Constance Scharff

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Fixing her sights on the birds – Constance Scharff belongs to the young generation of neuro bird researchers who have conquered new research ground in the USA.

Eighty percent of married female academics in Germany have academic spouses. The problem of "coupled careers" is one that affects women in particular. The fact that it is possible for both partners to successfully pursue their separate careers is demonstrated by the achievements of **CONSTANCE SCHARFF***: whilst she is leader of the C3 Research Group at the* **MAX PLANCK INSTITUTE FOR MOLECULAR GENETICS***, her husband,* **ARTURO ZYCHLINSKY***, is director of the Cellular Microbiology Department at the* **MAX PLANCK INSTITUTE FOR INFECTION BIOLOGY**.

PHOTOS: NORBERT MICHALKE

Birds are cosmopolitans and can therefore be found all over the world. As migratory birds, which spend the summer in the North and winter in the warmer southern climes, they can also be described as being "travellers between two worlds". In this sense, Constance Scharff can also be regarded as a cosmopolitan: born in Northern Germany, she moved to Marburg in 1979 to study biology and three years later left Marburg to travel to Manhattan. What was originally only meant to be a student exchange extended into a visit lasting almost ten years. At the beginning of the 1990s she returned to Europe for three years – this time to Paris – thereafter spending a further seven years in Manhattan. She has now touched down in Berlin – bringing her birds with her; for these have been the focus of her scientific research for more than ten years.

Eight pairs of small zebra finches have taken up residence in the former caretaker's apartment at the Max Planck Institute for Molecular Genetics in Berlin. But this is just the beginning: in mid-May Constance Scharff is expecting a further delivery of birds to join the rest of the flock. The institute will then have a proper stock of birds. "But we had to start somewhere", she says. Since September of last year Constance Scharff has been working as a C3 scientist at the institute and her SFB grant application was already approved a long time ago. She joined the Molecular Human Genetic Department led by Hans-Hilger Ropers, within the framework of the C3 Programme launched by the Max Planck Society. Ropers has shown that he is open to new concepts and model systems. However, up until a few weeks ago, the laboratory space that had been allocated to the new working group was unavailable and so Constance Scharff and her newly acquired team were forced to "join the queue". Making a virtue out of necessity, the team opted for "space-saving" experiments, starting with several molecular genetic experiments. Their hospitable colleagues from the neighbouring research group were able to provide them each with fifty centimetres of laboratory bench space for the necessary pipette work. Fortunately, in the meantime, the team has moved into its own laboratory space.

NEW CELLS FOR NEW TUNES

Mice with genes that have been modified or switched off, that is to say mice that have been "recreated" so to speak, are currently defining the nature of biomedical research. So how come Constance Scharff is devoting herself to bird research? "Of course, mice, flies, or threadworms offer the power of genetics and have therefore brought us a multitude of elegant methods and valuable findings. Unfortunately, none of these organisms have the ability to learn acoustic forms of communication. In contrast to this, a whole range of parallels exist between song learning in birds and the acquisition of human speech", says Scharff. Even Charles Darwin observed that the first rudimentary attempts of young songbirds to produce sound had something in common with the attempts made by young children to speak. It is also becoming increasingly clear that certain aspects of these processes are controlled by similar neuronal mechanisms.

It is above all the experiments carried out by Fernando Nottebohm from the Rockefeller University, Constance Scharff's PhD mentor, that are responsible for revolutionizing our thinking about brains. In a series of elegant experiments, Nottebohm and his team showed that, in the case of canaries and zebra finches, new neurons are constantly being created during adulthood and that these neurons migrate to specific song controlling regions and become integrated there into the existing neuronal circuits. A long-standing neurobiological dogma that the number of neurons in the brain of vertebrates was unalterably fixed on the day of birth was thereby upturned. Today we know that the production and successful integration of neurons into adult brains takes place not only in the case of songbirds but also rodents, apes, and even humans.

In 1984 Constance Scharff comes to work in Fernando Nottebohm's laboratory. Prior to this, she has spent two years at the Adelphi University in Garden City, New York. Overseas she had managed to escape the somewhat theoretical and therefore often boring basic studies in Germany. "All my friends applied to an American organisation for a stay in the USA. I decided to jump on the bandwagon, almost at the last minute", she explains. Courses attended by no more than 10 to 15 students, and the opportunity in almost every laboratory of taking part in projects, not only teaches students how "the business of science is really done", but also awakens in them a sense of curiosity which inspires them to design and carry out their own tests. It is Carol Diakow, then Assistant Professor in Adelphi, who is responsible for steering Constance Scharff's long-term fascination for behavioural neurobiology towards experimental research. She therefore stays on Long Island and does not return to Germany as originally planned. She applies to several American universities: the Rocke-

The other side of "couple careers": whilst Constance Scharff is still in the laboratory testing tissue under the microscope, ...

... Arturo Zychlinsky is at home keeping their two daughters Milena and Anna occupied.

feller University in New York, the University of Madison in Wisconsin and the University of California in Berkeley. "I was already getting a little homesick and wanted to return to Germany, but on the other hand I was determined to find out how far I could get."

The Rockefeller University takes on around 20 new students every year. Only a few students from the vast number of applicants are selected and invited to attend a personal interview. Constance Scharff has to undergo six or seven interviews at all three universities. Hardly any of the questions asked relate to factual knowledge. Most professors were interested in sounding out the scientific curiosity of their potential students, the diversity of their interests, and their open-mindedness. Constance Scharff passes the "test" with flying colours and is accepted by all three universities. And at this point, she becomes so captivated with Manhattan that her desire to return to Germany becomes secondary. Scharff therefore enrols at the Rockefeller University and in 1991 completes her PhD with Fernando Nottebohm on the neuronal basis of song learning in birds.

Yet, Constance Scharff does believe that there is more to life than science alone. At the end of the eighties she meets Arturo Zychlinsky, a fellow Rockefeller student, who is later to become her husband. And she is sure that she does not want to sacrifice her desire to have children in favour of a scientific career. The couple marry in New York and decide to move to France both as postdocs.

However, as she works on her ambitious project at the Institut d'Embryology Cellulaire et Moléculaire in Paris, she is confronted with more than enough challenges – not least when her daughter Anna is born in February 1992. "This did slow down my career", she says. "But after Arturo had published his first NATURE article at the same time as our daughter was born, it was clear that he would be the first to look for a job."

Family and career united

Two years later, Arturo Zychlinsky is actually offered a position at the Skirball Institute of Molecular Medicine at the New York University Medical School. By sheer coincidence, Fernando Nottebohm contacts Constance Scharff also at this time. A project that she had initiated three years before has received research funding and he asks her to lead this project as Postdoctoral Associate in his laboratory. This is how Scharff and Zychlinsky, as a husband and wife team, actually succeed in further pursuing their separate professional careers. Their second daughter Milena is born is in June 1995. In view of the excellent "Child and Family Center" day care facilities on the campus at the Rockefeller University and the fact that "working science moms" are the order of the day, Constance Scharff has no problem combining family and career.

She therefore starts her experiments again into how and where song learning takes place in the brain of zebra finches. Her main focus of interest is centred on one of the key regions, the "high vocal centre", or HVC, without which songbirds cannot sing. Two different neuronal pathways have their origin here: the motor pathway is essential for song production; the relevant HVC neurons send their axons, i.e. their nerve fibres, into the so-called RA region which monitors the muscles of the vocal organ in the throat. The second pathway controls the learning of the song. The corresponding HVC neurons project into the "Area X". In contrast to the other cells, these cells are created exclusively during embryogenesis and are no longer renewed at a later date.

Neurons in the brain can be selectively eliminated using a method developed by Jeff Macklis at Harvard which Constance Scharff has adapted to suit her own object of study, the zebra finch: when the substance chlorine e6 is microinjected into the RA region, it will find its way by means of retrograde transport (in the direction of the cell body) into the HVC>RA projection neurons. This drug can be photoactivated by means of a laser, causing neuronal death of all cells that contain the substance. As a result, the birds lost their ability to sing complex melodies. If the birds are injected with a radioactive substance which incorporates itself into the DNA of dividing cells, it is possible to determine whether new cells have been created to replace the dead cells. In the experiments carried out by Constance Scharff, the birds treated in this way displayed three times as many new neurons in this region than the control birds. And the extent of this neuronal replacement was mirrored by the birds' ability to regain their ability to sing. One of the test birds even mastered its exact pre-operative repertoire after three months. However, neurons, which project from HVC into the "Area X", are not replaced following selective elimination.

As a result of these experiments Constance Scharff has gained new insight into the regenerative ability of the brain: she was able to show that neuronal death triggers the production of new cells and that this process can be stimulated by the selective elimination of cells. The good news: cell death is followed by the production of new cells and a functional disruption in behaviour could be rectified. The bad news: not all types of neurons possess this ability to regenerate.

What does a speech gene do in bird's brains?

One of the greatest surprises to scientists in recent years was the discovery that the majority of genes have been preserved across species. In fact, more than 98 percent of the human genome is identical to that of our closest relative, the chimpanzee. So what makes humans different from apes? Firstly, their communicative abilities. In the search for the genetic foundations of speech, scientists last year came across the Foxp2 gene in their study of a large family in which several members have speech difficulties. In the case of those family members who have a significant speech deficiency the gene is mutated, whilst those members with normal speech ability carry an intact Foxp2 gene.

Zebra finches are suitable test objects in many respects, not least because they are relatively easy to keep and breed in an aviary.

Under normal circumstances, Foxp2 carries the building instructions for a transcription factor, i.e. a protein which switches on specific genes. One hypothesis about the function of Foxp2 suggests that it controls the development of the neuronal pathways necessary for acquiring speech. In order to test this the researchers rely on an animal model which will allow them to track the neuronal processes that lead to abnormal development and consequently to impairment of the cognitive functions. The subject of Foxp2 mouse mutations is therefore hotly disputed. The breakthroughs could possibly be achieved in a completely different area than expected – namely in the field of bird research. The scientists working in Constance Scharff's research group in Berlin have now discovered that zebra finches also have a Foxp2 gene which is 98 percent identical to the human Foxp2. This reinforces the hope that under certain conditions this animal model can provide more information than the laboratory mouse living in a plexiglas box. This is because songbirds, with their acoustic communicative ability, are closer to humans than mice. "One must always keep in sight the brain's end product, as it were, namely the production of species-specific behaviour", says Constance Scharff. Perhaps the Berlin neurobiologists will succeed in demonstrating how Foxp2 contributes towards song and therefore indirectly to speech. In the USA in the meantime, a whole new generation of young neurobiologists using songbirds as a model has emerged and, as a result of their work, new chapters are being written into the established textbooks. And what about Germany? One enthusiastic researcher and a hundred zebra finches are in full flight across the "neurolandscape" in Berlin.

CHRISTINA BECK