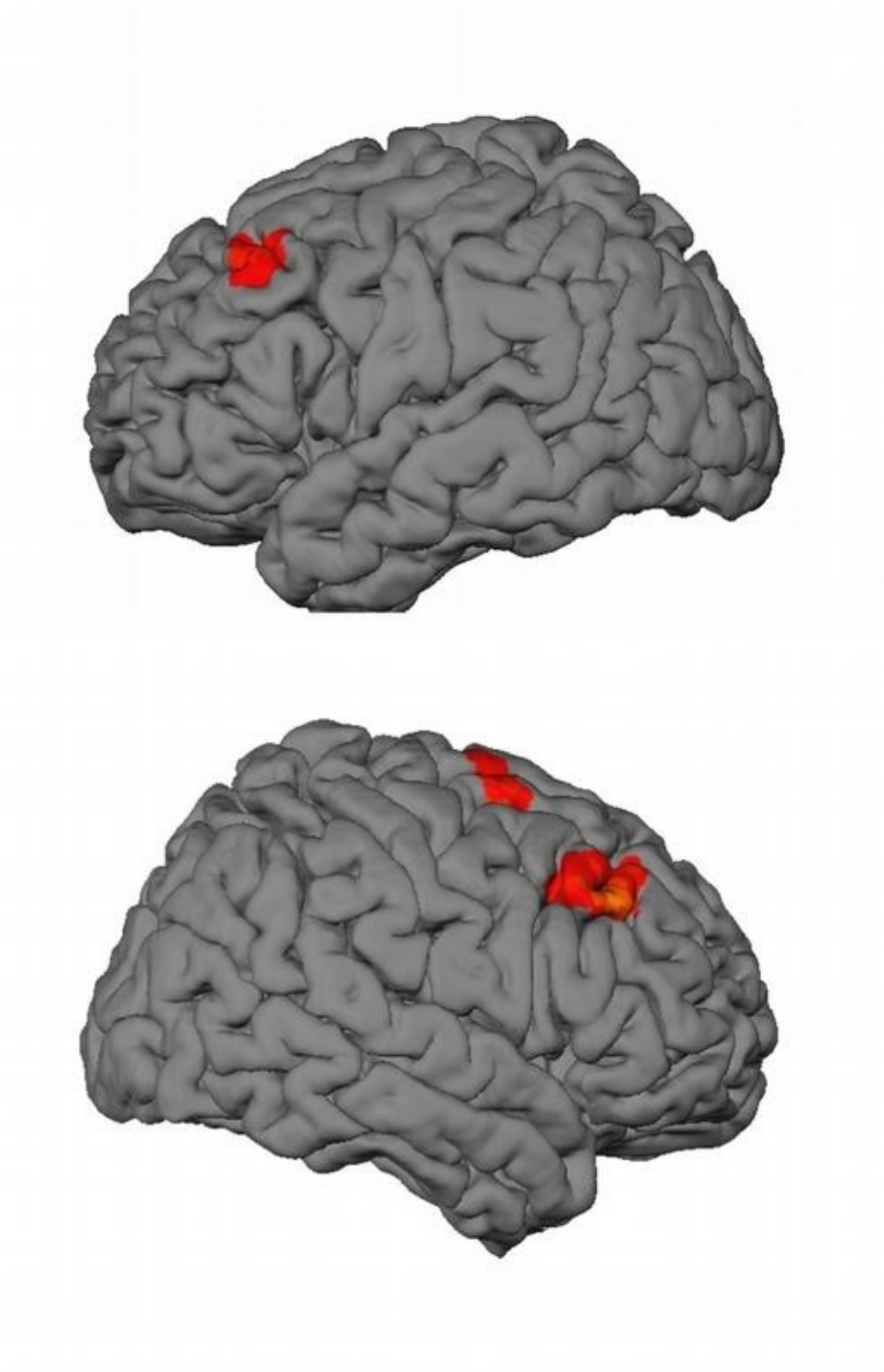
The picturesque 2000-year-old city of Ladenburg located on the river Neckar between the cities of Heidelberg and Mannheim was home to the world-famous inventor Karl Benz and his determined wife Bertha. In 1888, Bertha was the first person to drive an automobile over a long distance (from Mannheim to Pforzheim), a journey that brought worldwide attention to her husband's Benz Patent-Motorwagen. The Daimler and Benz Foundation was established in Ladenburg with the objective of contributing to clarifying the interplay of forces between humanity, technology and the environment by supporting interdisciplinary science. The research projects funded by the foundation and the events the foundation organizes stand out for their interdisciplinary orientation and the dialogue that they encourage between experts from completely different fields of research including the natural sciences, the social and engineering sciences, psychology, political sciences and medicine. Among the more prestigious activities of the Daimler and Benz Foundation is the annual "Bertha Benz Lecture" which promotes women's contributions to science and society. In 1992, Angela Merkel, then a young minister who went on to become German chancellor, gave a lecture on the problems of women and young people in the new German states; and in 2008 the famous behavioural researcher Julia Fischer reported on new insights into the evolution of language. The 16th colloquium which was presided over by the foundation's two chairmen, Professor Dr. Eckard Minx and Prof. Dr. Rainer Dietrich (both from Ladenburg), focused on the topic "Genes and the environment – how we become what we are". Renowned international scientists gave lectures approaching this subject from many different angles.

Genome-wide association studies – from gene to disease

Karl-Benz House in Ladenburg, headquarters of the Daimler and Benz Foundation.

These days the issue of heritability of intelligence no longer sparks off ideological debates. Nowadays, people who support this belief are no longer seen as reactionary and they can refer to twin studies that show that environmental factors as well as genes play a considerable role in shaping personality – a person's likes and dislikes, talents, character traits and disposition to disease. The human geneticist Professor Dr. Markus Nöthen (University of Bonn) sees intelligence as a multidimensional phenotype and, in his lecture, pointed to the complexity of the genetic contributions that lead to the development of different dimensions of personality.

The knowledge that gene-gene interactions play a major role in the development of multifactorial ("polygenic") diseases such as type 2 diabetes, myocardial infarction, prostate carcinoma and multiple sclerosis is not new. However, considerable progress in the identification of human polygenic diseases has only been made recently with so-called genome-wide association studies (GWAS). This is a relatively new method of investigation and it searches the genome for small variations (known as



Location of a gene variant, which represents a risk factor for schizophrenia, in the dorsolateral prefrontal brain cortex.
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single nucleotide polymorphisms or SNPs) that occur more frequently in people with a particular disease than in people who do not have the disease. Researchers can look at hundreds of thousands of SNPs simultaneously and identify genes that may increase the risk of developing a certain disease. A National Genome Research Network (NGFNplus) project initiated by Professor Dr. Andreas Meyer-Lindenberg, Director of the Central Institute of Mental Health in Mannheim, led to the identification of eight genes involved in heritable schizophrenia and bipolar disorder. These genes are located in brain areas that are key to the working memory and the processing of emotions.

Professor Dr. Rainer Riemann (a psychologist from Bielefeld) differentiates between two models in order to describe the interplay between environmental and genetic factors: first, the "genetic and environmental co-variation" model according to which the phenotype of genes "changes" an individual's environment: a drastic example of this is the consumption of drugs (with a heritable component) or our school system, which supports talented schoolchildren more than less talented ones. The second model is the "interplay between genes and environment" model that relates to the direct influence of genes on an individual's environment. A well-known though disturbing example of this model is a landmark study carried out in New Zealand ("Dunedin MAO study") which suggested that polymorphisms of the monoamine oxidase A (MAO-A) gene modified the risk of antisocial behaviour in boys exposed to familial adversity. For example, boys who were maltreated and showed antisocial disorder also had a lower MAO-A enzyme activity than normal boys. MAO-A is a mitochondrial enzyme located on the X chromosome; it is essential for the metabolism of the neurotransmitters serotonin and noradrenalin. The connection between the MAO-A gene and aggressive behaviour was initially shown in animal experiments.

How the environment affects genes

Queen bee (marked) and workers

The studies indicate that our genetic influences are reordered depending on the environmental circumstances to which we are exposed. The psychological models do not of course provide any information about the mechanisms of how the environment and our genes interact with each other. On the molecular level, these interactions are related in some way or other to epigenetic mechanisms, many of which have since been identified. The methylation of DNA and the modification of histones (histone code) are the most important epigenetic mechanisms known to date. Epigenetics

relates to the investigation of inheritable modifications of gene function that are not due to changes in the DNA sequence. Interest in epigenetic phenomena has increased exponentially over the last few years. According to Professor Dr. Frank Lyko, head of the Department of Epigenetics at the German Cancer Research Center (DKFZ), the human genome contains around 20 million methylated cytosine residues (always present as cytosine-guanine dinucleotide). Lyko's group of researchers investigates the relationship between DNA methylation patterns and phenotypic differentiation, degeneration and ageing of cells. Altered methylation patterns are the earliest molecular signs of human cancer. Substances that inhibit methyl transferases (i.e. enzymes that transfer methyl groups) represent new approaches for tumour treatment. Lyko and his team have shown in honeybees, whose genome has a much lower number of methylated nucleotides than the human genome, that the queen and the workers, which are genetically identical, have more than 550 genes whose methylation pattern differs. These differences are the result of royal jelly, a honeybee secretion that is fed to young bees to make a new queen, and which triggers the development of queen morphology.

Socio-epigenetics

The lecture given by Professor Dr. Moshe Szyf, a biochemist from McGill University in Montreal/Canada, on epigenetics and behaviour was one of the highlights of the colloquium. In cooperation with the neurologist Michael Meaney, Szyf has shown in rats that whether they develop into friendly and courageous or aggressive and anxious adults depends on how often the baby rats were licked and groomed – either by their mother or another rat - during their first weeks of life. The researchers found that the levels of the glucocorticoid receptor, a protein that regulates the reaction to stress hormones, differed in groomed and ungroomed rats. They found that the glucocorticoid receptor gene was switched off epigenetically in rats with inattentive mothers. The receptor is located in the hippocampus where it is the docking site for the stress hormone cortisol. As the glucocorticoid receptor gene was switched off, the mice were under permanent stress throughout their whole lives.

Syzf and his team have since extended their research to human beings. They compared the brains of people who had committed suicide and who were severely abused as children with those who were not. The data suggested that those who had been subject to abuse revealed identical methylation patterns in the hippocampal glucocorticoid receptor and the T-cells of the immune system. These findings open up exciting research perspectives. Can epigenetic alterations resulting from parental neglect cause social misconduct as the Dunedin MAO-A study suggests? Does epigenetics explain the statistically proven correlation between a weak immune defence system and an unhealthy life? And how does all this work? Is it correct to assume that parental attentiveness leads to the demethylation of DNA?

The scientists who participated in the "Genes and the environment – how we become what we are" all agreed that the human epigenome is far more complex and individual than the human genome and that researchers have so far only just scratched the surface of the topic. Researchers in Germany and abroad hope that an understanding of epigenetic mechanisms will open up new therapeutic approaches, both for cancers that are caused by epigenetic alterations as well as for patients suffering from trauma or chronic stress.

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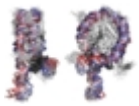

Epigenetics – heritable traits without changing the DNA sequence