Wolf Singer

Born:

Munich, Germany
March 9, 1943

Education:

Ludwig Maximilian University (LMU), Medicine (1962–1968)
Sorbonne, Faculté de Medicine et des Sciences (1965–1966)
State Examination in Medicine and Defense of MD Thesis at LMU Munich (1968)
Approbation as General Physician (1970)
Habilitation for Physiology (PhD), Technical University (TU) Munich (1975)

Appointments:

Independent Group Leader at the Max Planck Institute for Psychiatry, Munich (1975–1981)
Professor for Physiology at Technical University Munich (1980)
Director at the Max Planck Institute for Brain Research, Frankfurt (1981–2011)
Founding Director of the Frankfurt Institute for Advanced Studies (FIAS), Frankfurt (2003–present)
Chairman of the Ernst Strüngmann Forum (2006–present)
Founding Director of the Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with the Max Planck Society, Frankfurt (2008–2011)
Senior Fellow at the Ernst Strüngmann Institute for Neuroscience (2011–present)
Director emeritus at the Max Planck Institute for Brain Research (2011–present)

Honors and Awards (Selected):

Warner Lambert Lecture, American Society for Neuroscience, 1989
Neuronal Plasticity Prize of the Ipsen Foundation, 1991
Member of the Pontifical Academy of Sciences, 1992
Founding Member of the Berlin-Brandenburg Academy of Science, 1992
Ernst Jung Prize for Science and Research (Zuelch Prize), 1994
Hessischer Kulturpreis, 1998
Koerber Prize for the European Sciences, 2000
Chevalier de la Légion d'Honneur, 2002
Krieg Cortical Discoverer Award of the Cajal Club, 2003
Betty and David Loetser Prize, University Zurich, 2003
Communicator Prize, German Research Council, 2003
Dr. honoris causa, University Oldenburg, 2005
Dr. honoris causa, Rutgers University, N.J., 2008
Order of Merit (First Class) of the Federal Republic of Germany, 2011
Cothenius Medal, Leopoldina, 2013
Fellow of the European Molecular Biology Organisation (EMBO), 2014
Fellow of the American Association for the Advancement of Science, 2014

The early work of Wolf Singer concentrated on signal transmission in the visual thalamus and cortex and its modulation by nonretinal projection systems. Subsequently, he studied the synaptic mechanisms mediating experience dependent modifications of cortical architectures combining in vivo experiments in kittens with in vitro analyses of rodent cortical slices. Following the discovery of synchronized oscillatory responses in the visual cortex in the mid-1980s, his research focus shifted to the analysis of cortical dynamics in cats and monkeys. This work led to the proposal that the brain uses precise temporal relations between distributed neuronal responses for the encoding of semantic relations. This approach has later been extended to patients, using fMRI, EEG, and MEG technology and revealed characteristic disturbances of temporal coordination in patients suffering from psychiatric disorders. His current research tests the hypothesis that cortex exploits for its computations the high-dimensional, nonlinear dynamics of recurrent networks.

Wolf Singer

Early Years

Born during a horrendous and volatile period of history, I spent the first night of my autonomous life in the hospital's bomb shelter separated from my mother Sieglinde Singer, for my birth (on March 9, 1943) coincided with the first comprehensive air strike on Munich, one that left the clinic's roof ablaze. Reunited the next morning, a completely unanticipated knock at our hospital room's door introduced me to my father Joachim Singer. He was a medical doctor who, because of his expertise in mountain climbing, had been assigned to an army division in the Caucasus Mountains. Wounded by friendly fire, he appeared unexpectedly due to medical leave. This furlough was not to last, for soon he was ordered to return to the Eastern Front. On his way there, he learned that his unit had been destroyed in battle, and thus he headed back to Germany. En route he encountered, completely by chance, his younger brother Peter, a physicist who had been studying with Heisenberg, and who was being deployed to the Crimea with his unit. As with many families at that time, my father's family straddled two continents: His older brother, Hermann, had immigrated to Pennsylvania years before the war to join my paternal grandmother, a U.S. citizen and former cultural attaché in Berlin, who by that time had divorced from her German husband, my grandfather. The other brother, Peter, disappeared sometime after that chance encounter under unknown circumstances.

For the remaining years of the war, I lived with my mother and her parents in Soyen, a tiny village in upper Bavaria close to Wasserburg/Inn, where my grandfather was the head of a primary school. When the Third Reich collapsed, my father was in the eastern section of the Alps. To escape Russian captivity, he set off for home by foot, taking with him a wounded comrade. Despite several critical encounters with Russian soldiers, he was able to continue unhindered, for they took him to be an American army surgeon because of his perfect English. Once again, he appeared, most miraculously, at our door.

I grew up immersed in the idyllic setting of that small Bavarian village. The oldest of three siblings—a sister (Katrin, born in 1946 and living in the United States since 1988) and younger brother (Peter, born in 1954)—my grandparents lovingly cared for us while our parents struggled to secure our existence. My father abandoned his earlier dreams of an academic career to work as a general practitioner. Fragmented memories remain from those early years of American soldiers; care packages; excursions into the woods to gather berries and mushrooms; visits to farmers to collect much-needed sustenance (given in exchange for my father's medical assistance); the daily way to school, which took close to an hour on foot but far less on skis in the winter, and the freedom to choose which way to take; the odors of hay, dung, and moss; holy mass on Sundays; and long evening walks to remote chapels, where I was drawn to the solemn chants, accompanied by my grandfather on the organ, the candles, and the wafting scent of incense.

This idyll came all too abruptly to an end when I turned 10 for one simple reason: There were no secondary schools within reach of my village. Thus, I needed to go to boarding school.

The *Landschulheim Neubeuern*, founded by Baroness von Wendelstadt and Countess Degenfeld-Schonburg at the beginning of the 20th century, educated its pupils in the humanistic tradition. Situated in the *Schloss Neubeuern*, perched on a solitary rock in the middle of the valley overlooking the river Inn, the school offered not only a spectacularly beautiful view of the Alps but also a rich cultural history. Countess Degenfeld was a cultivated lady. She was host to the George-Kreis, a literary group named after the poet Stefan George that included many highly regarded German writers and academics. Richard Strauss and Hugo von Hofmannsthal were her guests when they conceived of the opera *Rosenkavalier*. The school was quite exceptional for its day. From the outset, it was open to girls as well as boys and students from around the world. Religious freedom was guaranteed and facilities provided to accommodate all practices. Not surprisingly, the school was closed by the Nazis during the war, but it reopened in 1948 with a renewed commitment to humanistic education.

My departure from home left me feeling lonely and vulnerable. The stunning beauty of the school's surrounding landscape, though, served as my main source of consolation. Thinking back, I realize now how much my daily encounters with such beauty shaped and influenced me. Fortunately, school left little room for self-pity, for in addition to our academic courses, we were required to learn a trade. Any "free" time was spent honing the necessary skills to qualify as a metal or wood worker. The rationale behind this technical training was not entirely educational: the school was in dire need of furniture and other goods. We were also expected to master a musical instrument, but I promptly abandoned piano lessons because I detested the methodical translation of notes into finger movements. With the help of my classmates and a decelerated tape recorder, I managed to teach myself how to play the string bass and later the clarinet, joined the jazz band, and greatly enjoyed playing by ear.

My true passion during this time—one that held and perhaps drove my professional orientation later in life—was bricolage. At school, I built a fleet of gliders and motor-driven airplanes and boats, some of which were controllable using self-made, tube-based remote controls, all of which had limited lifetimes. Once transistors became available, I was able to build much lighter remote controls as well as tiny radios, which could be hidden in hollowed-out books—precious items, since we were not allowed to listen to the radio at school. During my visits back home, I gradually transformed my bedroom into a lab equipped with primitive versions of many of the same “toys” that I would encounter much later in real labs. Because holiday excursions were the exception rather than the rule, I devoted as much time as possible to my experiments—probably too much, as might be said for later years as well. A lesser passion, but nonetheless tangible goal while at school, was to climb all the mountains visible from the terrace of *Schloss Neubeuern*. My father had succeeded in passing along his love for rock climbing and hiking to me, and I was eager to explore.

I completed my secondary studies in 1962. In Germany, it is tradition to take a break after one completes the *Abitur* (or baccalaureate) and before university studies begin. So, together with three friends, I set off for eight weeks to camp my way through Finland, up to the North Cape, and back down via Norway and Sweden. This experience not only taught us the wonder of being entirely free and self-paced but also exposed a far darker truth: When speaking to people along the way, we witnessed how our enthusiastic chatter—spoken with the intent of getting to know people—had the complete opposite effect. Our accents evoked terrible memories in those who had suffered at the hands of the Nazis, inextricably binding us to this dark period of German history. I had learned of the atrocities that Germany had perpetrated during the war. My parents were very articulate, as were the educators at the boarding school. But this experience left its indelible mark on me.

First Steps in Academia

Although, or perhaps because, my father had been such a shining role model of a practicing MD, I was determined not to pursue medical practice. I did, however, believe that the study of medicine could teach me about life and the human condition by revealing its biological underpinnings as well as the causes of failure.

The transition from the protected and in many respects artificial microcosm of boarding school to Munich, with all its temptations and anonymity, troubled me, as did the overwhelming course offerings provided by the university. I discovered countless alternatives to medicine, and after the first two semesters of basic courses, doubts grew ever stronger as to whether I had chosen the right area of study. My medical studies introduced me to most of the natural sciences and gave me the opportunity to see what was inside a human body through hours of meticulous dissection. Still, I felt that it afforded only glimpses into a universe that we were discouraged from exploring in depth. So I took courses for physicists and became fascinated by abstract and quantitative models, only to discover that this offered limited insight into the secrets of living matter. Philosophy seemed to be the way out, as I perceived it to be the meta-discipline that attempts to combine the knowable into a unified framework. So I enrolled in seminars of philosophical propaedeutics under the direction of Wolfgang Stegmüller (an analytical philosopher), and for a while was fully absorbed by the rigor of thought. Soon I began to realize that different options existed to interpret that which I previously viewed as facts. Unifying worldviews as proposed by Teilhard de Chardin, whom I had read with enthusiasm during boarding school, now appeared as only one of many possible stances. I felt unable to decide between naturalistic, constructivist, or phenomenological positions, and thus after a period of cerebral gymnastics, I humbly resumed my medical studies.

Focal Experiences

A sequence of three closely spaced events terminated this period of trial and error. The first involved my participation in a special course in anatomy, in which we were allowed to dissect human brains and trace macroscopic fiber tracts. Picking apart the organ that supports cognition, consciousness, and culture, and whose malfunction is at the root of mysterious psychiatric diseases, was a seminal experience—one that fully reconciled me to my studies. I chose to work in neurosurgery wards for the requisite internships during university breaks, first in Munich and then later at the Hôpital Foch in Paris, where earlier I had worked as an auxiliary nurse. I thought that nothing could be more fascinating than directly interfering with the brain in the context of therapeutic interventions. In Munich, where I was allowed to assist operations with large craniotomies to remove tumors, I remember being shocked by the crudeness with which brain tissue, whose delicate structure we had studied in the dissection course, was removed through suction. In Paris, I worked in the ward of Professor Guillot, a leading expert in stereotactic surgery who specialized in the treatment of Parkinson's. At that time, the method of choice was the coagulation of the subthalamic nucleus, and the difficulty was to locate this small structure. Neither computer tomography nor magnetic resonance tomography existed at this time; localization relied on X-ray films and arteriography. In the latter, film cassettes needed to be removed from the stack quickly and at regular intervals to obtain time-resolved representations of arterial and venous compartments—a procedure that constituted one of my jobs at the Hôpital Foch. I still can hear the command *feu* to which I had to respond *enlevé*. Surgical interventions were performed in lightly sedated patients because target location was complemented by electrical stimulation and subsequent evaluation of the patients' responses. For the first time, I saw how artificial activation of neurons in the brain can cause sensations and complex movements. I remember vividly how puzzled patients were when they realized that some agent, which they were unable to locate, had moved their limbs.

At the time of these initial concrete encounters with the mysteries of the brain, I was admitted to the *Studienstiftung des Deutschen Volkes*, a prestigious organization that supports select students with stipends, tutorials, and interdisciplinary schools. This brought me into contact with a network of brilliant students and academic mentors from all walks of science. We interacted intensely at summer schools and organized study groups throughout the year on such themes as "symmetry," "time," and "equilibrium." Through this, I experienced for the first time the joy of joint intellectual adventures.

The third event, which determined the rest of my life, came in 1964. Two directors from the Max Planck Institute (MPI) for Psychiatry—Paul Matussek (a psychoanalyst and orthodox Freudian) and Otto Creutzfeldt (a neurophysiologist)—offered a seminar on the neuronal underpinnings of consciousness. I signed up immediately, for my greatest wish was to understand how mental phenomena could result from the interaction of material elements. Matussek approached the issue from a first-person perspective, whereas Creutzfeldt concentrated on results from Sperry and Gazzaniga's work on split-brain patients. I learned that stimuli presented to the nondominant hemisphere can undergo extensive processing and even trigger actions in a person who is unaware of the stimulus, thus believing that the actions were self-initiated. Herein lay the deep questions concerning the relationship between mind and matter, the conscious and the subconscious, the conundrum of top-down causation, agency, and free will. I doubt that these terms or concepts were explicitly mentioned at that seminar, yet somehow my intuition led me to think that the exploration of such questions would constitute a most fascinating challenge. I approached Creutzfeldt after the seminar to ask whether there was a chance to do research on such topics under his mentorship. Only in my second year of medicine, he smiled and told me that I needed to learn a lot more beforehand and that once I had passed the preclinical exams, we should reconsider the issue. I took his statement to be a "yes."

Shortly after this brief encounter with my future mentor, and my firm decision to engage in brain research, I received confirmation that my application to study for one year at the University of Cambridge had been approved. I finished my preclinical studies in Munich, passed the required exams, and took another eight-week break with my friends (the same ones from the Scandinavian trip) to travel to Greece. Our in-depth exploration of the cradle of European civilization culminated in a one-week retreat at the monasteries of Mount Athos, thus concluding our *tour d´Europe*. When I returned to Munich, I officially withdrew from the university and moved to Cambridge to attend a language course at the Bell School, arranged by the *Studienstiftung* for foreign students who had been admitted to British universities.

Stolen Moments

The move to Cambridge in 1965 turned out to be as pivotal an experience as the seminar on consciousness, in terms of my private life. At the Bell School, I found myself in a vast community of students from all over Europe and shared with them the overwhelming experience of freedom, to which the insular character of England certainly contributed. In my class there was one particular French girl—a sophisticated, cultivated individual—who piqued my interest greatly, but she seemed well beyond my reach. For several weeks I even ignored that she could understand all of our German conversations, having studied in Heidelberg. On some evenings, I organized hypnosis sessions with several students, the French girl included, having learned the technique in Munich from a pupil of J. H. Schulz, who invented autogenic training. It was great fun, and the hypnosis worked. Some of the subjects reliably executed posthypnotic commands without being aware of them and gave explanations in an intentional format: "I opened the window because it is hot in here." This direct evidence for the power of subconscious processes impressed me deeply, reinforced what I had heard about the split-brain patients, and contributed to my burgeoning interest in the conundrum of free will.

At the end of the language course, the school organized a trip to London, including a Prom concert at the Royal Albert Hall. Preferring to take my own car (an old Volkswagen) rather than ride the bus, I invited the French girl to join me. We arrived early and went for a cup of tea, during which time some petty thief promptly cleaned out my car. At the time, this could hardly be viewed as a serendipitous event: Francine lost her handbag, complete with passport, money, and plane ticket, and thus unable to leave the island, as planned, the next day. It took countless trips to the French consulate, switchboard-mediated phone calls, and numerous telegrams (there were no fax machines at that time) to restore her identity. These additional weeks together, however, enabled us to become close friends, and for the next three years, we chased each across Europe. Had that thief picked a different car, our lives would have progressed on entirely different paths, perhaps never to see each other again.

Eventually Francine flew back to her world and I proceeded to the matriculation office at the University of Cambridge. For reasons that still aren't clear, my entire dossier detailing my acceptance was missing, leaving no possibility to begin my studies. Returning to Munich was not an option, since I had officially withdrawn from the university. I could have waited around in Cambridge for the next term, but instead decided on the spot to drive to Paris and register as an étudiant libre at the Sorbonne, where I was able to take all the courses that I would need later to continue my studies in Munich. Free to work in hospitals of my choice, I opted for St. Anne, to gain experience with psychiatric patients, and for the Salpétrière, which at that time was the mecca of neurology. I attended seminars by Professor Garcin, who analyzed patients and derived sophisticated diagnoses based solely on anamnesis (medical history), observation, and standard neurological examination. One of his diagnostic features that I clearly remember is *la main thalamique*.

Because I had interpreted Creutzfeldt to say that I eventually could study with him, I wrote to him to ask what I should study to qualify for work in his department. The reaction to this naïve question was overwhelming and a testimony to the admirable mentorship that this great scientist exhibited throughout his life. He contacted his friend and colleague, Pierre Buser, another icon in neuroscience, who generously allowed me to enroll in his course for neuroscience. This course was part of the *troisième cycle*, a level reserved for postgraduates wishing to specialize in a particular area. Much too young and inexperienced, I joined a small group of about 10 students and was introduced to electrophysiology through courses that took place every afternoon at Jussieu (now Université Paris 6). I was allowed to perform surgery on cats and practice field potential and intracellular recordings from motor neurons in the spinal cord. Professor Pearl, an expert in spinal cord physiology, happened to be spending a sabbatical in Buser's lab and volunteered to supervise the course. During these decisive months, I learned all the steps required to conduct a complex *in vivo* experiment in a mammal. The preamplifiers, which we built ourselves, were based on the principle of cathode followers to minimize the grid currents of the tubes. Because Mosfet transistors did not yet exist, the challenge was to come up with high input impedance and low noise.

These truly exceptional opportunities to study in Paris, along with the city's cultural offerings (through a quirk of fate I attended the legendary 1965 performance of *Norma*, with Maria Callas and Fiorenza Cossoto at the Opera Garnier), quickly negated all regrets I may have had about not staying in Cambridge. Paris and France became my second home. My only regret during this rich phase of life was that Francine was not there. She was studying in Geneva, which at that time was far away, thus precluding any spontaneous rendezvous. In addition, contact with my French peers was limited to discussions in bistros, as inviting me home was considered problematic, because of my German accent. In the midst of all the excitement, I often felt quite alone.

Back to Munich

In the summer of 1966 I returned to Munich to resume my medical studies and discussed with Creutzfeldt a possible thesis topic: I wanted to pursue split-brain research and he proposed that I examine whether commissurotomy would interfere with interhemispheric synchrony. This would involve electroencephalogram (EEG) recordings from implanted electrodes and commissurotomy. At the time, I had no idea what synchrony meant. Creutzfeldt suggested that I investigate whether transitions between synchronized and desynchronized states or the occurrence of alpha spindles would be less coordinated after commissurotomy. First, however, I needed to learn how to produce split-brain preparations, so Creutzfeldt wrote to Giovanni Berlucchi, a leading expert in split-brain experiments. Berlucchi who worked at the Moruzzi School[1] in Pisa, together with other eminent scientists, immediately agreed to teach me how to cut the commissures. In Pisa, Berlucchi patiently instructed me for several weeks in his method, guided my hands, and, at the end, presented me with a collection of the special spatulae he had engineered to retract the hemispheres. He also taught me how to section the chiasm using a transbuccal approach. I will forever be grateful to him for his hospitality and generosity during my stay.

After Pisa, I started to work in Creutzfeldt's lab at the MPI for Psychiatry. Because of flexible curricula, I was able to complete the clinical portion of my medical studies while working on my thesis. I entered Creutzfeldt's lab in its golden age: Creutzfeldt worked with Hans-Dieter Lux and guests from Japan (Ito, Watanabe) on the visual cortex, obtaining intracellular recordings with sharp electrodes and comparing these with field potential recordings in search of the underpinnings of the EEG; Max Straschill and Peter Hofmann were working on eye movements and the optic tectum; Bert Sakmann and Heinz Wässle were recording from the optic nerve; Henning Scheich and Uwe Heinemann worked in the EEG lab; Erwin Neher joined a bit later and teamed up with Lux to prepare the grounds for whole-cell recordings from snail neurons with fire-polished electrodes; and there was a continuous influx of guests from around the world who contributed their know-how. Together with the departments of anatomy, pharmacology, biochemistry, and the primate lab of Detlev Ploog, all of the classical disciplines of neuroscience were represented in-house. In addition, the institute was composed of an integrated research clinic for psychiatry and neurology. This remarkable density of expertise provided the most amazing fertile ground for research and collaboration.

Creutzfeldt's style, in terms of running a department, was quite unique. He granted us maximal freedom and let us learn by doing. He was always available when we needed his advice and took whatever time was necessary (which explains perhaps why he was always late). The lab was a common source platform. In principle, this was great as it permitted us to swap equipment. But it did, on occasion, result in unexpected problems (more than once a BNC cable was removed from the depths of a rack, and it took hours to discover what had happened). Considering the remarkably successful

[1] Pisa was a center of excellence in systems neuroscience due to Morruzzi's legacy. His impressive scientific offspring—Emilio Bizzi, Giacomo Rizzolatti, Lamberto Maffei, Piergiorgio Strata, and Giovanni Berluchi—have ably continued this tradition.

careers of all of those who were nurtured in Creutzfeldt's department, it is tempting to conclude that freedom and creativity are causally related.

Once I had collected my data (which today would be recognized as electrocorticography (ECoG) recordings of resting state activity and evoked potentials), I needed to find a way of processing it. Since we had no computers, evoked potentials could be visualized only by superimposing traces on the scope and taking pictures; evaluation of the continuous signals required inspection of traces produced by an EEG machine. Because the synchrony of the arousal-related state transitions was not influenced to a high degree by commissurotomy, I looked for more subtle markers, such as phase synchronization and co-occurrence of spindles. This required cross-correlation analysis. The only way to achieve this was to cut the EEG recordings, mark the zero crossings with a pencil, select a bin width, align several meters of continuous EEG records on the floor, shift them manually bin by bin against each other, and count the coincidences. This worked and showed a decrease in phase synchrony after commissurotomy. This analysis, however, was limited to the low-frequency bands, not only because of the archaic method but also because the ink pens could not cope with frequencies above 20 Hz. It took 20 more years before I resumed such analyses, albeit in an entirely different context. Only at the very end of my thesis was I able to obtain use of the first computer that could average evoked potentials as well as compute auto- and cross-correlations: the famous computer of average transients (CAT). It had ferrite magnets for memory, one could see the individual bits on the memory card, and altogether it had 4 K of memory—two seconds of data with one millisecond resolution for a cross-correlation. It was sensational, but of little help.

Upon completing the experimental portion of my research, I needed to shift attention slightly and complete another term of clinical work. I chose to do this in Paris and took with me the processed data (essentially films and EEG paper) to finish my evaluation. On the way back from Paris, during a brief stop at a restaurant along the French–German border, my car (the same old Volkswagen) was broken into again. This time, all the material for my thesis as well as the textbooks needed to prepare for my imminent final exams were taken. After two days of combing through all the garbage depots in the region, I reconciled myself to the fact that this material was gone forever. It was hard to find a serendipitous effect from this theft. Thus, more experiments needed to be conducted. By the time I submitted my thesis, I had compensated for most of the lost material. The thesis was published in *Experimental Brain Research*, in German with an English abstract—a common practice at that time (Singer and Creutzfeldt 1969).

The Phase Transitions toward Independence

After passing the final exams for my medical studies and defending my thesis in the autumn of 1968, Francine and I accomplished what we had apparently been striving for since Cambridge: we married on December 31. Much, of course, had happened in the interim. Francine had finished her studies of German literature in Geneva and cooperated with the historian Saul Friedländer on the history of the Third Reich, before moving to Paris where she worked as a translator for the publishing house Casterman. And although my medical studies were now behind me, two years of clinical training at the Munich university hospital were required before I could be licensed as an MD. Thus, our life together needed to begin in Munich, rather than Paris—a decision made even more attractive because of an offer from Creutzfeldt to let me finish various projects that I had undertaken after the commisurotomy experiments. What could have easily erupted into a dual-career problem was avoided due to Francine's willingness to move to Munich, for which I will forever be grateful.

Although I relished my thesis project because it involved delicate surgery and the handling of awake animals, major conclusions about brain functions could not be drawn, other than that commissures play a role in the temporal coordination of low-frequency oscillations. There were just too many unresolved questions with regard to the cellular correlates of the EEG and the functional implications of the conspicuous frequency changes. So, I began to record from the lateral geniculate body of cats with pipettes, hoping to be able to obtain intracellular recordings, as others were able to do in the cortex, and to look for stimulus-dependent changes in transfer functions. This turned out to be quite challenging, but one peculiar and encouraging observation emerged: after electrode resistance increased, as one probed for neurons, the spikes became positive and monophasic and one could see what looked like excitatory postsynaptic potentials (EPSPs), the frequency of which was clearly resembling that of ganglion cell discharges. There was no clear DC shift, but I observed depolarizing and hyperpolarizing fluctuations of the membrane potential that correlated well with the discharges. These recordings, which we called "quasi-intracellular" recordings, allowed me to get reasonably comprehensive samples of cells to study the dynamics of signal transmission and inhibitory interactions. For the first time, I had seen parts of the brain work in an interpretable way and experienced the excitement of having uncovered something that no one had ever seen. These observations formed the basis of my first publications in English (Singer and Creutzfeldt 1970).

One conspicuous finding from these first "quasi-intracellular" recordings of geniculate cells was that transfer functions did not only change as a result of stimulus conditions, they did so, even more, in conjunction with global state changes that occurred despite constant levels of anesthesia. When the EEG displayed delta waves, cells hyperpolarized and failed to transmit retinal EPSPs, they exhibited enhanced inhibition by other retinal channels and changed from a sustained to a bursting discharge pattern. From Morruzzi and Magoun's as well as Jouvet's seminal studies, it was known that the projections from the mesencephalic reticular formation, the ascending reticular arousal system (ARAS), were responsible for a suppression of slow EEG waves and that this suppression caused desynchronization (i.e., an increase of low-amplitude high-frequency oscillations that occur at the expense of large-amplitude slow oscillations). Because all of these signatures of arousal could be elicited by electrically stimulating the reticular formation, I set out to study the effects of stimulating the reticular formation on intracellularly recorded responses in geniculate neurons. Initial experiments were performed together with Ursula Dräger, who had come to Creutzfeldt's lab before moving to Harvard to work with Hubel and Wiesel (Singer and Dräger 1972). Perfecting our approach, we obtained true intracellular recordings with the appropriate negative DC shift and overshooting spikes, and saw that reticular stimulation caused a complete blockade of IPSPs, irrespective of whether they occurred spontaneously or were induced by light stimuli or electrical stimulation of the chiasm or the optic radiation. This explained the changes in transfer function and gave rise to a long series of studies that continued well into my first years at Frankfurt. The first review of this line of research appeared later in *Physiological Reviews* (Singer 1977) and served as the basis for my *habilitation*[2] at the Technical University of Munich.

Phase transitions of all sorts were under way, but one particular event marked my life more than any scientific discovery: the birth of our twin daughters, Nathalie and Tania, in December 1969. This intended expansion of our family changed our lives and priorities in a profound and wonderful way, far beyond anything that could have possibly been previously imagined—a fact that remains constant and unchanged to this day. As parents, we learned that the girls could not only survive but thrive, even if we were not omnipresent, and so Francine began to work for the *Bayerische Rundfunk* (Bavarian Broadcasting), taking care as an editor and presenter of the program in French language. Even as infants, the girls had clear agendas, irresistible charm, and, if required, were able to insist on what they needed. When necessary, we were able to rely on experienced and caring grandparents on both sides, and so somehow our lives transitioned without too much worry.

Around this time, I received a grant to pursue the basics in behavioral and cognitive psychology in another country. Having completed my clinical training in internal medicine, obstetrics, and surgery, I was free to move and chose the department of psychology at Sussex University, headed by Stuart Sutherland, because it seemed to combine behavioral approaches with neuroscience, at least on a conceptual level. So, in the winter of

[2] Earned after one has obtained a PhD, the habilitation is the highest academic qualification a scholar can achieve in Germany. It is based on a thorough, external review of independent scholarship and qualifies a person to teach at a university and supervise PhD students.

1970–1971, the four of us moved to Brighton. It was the year of the miners' strike, which meant that there was no coal to be had for the furnace and, most of the time, no power for the electric heater. On more than one occasion, we went to bed fully dressed. Using the children's buggy to collect wood in the nearby forests, we embraced the situation as an adventure rather than a nuisance. My mentors in the department were Fred Miles and Bill Phillips. I learned to shape and condition pigeons in Skinner boxes and to compile training schedules with analogue circuits consisting of relays and all sorts of logical gates. Above all, I became acquainted with the psychophysical experiments of Bill Phillips—an encounter that proved crucial for my further orientation. With his access to a huge computer, he could produce checkerboard patterns on a cathode ray tube (CRT) screen. He examined the phenomenon of iconic memory—the ability to store information of complex pictures beyond the offset of the picture so that even small changes introduced in a subsequently presented picture could immediately be detected. As test patterns, he used sequences of random checkerboards, to which he either added or deleted one of the squares. Bill found that subjects easily detected changes of either polarity *if* the second pattern followed the offset of the first by no more than about 150 milliseconds. The effect depended critically on a precise retinotopic alignment of the patterns and showed only little interocular transfer. This suggested a retinal or thalamic mechanism. Because I had found powerful retinotopically specific inhibitory interactions between ON and OFF channels in the lateral geniculate nucleus (LGN) through my quasi-intracellular recordings, I was able to predict how the offset of a bright square would influence the responses to the reappearance of the same square, and how this response would differ from that of a newly appearing square. Under the assumption that these differences in ON responses supported change detection (the same would be true for OFF responses of disappearing squares), Phillips and I set off (with pencil and paper) to formulate a set of 12 predictions on how performance should depend on the temporal parameters of stimuli. Some of these predictions were extremely counterintuitive—for example, if the first pattern is flashed only briefly, detection of an added square should become possible only after longer interstimulus intervals, but then over a longer time period. The reason is the long latency of OFF responses to short stimuli. Step by step we tested these predictions and were able to confirm all of them. After returning from Sussex in summer 1971, I tested whether the responses in the geniculate actually behaved as predicted and found a perfect quantitative match between cellular responses and human performance (Phillips and Singer 1974; Singer and Phillips 1974). We had found a function for the inhibitory interactions between ON and OFF channels. Just as lateral inhibition between channels of similar polarity enhances spatial contrast and suppresses redundancy, inhibition between channels of opposite polarity enhances temporal contrasts and suppresses redundant responses to unchanged contours of briefly interrupted or occluded patterns. This synergetic experience between behavioral and neurophysiological approaches was eye-opening and has henceforth influenced much of my work; psychophysics has remained a complementary tool that I draw on to this day. Equally rewarding is my close friendship with Phillips, whose deep knowledge of cognitive neuroscience and genuine interest in neuronal mechanisms has been and still is a precious source of inspiration. We continued to cooperate and discovered a strange long-range effect between magno- and parvocellular-processing streams (Wilson and Singer 1981; Leonards and Singer 1997), which strongly suggested that the brain establishes semantic relations between precisely synchronized stimuli—a notion that gained importance later in my work on the binding-by-synchrony hypothesis. Phillips sent brilliant students to my lab, the last being Peter Uhlhaas, who joined me in Frankfurt in 2006 and led most of our work with psychiatric patients. My stay in Brighton exposed me to an entirely new sort of academic culture, one that differed in many respects from what I had experienced in Paris and Munich. Discussion seemed to be the top priority, catalyzed by sacred tea breaks and joint ventures to the pub. I vividly remember how surprised I was to learn that the huge computer at the institute—which must have cost a fortune at the time—was not used around the clock, even though there was ample competition for its use. It sat idle during tea as well as over the sacred weekend. It took me until much later before I discovered the virtues of discourse and the primacy of thinking over doing. My only regret is that I did not pay sufficient respect to these priorities earlier.

In 1971, another remarkable event took place that brought me into contact with virtually all the famous neuroscientists in the field of systems neuroscience. Creutzfeldt organized a large international neuroscience symposium that was to take place in August at an Austrian resort. Unfortunately, shortly before the meeting, the resort went bankrupt, and thus another location capable of accommodating close to 200 participants needed to be found quickly. Immediately my thoughts went to my boarding school at *Schloss Neubeuern*, knowing that the school would be closed in August for summer holidays. Discussions with the school's administration followed, personnel were called back from holidays, and the conference was moved to the castle. It was probably the first and last time that the world's most eminent neuroscientists had to share rooms with up to six beds and use common bathrooms. Such were the conditions imposed on David Hubel, Torsten Wiesel, Sir John Eccles, Janos Szenthagothai, Peter O. Bishop, Peter Schiller, Masao Ito, Larry Weiskrantz, Vernon Mountcastle, and Konrad Akert as well as many others. It was my first encounter with the "grand world." The intimate setting of this week-long conference—complete with its necessary improvisations and inspired by the surroundings—allowed us as young researchers to get to know these top-level scientists from their best side. The Neubeuern Meeting was a historical event, as all those still alive will certainly attest.

Shortly thereafter, Creutzfeldt accepted an offer from the Nobel laureate Manfred Eigen to join him as a director of the newly founded MPI for Biophysical Chemistry in Göttingen. Creutzfeldt offered me a position in his new department, but I hesitated, partly because I felt the need to forge my own way. Also, the ability to combine clinical research in neurology and psychiatry with basic research—a distinguishing feature at the Munich institute—was particularly important to me. Munich offered unique chances for collaboration, some of which later bore fruit. But perhaps the real reason behind the decision to stay in Munich happened on a more personal level: We loved our life there, and Francine had just begun to grow roots in this town.

Ambiguous feelings began to surface about my decision to remain at the institute. Most of my colleagues had left or were about to leave. The farewell party for Creutzfeldt late in 1971 was a particularly sad event, although it also marked the beginning of a new epoch in many ways. Bert Sakmann, who had made a detour to the lab of Bernhard Katz before moving to Göttingen, joined Creutzfeldt's new department together with Erwin Neher. (The consequences of their teamwork—logical continuations of the approaches Neher had practiced with Lux and Sakmann with Katz—led to the 1991 Nobel prize, awarded for the invention of the patch clamp technique and the discovery of single channel gating currents.) Lux was named the new director of the MPI neurophysiology department and accepted me as a postdoc. He made it clear that he valued my cooperation but he also encouraged me to independently pursue my research interests, which differed from his. He allowed me to build my own lab in an annex, where I had use of three adjacent rooms. Because Creutzfeldt had generously left behind most of the needed equipment, I was able to continue my experiments within a short time.

Another decisive event that spurred me along the path toward independence involved my recruitment into the *Sonderforschungsbereich Kybernetik* (collaborative center for cybernetics). Financed by the *Deutsche Forschungsgemeinschaft* (German Research Council), this consortium of physiologists, mathematicians, physicists, and behavioral psychologists aimed to apply methods developed in the young field of cybernetics to the investigation of the nervous system. It was created to unite behavioral work being done at the MPI for Behavioral Research in Seewiesen[3] with psychophysics and mathematical modeling from the physics departments at the Technical University of Munich. My participation in this long-term project (which lasted 12 years) profoundly influenced my thinking, kindled my interest for theoretical approaches, and provided a rich intellectual environment. It also ensured my growing independence by providing me with

[3] Seewiesen is where Konrad Lorenz observed his geese and von Holst and later Horst Mittelsteadt pioneered the reafference principle and the notion of corollary discharge.

the necessary funding to hire personnel and buy my own equipment. Most important, the consortium required me to teach neurophysiology to students in nonmedical disciplines. This forced me to structure formal lectures, chair oral and written exams, and eventually to recruit PhD students on my own.

These academic activities ran parallel to my duties at the medical faculty, where I was required to conduct practical courses in preparation for the *Venia Legendi* (certification to teach at the university level). These practical courses aimed at exposing medical students to in vivo experiments on anaesthetized rabbits. Even in the 1970s, fierce discussions erupted over the ethical use of in vivo demonstrations to explain physiological processes. Sometimes, students would refuse to participate, thus prompting the need for in-depth discussions. The most efficient argument that changed their mind was not that something useful would be learned that could affect their performance as an MD but rather that such rabbits usually are eaten and sacrificed under much less humane conditions. For many students, these courses provided the first, and for many the only, opportunity to study live critical processes in a controlled setting and to experience the extent to which cardiovascular functions need to be coordinated by the nervous system to support life. Despite the options that virtual reality simulations are able to create, I am convinced that a minimum of such direct, hands-on experience is necessary in medical training, especially for MDs who do not go into surgery but may still have to cope with critical situations.

Excursions from Science

As of about 1974, the immediate future seemed reasonably secure and I was well situated to pursue my own research agenda. Before describing the directions that this took, I wish to highlight several nonscientific events that contributed to my development.

The first event concerns the dichotomy between medical practice and scientific enquiry. Almost immediately after I completed my clinical training and was licensed as an MD, I began to regret the distance from patients that research demanded. At times I doubted whether I should do something more useful and less frustrating than science and become a clinician. In search of a compromise, I arranged to work in my father's practice as a general practitioner twice a week: on Monday and Friday evenings, when his practice was open to those who could not come during the day. I continued this routine until I moved to Frankfurt in 1982, not only because it was extremely rewarding on a personal level, but because it provided a much-needed balance to research.

The second concerns a series of collaborations that emerged out of the neurological department of the institute, which I attribute to the openness and charisma of Yves von Cramon, a neurologist (and later director at the MPI for Cognition and Neuroscience in Leipzig). Yves was a walking encyclopedia of human brain anatomy and neurological syndromes, and, as a passionate clinician, he encouraged me to delve deeper into neurology. His passion was infectious, so I donned a white coat and took over a neurology ward with 12 beds, under the naïve assumption that I could accomplish my clinical duties in the morning and conduct research in the afternoon. The ward was run by excellent nurses, and I had no acute patients. This experiment lasted for about a year and could have lasted longer, even though it did slow down my research and divert my attention. The main problem, however, was that I was unable to cope with the daily switches between roles. In the morning, as a clinician, I had to reach clear and definitive decisions, often on the basis of weak evidence, and stick to them for the sake of therapeutic continuity. I also needed to conceal my doubts so as not to jeopardize any positive effect of the patient–doctor relationship. Then as a scientist, in the afternoon, I needed to transform into a skeptic who doubts, despite robust evidence, and constantly worries about alternative interpretations. I experienced why it is so difficult to nurture, in one and the same person, the different mind-sets required for clinical and scientific work (for an extended discussion on this topic, see Bleuler 1970).

The third incident unfolded after I received an entirely unexpected letter from the army. Informed that I had been passed over for military duty after I completed high school, I was now being called up to fulfill my military service as a medical doctor for the next 18 months. The army desperately needed licensed MDs. The fact that I was running a lab and was responsible for my first PhD students was completely irrelevant to the army. What eventually confined this disaster to a period of six months was the fact that I was engaged as an academic teacher. I was sent to an army post in Munich, where, to my great delight, I ran into Bert Sakmann and a few others with whom I had studied. After the usual march-and-stand-still routine, we were instructed in the duties of a military MD; in particular, triage and the top priority of reestablishing combat fitness. This all happened at the peak of the Vietnam War, and much of the film material used for instruction had been produced by the U.S. Armed Forces. We found ourselves in an absurd and surrealistic world, yet it was all too real. After two months of basic training, I was promoted to the grade of a captain and ordered to the army hospital, where I was to serve as second-in-command at the psychiatry division. To my great surprise, I was my own boss, with my own adjuvant. I could dispose over an official car including a driver (something which has never happened to me since), and I could discharge soldiers from the army without asking anyone's permission. All in all, the episode was highly instructive and much less catastrophic than I initially imagined it would be.

The First International Invitations

After my early work on the intracellular analysis of the retinal and extraretinal control of thalamic transmission made it over the Atlantic, I received two wonderful invitations that had long-lasting consequences. The first was an invitation to attend a symposium of the Neuroscience Study Program in Boston.[4] This trip, my first to the United States, brought me into contact with eminent colleagues. I recall one remarkable discussion between János Szenthagothai and David Hubel: Szenthagothai presented his fantastic Golgi pictures of the cerebral cortex, showing for the first time the horizontally spreading axon collaterals of pyramidal cells in the visual cortex, which could span several millimeters. Hubel and Wiesel had confirmed, in the visual cortex, the columnar organization first described by Mountcastle in the somatosensory cortex. Both this strict topographical organization and the small size of the receptive fields seemed incompatible with any lateral interactions. Thus, Hubel argued that these long collaterals could not have a function in information processing but rather they probably served some mechanical or trophic purpose. Cortex was considered a feed-forward filter network, and the contextual integration of signals from outside the classical receptive field was not thought possible. Szenthagothai postulated such integration, but it took several decades before the evidence was forthcoming. Charles Gilbert, working with Torsten Wiesel at Rockefeller, was among the first to analyze with modern tracing techniques and electrophysiological methods the anatomy and function of these tangential connections and demonstrated their critical role in shaping the responses of cortical neurons to contextual stimuli.

The second set of invitations took me around the world: I was invited to a satellite symposium organized by Peter O. Bishop in Canberra, Australia, as well as to the main meeting of the IUPS (International Union of Physiological Sciences), which was to take place in New Delhi in 1974. An additional invitation followed from the Instituto Venezolano de Investigaciones Científicas (IVIC in Caracas, where an impressive number of prominent neurobiologists were to gather, among them Horacio Vanegas, who had spent some time at the Munich institute). These invitations were too tempting to pass up so, although the children were only about four, Francine and I decided that I should go. I booked a ticket on PanAm flight number 1 (the designation for an around-the-world flight) and departed for Caracas. In addition to the IVIC meeting, I met the family of Ernst Poeppel's wife. (Ernst and I shared a miniscule office in Creutzfeldt's lab before he left to be the head of the medical psychology department at Munich University.) From Caracas I flew on to Mexico, where Francine joined me for two weeks. We explored the Yucatan and the Sierra Madre mountains, and visited Pablo Rudomin, the famous electrophysiologist, and his wife, who was a painter. After Francine returned home, I continued along the West Coast, stopping in San Diego to give a talk

[4] Founded by F. O. Schmitt in 1962, in conjunction with the American Academy of Arts and Sciences, the Neuroscience Study Program provided a focus, through its conferences and publications, for research in neurosciences throughout the world.

at the Salk before going to San Francisco and Stanford to visit Christian Guilleminault (a sleep researcher and friend), who worked in William Dement's lab (one of the pioneers of sleep research). From there, I flew on to Australia where I met up with Creutzfeldt and became acquainted with the Canberra school. After Canberra, I originally had planned to go hiking in Nepal before the IUPS meeting. Because my hiking gear had been stolen in Mexico, I accepted Creutzfeldt's proposal to spend a few days with him in Thailand. Our visit in Bangkok was fascinating for many reasons, not the least due to Creutzfeldt's offer to address him by his first name.[5] From there Creutzfeldt went straight to Delhi, while I took a side trip to Kathmandu (which was still a medieval village) to explore its surroundings by bike. Over the course of this trip, my European chauvinist prejudices diminished greatly as a result of these fascinating encounters with different ancient cultures. It left me to ponder, on more than one occasion, the relevance of my highly focused science, the mosaic stones of which I carried with me on slides, which seemed so completely disconnected from the marvels I witnessed. After spending the required bribe, I took a flight to Delhi that had a long stopover in Calcutta—an experience that left me deeply depressed, even more so after I participated in the luxurious reception ceremonies that awaited in Delhi, which exceeded anything that I could have possibly imagined.

Eight weeks after my departure, I returned home. My view of the world and my place in it had profoundly changed. Everything had shrunk and become unfamiliar, and it took time to figure out what really mattered.

Difficult Decisions

During these formative years in Munich, I received two offers for tenured chairs. The first came, in 1972, from the University of Bielefeld to lead the Department of Human Biology. Although I did not have a permanent position in Munich, I declined the offer straight away because I felt that it had come too early in my career.

The second followed in 1976 from the Brain Research Institute in Zurich, which was headed up by Konrad Akert and Michel Cuenod. The decision surrounding the Zurich offer, however, was much more difficult. This process began with my participation at an international conference in Davos, Switzerland, at which all the principal investigators from the Zurich Institute were present. Unaware that the conference was a type of exam or interview, I embraced the scientific discourse and enjoyed the surroundings.[6] I was drawn to the offer, not the least because of the

[5] The importance of this cannot be underestimated; however, I know of no counterpart in Anglo-Saxon countries to convey its gravity.

[6] The conference was held in the famous Schatzalp Hotel that had served as the setting for Thomas Mann's novel *Der Zauberberg* (*The Magic Mountain*).

charisma of both Akert and Cuenod. The research environment was excellent, and I already knew many of the colleagues (e.g., Klaus and Marie Claude Hepp), which would have helped the transition. Those who I consulted all advised me to take the offer, as it was clear that Munich could not offer a long-term perspective. However, I felt that I had what I needed (at least for the present) in Munich: My lab was the right size and cooperation with the clinic was excellent. Above all, my family was well adjusted. The decision was made in Dubrovnik, at the International Neuropsychology Symposium (in 1979), just after I had been elected to the society. Thus, we continued to live and work in Munich.

The Shift to Developmental Neuroscience

My research into the lateral geniculate was drawing to an end because I had gone as far as I could (and would not resume until after I moved to Frankfurt and had the means to investigate in detail the mechanisms underlying the nonretinal modulation of thalamic transmission). For the final experiments in the thalamus, I greatly profited from the extraordinary expertise in membrane physiology of Lux, who taught me how to build high-impedance preamps and bridge circuits for current injection as well as how to fabricate ion-selective electrodes. We used these to measure extracellular potassium concentrations to explain the origin of the depolarization of optic tract terminals associated with reticular stimulation, which was considered to be an indication of presynaptic inhibition. Showing that this depolarization of primary afferents was caused by increases of extracellular potassium, we were able to disprove the hypothesis of presynaptic inhibition, which was popular at the time (Singer and Lux 1973).

My next goal was to trace the flow of visual responses beyond the geniculate, applying the same combination of methods as before. Aided by a real computer—the famous PDP-8 with 8 K core memory and DEC (Digital Equipment Corporation) tapes for data storage—my group performed current source-density analysis of field potentials evoked by light and electrical stimulation, a method implemented in the lab by my first postdoc, Ulla Mitzdorf (Mitzdorf and Singer 1978). This procedure greatly facilitated the laminar analysis of signal flow in cat and monkey visual cortex and enabled us to confirm the serial flow of signals from layer IV to supra- and infragranular layers. It also led to the discovery of monosynaptic activation of complex cells. The greatest surprise came from area 18, which was thought to be a higher order visual area: We found that it was activated by a direct input from the geniculate, similar to area 17. Conduction time analysis indicated that this input was provided exclusively by ganglion cells of the Y-type, the homologue of the magnocellular pathway in primates. Because of the nonlinear properties of this ganglion cell type, monosynaptically driven cells in layer IV of area 18 looked like complex cells. This observation led Hubel and Wiesel to suggest that area 18 was a secondary area, similar to monkey V2. According to our research, however, area 18 was a primary area that worked in parallel to area 17 and is specialized in the processing of fast movements. This work, conducted with my first PhD student, Felix Tretter, and my second postdoc, Max Cynader, was reported in the *Journal of Neurophysiology* (Tretter et al. 1975a). We were overwhelmed by the difficulty of establishing clear relations between receptive field properties and the complex interplay of excitatory and inhibitory potentials. The methods that had worked well for the geniculate were insufficient to address the complexity of cortical circuitry. We lacked both theory and techniques. Thus, I decided to change strategy and delve into the development of this structure, under the assumption that studying the maturation of functions would facilitate the approach.

Around this time, Pettigrew (1974) and Blakemore (Blakemore and van Sluyters 1975) published data on the effects of selective rearing in the orientation selectivity of cortical neurons of kittens, triggering a fierce controversy with those who claimed that the cortex was hardwired and not susceptible to experience-dependent modification. If everything is determined right after the eye opens and can degenerate only as a result of deprivation, as shown by Hubel and Wiesel (1970), studying development would only serve to complicate, rather than simplify, the search for principles. Clarity was needed, and we decided to verify to which extent orientation and direction selectivity were expressed at birth and modifiable through experience. In our experiments, dark-reared kittens were placed for a few hours each day on a stationary chair positioned in the center of a rotating drum, the inside of which had been painted with regularly spaced stripes. We observed that this selective experience induced a strong bias in the distribution of orientation and direction preferences (Tretter et al. 1975b). We also found, quite unexpectedly, that about 30 percent of the cells in supragranular layers developed multiple receptive fields, the spatial separation of which corresponded precisely to the spacing of the stripes of the grating. We hypothesized that this was due to selective strengthening of long-range reciprocal excitatory connections between the coherently activated columns according to a Hebbian mechanism (Singer and Tretter 1976). This finding greatly influenced our future projects, for it suggested that experience has a constructive effect on the development of cortical circuitry, that the modification of cortical circuitry followed Hebbian learning rules, and that the long-range collaterals (described earlier by Szenthagothai) actually had a function (see above) and served lateral integration. Together with Joseph Rauschecker (my second PhD student), we set out to prove that the selective strengthening of excitatory connections depended on correlated pre- and postsynaptic activity using monocular deprivation, restriction of vision to contours of a single orientation with cylindrical lenses, interocular rivalry, and strabismus as paradigms (Rauschecker and Singer 1979, 1981). To derive a more comprehensive picture of columnar remodeling, we applied the recently introduced C14 deoxyglucose method, which revealed that most of the functional remodeling occurred outside layer IV, most likely at the level of intracortical connections (Singer et al. 1981). This finding was confirmed with the current source-density method (Mitzdorf and Singer 1980; Kossut and Singer 1991). Because there were no image-processing systems at the time, we reconstructed serial sections by staggering photographically magnified autoradiographs or hand drawings between stacks of acrylic glass plates. These compact blocks created impressive three-dimensional representations of the columnar system of cat visual cortex and clearly revealed the massive influence of experience on the functional architecture.

In the mid-1970s, Ruxandra Sireteanu and Michael von Grünau joined the lab and we complemented the electrophysiological studies in selectively reared kittens with behavioral testing. We discovered that strabismic kittens had strongly reduced numbers of vertically oriented neurons and that this coincided with reduced visual acuity and contrast sensitivity for vertical gratings in both kittens and strabismic human subjects (Sireteanu and Singer 1980). Thus the relative number of feature detectors seemed to matter for perceptual functions.[7] Psychophysics in human subjects with altered visual experience became an important line of research in the lab that nicely complemented the electrophysiological studies in kittens and attracted experts from abroad, such as Daphne Maurer.

In humans, we attempted to find perceptual correlates of the experience-dependent modifications that we had observed in kittens. One of Sireteanu's students, Maria Fronius, suffered from strabismic amblyopia but was nonetheless an expert tennis player. To approach this apparent conundrum, we assumed that her peripheral visual field had preserved binocular functions. We knew that neurons in the suprasylvian cortex of strabismic kittens retained binocular receptive fields, presumably because these fields are large and overlap despite squinting (Sireteanu et al. 1981), thus allowing for partial fusion. We tested binocular functions in Fronius and found that she was perfectly able to perceive motion in depth, although she had no stereopsis for stationary patterns.

Having observed the dramatic functional and structural consequences of deprivation, we wondered why nature made development dependent on experience, thereby exposing it to the fatal consequences of deprivation. Because we had observed that activity-dependent changes in circuitry followed a Hebbian correlation rule, we proposed that experience-dependent pruning was used to ensure precise convergence of afferents from corresponding retinal loci on common binocular target cells in visual cortex—the prerequisite

[7] It took us another decade to discover that amblyopia also was associated with changes in cortical dynamics and that it caused reduced synchronization among neurons (Roelfsema et al. 1994).

for binocular fusion and stereopsis. This convergence cannot be achieved with the necessary precision by genetically encoded markers because retinal correspondence depends on the final size of the skull and interocular distance. Our assumption was that afferents coming from precisely corresponding retinal loci should convey highly correlated responses because they are driven by the same contour in the visual field. Thus, we hypothesized that experience serves to select from a repertoire of overlapping afferents, those that exhibit the best correlated activity patterns, and that it does so using a Hebbian correlation rule. Such a selection mechanism would only work, however, if plasticity was supervised, because it requires that the eyes are still and fixating. Therefore, we began to search for mechanisms that could gate developmental plasticity.

Michel Imbert and his group in Paris had established that ocular dominance changes could not be induced in anesthetized, paralyzed kittens, thus suggesting that driving cortical cells with light stimuli is insufficient to induce synaptic changes. Reasons proposed were that the Hebbian process had a threshold that is reached only once the excitability of cortex is raised by the ARAS or that more specific corollary signals are required about the state of the oculomotor system or the position of the eyes. Together with Pierre Buisseret, we tested the latter and disrupted the proprioceptive input from the extraocular muscles bilaterally by severing the ophthalmic branches of the trigeminus intracranially as they exited the Gasserian ganglion. This did not interfere with eye movements, which are ballistic and thus not controlled by feedback from the muscles. It did, however, completely prevent ocular dominance shifts following monocular deprivation and strabismus (Buisseret and Singer 1983). We concluded that input from the extraocular muscles enabled plasticity, in agreement with our working hypothesis. Later I found that stretching the extraocular muscles after detachment from the eyeballs caused short latency responses in cortical neurons: (a) stretching the lateral rectus muscles activated cells with vertical receptive fields; and (b) stretching the superior and inferior recti triggered responses in cells with horizontal orientation. Unfortunately these findings have not been validated, by me or others, although it might clarify the enigmatic role of this proprioceptive system.

Rather than investigating further the pathways that mediate these proprioceptive effects, I pursued the stated hypothesis to see whether it was possible to reinstall plasticity by pairing reticular stimulation with monocular light stimulation in anesthetized, paralyzed kittens. This worked, and we obtained ocular dominance changes after a few hours. We were able to follow the time course of these changes by repeated comparison of evoked potentials elicited with electrical stimulation of the two optic nerves (Singer and Rauschecker 1982). These results suggested that the overall level of excitability or some internally generated permissive signals also played a role in gating synaptic plasticity, a hypothesis that we continued to investigate in detail in Frankfurt.

In the late 1970s, Uri Yinon contacted me to ask whether we could help him record from the visual cortex of cats in which he had induced a rotation of one eye while they were young to study compensatory processes. To our great surprise, these animals displayed no ocular dominance shift toward the open rotated eye, even though the other eye had been sutured closed to ensure use of the rotated eye: neurons in the visual cortex responded to stimulation of either eye and had normal receptive fields. This suggested that retinal signals are able to induce Hebbian modifications only when identified as appropriate in a more global visuomotor or polysensory context. Because of the heterogeneous history of these cats, we repeated the experiments and confirmed the findings (Singer et al. 1982a, 1982b). A more quantitative analysis of response properties revealed, however, that cell responses were more sluggish and less well-tuned than in normally reared animals, conditions resembling to some extent those previously observed in binocularly deprived cats. This substantiated the outcome from behavioral tests: Initially, the animals exhibited ocular and head nystagmus, but after a few days, they appeared to neglect vision altogether, although they kept their rotated eye open, walked over visual cliffs, and showed strongly reduced visual-orienting behavior. They got along very well in the colony, however, apparently relying on their whiskers and auditory cues. We hypothesized that the mismatch between retinal signals and eye, head, and body movements as well as other sensory maps (especially the vestibular coordinates) would prevent the generation of permissive extraretinal signals, which seemed to be required to gate experience-dependent plasticity. This evidence for the implementation of such supervising systems motivated much of the developmental work that was later continued in Frankfurt.

The Move to Frankfurt in 1982

The MPI for Brain Research in Frankfurt has a long history. It is considered to be the continuation of the Kaiser Wilhelm Institute for Brain Research, which was established in 1914 by Oskar Vogt and housed in Berlin-Buch until the end of World War II. After the war, its various departments were dispersed throughout Germany. In 1948, the Max Planck Society was founded to succeed the Kaiser Wilhelm Society and in 1962, the MPI for Brain Research was established in Frankfurt to reunite the departments of neurobiology and neuropathology under the direction of Rolf Hassler and Wilhelm Krücke, respectively.

In keeping with its statutes, the Max Planck Society sought advice on possible future scientific directions for the institute in advance of Hassler and Krücke's retirement. An international commission was convened, chaired by the neuroanatomist Max Cowan, and in 1981, the decision was reached to reorient the institute's focus toward basic neuroscience by creating departments in neuroanatomy, neurophysiology, and neurochemistry.

Heinz Wässle (who headed up an independent research group in the Miescher lab at Tübingen) and I were chosen to establish departments in neuroanatomy and neurophysiology, respectively, and Heinrich Betz joined us in 1991 to initiate the neurochemistry department.

For me, to be nominated as a Max Planck director at the age of 39 years was the fulfillment of the boldest dream any young scientist could dare to have. Equally, however, it was also the source of many doubts: Would I be able to fill the lab and run a department, could I continue running experiments myself, would there be close cooperation with clinical partners, would Francine be able to find a job to match the one she had in Munich, could the twins cope with losing their friends and successfully enter a very different school system,[8] would such a move represent what we truly wanted and needed at this stage of our lives? This time, the decision was clear: I did not hesitate to accept the honor.

Most of the members from my Munich lab were unable to move to Frankfurt for personal reasons. The only experienced scientists that accompanied me were Sireteanu and von Grünau, both experts in psychophysics.

The move brought changes on many levels, and I cannot emphasize enough my gratitude to Francine during this time: Her support, compassion, and determination steered our family through this turbulent phase and put all my worries to rest. It did not take us long to recognize and value the open-minded culture in Frankfurt—its tolerance, progressive cultural scene, novel brand of friends—and the freedom that this new start enabled. Francine and I adapted well, but the move proved difficult for the twins, who even to this day consider Munich (and Bavaria) to be their home. Francine kept her position at the radio, a decision that introduced mobility and new perspectives into our lives. To carry out her professional duties, she needed to be physically present in Munich for one week every month. During this time, I assumed full responsibility for our teenage daughters, from age 12 onward until they left for the university. A few years after our move, Francine also was appointed as lecturer at the university of Frankfurt.

Institutional Legacies

Upon arrival, Heinz Wässle (who had started work a few months earlier) and I encountered a functional institute: The animal house, the electron microscopy (EM) group, the administrative units, and the workshops were all staffed and functional. We immediately began by integrating the scientists and technicians whose contracts exceeded those of the retiring directors into our departments. Among these, Manfred Klee and Wolfgang

[8] School curricula differ drastically between states because of agreements put in place in the federation of Germany.

Precht moved into my department. Klee, a highly renowned neurophysiologist, was one of the pioneers of slice preparations and investigated the cellular mechanisms and the pharmacology of epilepsy. Precht studied the vestibular system. From the onset, my department had considerable and complementary depth in expertise and, for a while, the majority of staff positions in the department were filled by colleagues who were already at the institute. I also inherited technical staff with great expertise in histology.

The institute was located in Niederrad (a district of Frankfurt positioned along the southern banks of the Main River), directly across from the medical complex of the Goethe University. The critical mass of the institute was enhanced through its association with the Edinger Institute.[9] Originally a part of Kruecke's department during his tenure as a MPI director, this neuropathological institute became part of the Goethe University upon his retirement. Led by Professor Schlote (an expert electronmicroscopist), it retained office space in our institute, occupying one complete floor. Another group that was carried over from the previous directors was the research unit of Professor Heinz Stephan, a renowned comparative neuroanatomist who studied the evolution of the vertebrate brain and had a fantastic collection of brains and histological sections from a large variety of vertebrates.

The institute also contained various artifacts throughout the building. The walls of the corridors on each floor of the five-story building, for example, were lined with wooden cabinets that contained thousands upon thousands of histological slides from patients. These slides had been collected over the entire course of the institute (i.e., from its beginnings in Berlin-Buch to the present). When Wässle and I arrived, we delegated the responsibility for these collections to the Edinger Institute, oblivious to the horrible legacy concealed therein.

A few years after our arrival, the historian Goetz Aly obtained evidence that made him suspect that some of the specimens in these collections had been prepared from the brains of victims of the "euthanasia" program carried out by the Nazis. Aly came to the institute, studied the dossiers, and proved by correlation (using data from the respective clinics) that our collections included slides from at least 34 people who had been killed by the Nazis and whose brains had then been examined by scientists at the Kaiser Wilhelm Institute for Brain Research in Berlin-Buch. Recent research carried out by Heinz Wässle revealed that these collections most likely contained samples from several hundred victims of the euthanasia program.

Once again, the indelible mark from Germany's horrendous past came back into full focus—this time accompanied by an abyss created under the guise of scientific enquiry.

[9] See http://www.edinger-institut.kgu.de/.

Alexander Mitscherlich, one of the founders of psychosomatic medicine and a member of the Frankfurt School, has written extensively about the crimes committed by our colleagues in the name of science during the Third Reich (e.g., Mitscherlich and Mielke 1949). However, the presence of concrete evidence to these odious crimes, housed in the wooden cabinets that lined the very halls of our institute, came as more than a shock to us. Although earlier we had delegated responsibility for the collections to the Edinger Institute, Heinz Wässle and I assumed full responsibility. It proved impossible to determine which slides were taken from the victims versus those that been extracted from patients who had died from disease. Thus, all material that had been collected between 1933 and 1945 was locked away in steel cupboards until a proper course of action could be determined. Concurrent with our experience, several other neuropathological institutes in Germany reported similar findings, and the matter quickly escalated to an issue of national concern.

In 1990, all slides prepared during the years 1933 and 1945 were buried in a grave at the Waldfriedhof in Munich, and a commemorative stele was erected to bear witness to the horrors that were committed in the name of science. Far beyond this, the true testimony to these atrocities must be reflected in how each and every scientist—present and future—approaches our craft: Our actions, and the knowledge that may result, hold great potential to do good, but we must be ever vigilant to protect its potential use from destructive purposes.

History continues to be made at the MPI for Brain Research. In 2014, the institute celebrated its 100th anniversary. For this occasion, Wässle and I worked together with our successors, Erin Schuman and Gilles Laurent, to document its full history. This publication (in German and English) provides, in more detail than is possible here, an in-depth analysis of the abhorrent actions that were conducted in the name of neuroscience in Germany during World War II (Max Planck Institute for Brain Research 2014). It also presents a vision for future directions, as the institute looks to engage in the next exciting episode of research.

Science during the First 10 Years in Frankfurt

Once settled in Frankfurt, my primary goal was to wrap up the studies on extraretinal control of visual transmission and extend the ongoing developmental studies. We set out to elucidate the mechanisms underlying the central gating of use-dependent synaptic plasticity, to find markers determining the time course of the critical period, and eventually to study in vitro the synaptic mechanisms that mediate the Hebbian modifications of synaptic efficiency. As in Munich, my lab combined psychophysics and electrophysiology to which immunocytochemistry and various axonal tracing methods were added. Polyclonal antibodies had become available for an ever-increasing number of proteins and neurotransmitter systems and fluorescent beads allowed tracing of cytochemically identified neuronal projections. In parallel, I wanted to investigate in more detail the synaptic mechanisms responsible for disinhibition in the LGN and the massive facilitation of polysynaptic responses in cortex induced by reticular stimulation. I wanted to conclude the earlier studies on the extraretinal control of thalamic and cortical transmission by identifying the synaptic mechanisms. I also had the intuition that the reticular-activating system might play a critical role in the central gating of developmental plasticity.

The new resources available in the department allowed us to expand our methodological repertoire. Still lacking the expertise in immunocytochemistry, I invited Vicky Chan Palay (whom I had met previously at F. O. Schmitts Fourth Neuroscience Study Program in Boulder, CO) to join us. An expert in cytochemistry and EM, Chan Palay came from Günter Baumgarten's group in Zurich and generously taught us the basics. Once we were at ease with this technique at the light microscopic level, we were able to benefit from the immense expertise present in our institute's technicians from the EM unit. We then ventured into combined light–EM immunocytochemistry with Vicente Montero, with whom I was acquainted in Munich, and Anna Dolabella de Lima. Later, after Alain Artola arrived, we implemented an in vitro lab to investigate synaptic plasticity with intracellular recordings in cortical slices and fluorescence-based calcium measurements in dendrites. Here, we profited from the generous help of Manfred Klee and Walter Zieglgänsberger, a personal friend from our common time in Munich. Sireteanu established a state-of-the-art lab for psychophysical studies and pioneered the preferential looking technique to study visual functions in toddlers. Last but not least, improvements were made to our computational infrastructure: We implemented a digital image-processing system for the quantification of deoxyglucose autoradiographs and equipped the physiology labs with PDP-11 computers and custom-made amplifiers, which allowed parallel recording from several electrodes.

During the time in which we set up a cat colony with comfortable dark-rearing facilities, we concentrated on the extraretinal gating of thalamic and cortical transmission. The main advances achieved were the ultrastructural identification of the targets of cholinergic, serotonergic, and noradrenergic projections originating in the brainstem and innervating the LGN and the visual cortex. The location of the respective synapses in the synaptic glomeruli of the LGN and at the dendrites of putative inhibitory interneurons within the main laminae and the reticular nucleus of the thalamus agreed well with the disinhibitory action of the ascending projections (de Lima et al. 1985), and we were able to confirm (with iontophoretic studies and intracellular recordings) that acetylcholine inhibited intrageniculate inhibition (Francesconi et al. 1988). The preferential, partially paracrine innervation of supragranular cortical layers by these "modulatory" projections agreed with the strong facilitation of polysynaptic cortical responses that we had identified previously using current source-density analysis. In addition, in the visual cortex, iontophoretic studies confirmed the substantial contribution of acetylcholine to disinhibition and facilitation of polysynaptic responses (Müller and Singer 1989; Lewandowski et al. 1993).

We interpreted these results in the context of the dual action of reticular stimulation. One effect is tonic and leads to a long-lasting desynchronization of the EEG, the electrographic signature of arousal. The other is phasic, lasts for about 200 milliseconds, and closely resembles the ponto-geniculo-occipital (PGO) waves associated with saccadic eye movements in rapid eye movement (REM) sleep. Waves with a similar topology and morphology also occur with voluntary saccades and have been addressed as eye movement potentials by Jeannerod and Jouvet. Jeannerod and Sakai (1970) had proposed that the eye movement potentials reflect corollary signals that suppress vision during saccades to avoid perception of self-induced motion. PGO waves actually had been shown to produce primary afferent depolarization of retino-geniculate terminals, which was taken as evidence for presynaptic inhibition. If reticular stimulation mimics PGO waves, however, our findings suggested a different interpretation. We observed that reticular stimulation facilitates transmission, erasing inhibition, and that the afferent depolarization was caused by activity-dependent increases in extracellular potassium (Singer and Lux 1973). Therefore, we proposed that this corollary modulation of transmission in retinotopically organized visual structures served two functions. First, it appeared to gate transmission as a function of the sleep-wake cycle and arousal by shifting the network from a correlated burst mode into a decorrelated sustained firing mode—a favorable condition for signal transmission and processing. Second, disinhibition appeared to reset the system with each change of fixation by erasing the inhibitory traces left over from the processing of the previously processed image. Saccadic suppression, we thought, simply could be accounted for by the retinal image shift. As the y-system (the equivalent of the magnocellular pathway in primates) inhibits the x-system (the parvocellular pathway) in the LGN (Singer and Bedworth 1973) and as the magnocellular ganglion cells respond vigorously to fast-moving contours, we reasoned that they would shut down transmission of signals in the parvocellular system during saccades.

Development and Synaptic Plasticity

Once our cat colony began to produce offspring, we were able to resume developmental work. One line that we pursued was the search for histochemical markers during the critical period: We concentrated on developmental changes of the modulatory projections from the brainstem and the basal forebrain, synaptic recognition molecules, calcium-binding proteins, glial markers, and nerve growth factors. We observed changes in virtually all the candidate markers examined. Some correlated with the time course of the critical period and might have played a role in its initiation or termination; however, we were unable to differentiate between global maturational processes and specific mechanisms that gated the critical period. These descriptive results reflected well the plethora of molecular changes associated with the early postnatal development of the visual cortex and provided the baseline for subsequent, more targeted studies. They did not allow us, however, to single out the relevant factors. Christian Müller, who investigated glial markers, continued this line of research after he left the lab and made the important discovery that injection of cultured glial cells could restore ocular dominance plasticity in the adult (Müller and Best 1989).

Exciting work followed, as we looked to identify the systems involved in the central gating of experience-dependent synaptic plasticity and to obtain causal evidence for the involvement of these systems. When Mark Bear joined the lab, we combined pharmacological lesions of modulatory pathways with local blockade of receptor systems, using implanted osmotic minipumps for prolonged intracortical delivery of drugs. First, we found that unilateral sectioning of the cingulum prevented ocular dominance plasticity in the lesioned hemisphere. This lesion disrupted the modulatory pathways that ascend from the brainstem and basal forebrain and project to occipital cortex. It also depleted the visual cortex of cholinergic and noradrenergic afferents. At that time, we were not aware of the massive projection from the anterior cingulum to the visual cortex. It is thus conceivable for this projection to have a gating function as well. Similar results were found, but never published, for the fornix: Unilateral sectioning blocked plasticity selectively in the lesioned hemisphere. Thus, a complex network of gating systems may evaluate the adequacy of sensory information and then activate the "print-now" command. Our approach, however, was to search for the final common path. We found that pharmacological lesion of the noradrenergic projection alone was not sufficient to block plasticity, whereas combined blockade of cholinergic and noradrenergic transmission did (Bear and Singer 1986). This accounted well for the earlier finding that reticular stimulation facilitated plasticity, because this stimulation activates both cholinergic and noradrenergic projections. Proceeding a bit further, we tested (with minipump infusion of receptor blockers) the participation of other modulatory transmitter systems and found that serotonergic pathways also had a facilitatory effect (Gu and Singer 1993, 1995).

A major step toward the identification of mechanisms was the discovery, again with minipump infusion of receptor blockers, that inactivating NMDA receptors completely abolished ocular dominance shifts in response to monocular deprivation without affecting the neurons' responses to light stimulation (Kleinschmidt et al. 1987). Evidence obtained earlier in Munich

(Rauschecker and Singer 1981) provided the motivation for this investigation; namely, that synaptic modifications followed a Hebbian correlation rule that evaluated the temporal contingency between pre- and postsynaptic activity. Thus, we were looking for a mechanism that could translate this temporal contingency into a metabolically relevant signal. Phillipe Ascher had just discovered the voltage dependence of the magnesium block of the NMDA receptor (Nowak et al. 1984) and thus this receptor appeared to be an ideal candidate.

The proof that the NMDA receptor played a critical role in mediating developmental plasticity had multiple and exciting consequences. It explained the correlation rule and suggested calcium as the relevant second messenger for both homosynaptic strengthening of active synapses and the competitive heterosynaptic suppression of less active inputs. It also suggested that developmental plasticity might depend on similar mechanisms as those in adult learning. Furthermore, it implied that plasticity had a threshold that could be overcome by increasing postsynaptic depolarization. This, however, presented a problem: We could no longer be certain whether the facilitatory effects of cholinergic and noradrenergic projections were mediated by specific second-messenger cascades, which acted synergistically with the cascades triggered by NMDA receptor-mediated calcium entry, or whether they acted simply by enhancing depolarization of the postsynaptic neurons. The depolarizing action of acetylcholine was well established. We had demonstrated that it reduces inhibition, whereas others had shown that it blocks the M current, a potassium channel. We left it there for the moment, because both interpretations provided explanations for our observations, and returned to these questions only after in vitro preparations were established.

The involvement of the NMDA receptor also suggested that gating of synaptic plasticity might not solely depend on global "now print" signals but also could be achieved through resonance in specific feedback loops. Positive feedback would add to the depolarization of the dendrites and help the plasticity threshold be reached by removing the magnesium block, thereby facilitating plasticity. Previously, we had seen that inputs to cells do not change if the latter cannot respond to afferent drive, because their position in the columnar system does not allow them to respond (Rauschecker and Singer 1979). We also observed that the input from a rotated eye is ineffective. It appeared plausible, therefore, to assume that changes in synaptic efficacy can take only place if input constellations resonate with the response properties of the network upon which they impinge. Thus, input from the rotated eye, even though it matched the response properties of primary visual cortex, may have failed to induce plasticity because it did not match with upstream polymodal networks, and these consequently failed to provide feedback signals that may have been required to lift cells in primary visual cortex above plasticity threshold.

Experience-Dependent Plasticity of Intracortical Connections

Our electrophysiological studies on gating mechanisms were conducted parallel to structural investigations into the plasticity of (a) ocular dominance and orientation maps and of (b) the layout of tangential intracortical connections, thus combining deoxyglucose imaging in cortical flat mounts with axonal tracing (Löwel and Singer 1992). Given the evidence of a critical role for correlated activity in the selective consolidation and strengthening of developing connections, we wondered whether the development of the network of tangential connections might follow the same rules. If so, these connections should selectively link columns that are most likely coherently activated (i.e., columns whose feature preferences match the statistical contingencies of the environment). To test this hypothesis, we traced the intracortical connections with fluorescent beads and superimposed the projection patterns on columnar maps, which were determined using the deoxyglucose method and later with imaging of the intrinsic signal. The outcome was fascinating. In dark-reared kittens, the trajectories of the tangential connections were entirely uncorrelated with the feature maps and ocular dominance columns; however, in normally reared or strabismic kittens, they were highly selective and connected columns with related functional properties (Löwel and Singer 1992). Together with the data from the kittens reared in the rotating striped drum, this was the first demonstration that the statistical contingencies of the outer world get imprinted in the layout of the network of the tangential association connections that convey contextual information from regions outside the classical receptive fields. One must remember that at that time, concepts of predictive coding and Bayesian inference were not yet being discussed in neuroscience. Otherwise, we would have certainly embedded our findings within such a framework. Despite our knowledge of recurrency and feedback from anatomical evidence, we adhered to using feedforward-processing concepts as they were accepted at that stage.

The in vitro Excursion

Our in vivo experiments allowed us to formulate a set of rules to describe the relations between the polarity of synaptic gain changes and the timing and amplitude of pre- and postsynaptic activity (for a review, see Singer 1995). Our hypothesis was that experience-dependent developmental changes in synaptic transmission are based on the same mechanisms as the phenomena of long-term potentiation and depression (LTP and LTD). To test this hypothesis, we extended our methodological repertoire to slice preparations of the rat visual cortex and decided to investigate whether the rules identified in vivo could be confirmed with intracellular recordings. At the time, all we knew was that tetanic stimulation of presynaptic afferents, if long and strong enough, would induce LTP of the stimulated inputs (Bliss and Lømo 1973) and that high-frequency firing of postsynaptic cells, induced by postsynaptic injection of depolarizing current pulses, would depress nonstimulated inputs (Christofi et al. 1993).

On the basis of evidence from the in vivo experiments for an involvement of NMDA receptors in developmental plasticity, we surmised that the polarity of a synaptic gain change should depend on the level of postsynaptic depolarization and that there should be three regimes separated by two thresholds for modifications. With weak depolarization, there should be no change; with intermediate depolarization, active inputs should depress; and with strong depolarization, they should potentiate. Considering local depolarization as the critical variable accounted well for the various outcomes of deprivation, because it is dependent on the activity and efficiency of the stimulated afferents, on the state of other inputs that are near enough to contribute to the depolarization of the spines under consideration, as well as on the strength of inhibition. As a critical variable for the translation of electrical signals into molecular changes at the synapses, we assumed intracellular changes in calcium concentration, differentiating between calcium entering through activated-NMDA receptor channels and voltage-gated calcium channels. We assumed that an intermediate increase should lead to LTD and large surges, requiring NMDA receptor activation, to LTP. This formulation happened long before spike timing-dependent plasticity was discovered by Markram and Sakmann (Markram et al. 1997) and by Mu-ming Poo (Bi and Poo 1999). Back-propagating spikes, the release of calcium from the endoplasmatic reticulum, as well as direct links between metabotropic glutamate receptors and intracellular messenger cascades were out of reach at that time. In a series of experiments, we confirmed the critical role of NMDA receptors in LTP (Artola and Singer 1987), verified the two threshold mechanism (Artola et al. 1990), and identified calcium as the involved second messenger through calcium imaging and application of calcium scavengers (Bröcher et al. 1992; Hansel et al. 1997). We were also able to understand why acetylcholine and norepinephrine facilitated plasticity, as we found that it enhanced depolarizing responses. Finally, by stimulating different subsets of afferents, we confirmed the prediction derived from the in vivo rules: Contingently activated afferents interact synergistically to mutually support their potentiation, whereas asynchronous activation results in competition and heterosynaptic depression of the less efficient input. Thus, we achieved close correspondence between the in vivo and in vitro experiments, which suggested that the mechanisms mediating experience-dependent circuit changes closely resembled those that support LTP and LTD. We reformulated the rule that we had identified in vivo to now consider postsynaptic depolarization and calcium fluctuations as critical variables. This rule, dubbed by others as the ABS rule

(Artola-Bröcher-Singer), explains at a mechanistic level the Bienenstock-Cooper-Munro rule (Bienenstock et al. 1982), which had been formulated on the basis of published data on the effects of visual deprivation.

When I think back to this time, I realize that it never occurred to us to write a comprehensive review of these slice experiments. It was a period in which LTP and LTD research in the hippocampus took off and attained great momentum. Increasingly, we became more a part of this research community, and identified less and less with visual neuroscience.

A Decisive Encounter

Before describing further work, a most influential encounter needs to be recalled, as it served to catalyze my contact with the Buddhist world, the Dalai Lama, and Matthieu Ricard.

Shortly after the move to Frankfurt, I was invited to attend a conference in Chile and became acquainted with Umberto Maturana and Francisco Varela who, among many others (e.g., Susanna Bloch, Bernardita Mendez, Marie-Eugenia Moneta, and Jaime Alvarez), had resisted the dictatorship of Pinochet, defending their science at great risk and peril. From them, I learned about the concept of autopoesis, which differed greatly from the behaviorist stance of considering the brain as a stimulus response machine. A pilgrimage on horseback was organized to Pablo Neruda's house (Chile's famous poet), which was located on the coast. I fell in love with this remote yet tormented enclave of European culture situated between the Andes and the infinity of the Pacific. Back home, I organized support for Alvarez's lab in Santiago through the *VolkswagenStiftung* and shortly thereafter was able to welcome Varela and his family to Frankfurt.

Varela was interested in investigating top-down effects on sensory processing; the autopoesis concept bore a close resemblance to a concept that would be addressed today as predictive coding. This coincided with my interest in the enigmatic function of the massive cortico-thalamic feedback projection from layer VI of the visual cortex to the lateral geniculate body, the anatomy of which had been analyzed in detail by Ray Guillery. While still in Munich, I had investigated, with Michael Schmielau, the effects of inactivating cortex by cooling or applying transcortical DC currents on thalamic transmission. We found that responses of LGN cells to small light stimuli were attenuated by stimuli presented to the nondominant eye, except when these were placed on precisely corresponding retinal loci. In this case, interocular inhibition gave way to binocular facilitation, and this facilitation was blocked by cortical inactivation (Schmielau and Singer 1977). We concluded that cortico-fugal activity reduced interocular inhibition for those channels that conveyed signals that could be fused perceptually, leaving signals from noncorresponding loci exposed to interocular inhibition and rivalry. This suggested that signal transmission in the LGN should be facilitated that matched cortical-processing requirements. In the experiments with Varela, we set up specific cortical activation patterns through patterned stimulation of one eye and then presented conflicting or matching stimuli to the other eye to study the effects of match and mismatch in the LGN. In present-day terminology, we set up a prior, or an expectancy, in the cortex and then probed how this prior affected transmission of information that either corresponded or contradicted expectancy. We observed effects compatible with a facilitation of transmission of matching patterns, but the effects were weak (Varela and Singer 1987). I now suspect that response selection acts on variables other than discharge rate, and if I had the chance to reinvestigate this question, I would look for changes in synchrony.

Varela remained in Frankfurt for two years before leaving for the École Polytechnique in Paris and founding a Centre National de Recherche Scientifique (CNRS) research unit for neuronal dynamics at the Salpétrière. While in Paris, he established close contacts with Buddhist teachers and initiated, together with the Dalai Lama, small workshops to investigate epistemic questions from the viewpoints of Eastern contemplative schools and Western science. This academic adventure gave rise to the Mind and Life Institute,[10] which was cofounded by Varela in 1987.

Varela died of a chronic disease in 2001, far too early. In his honor, colleagues organized a colloquium, and I had the privilege of being invited because of our long-lasting friendship and because Varela also had explored the field of oscillations and synchrony while in Paris. At this conference I met many active members of the Mind and Life Institute, including Matthieu Ricard,[11] and decided that I needed to learn more about what practitioners of meditation had discovered, from their first-person perspective, about the functions of the brain and its mental dimension. These encounters sparked a friendship that led us to engage in structured, taped discussions. Later transcribed and published in German (Singer and Ricard 2008), these dialogues form the basis for a more comprehensive book, *Beyond the Self*, which will appear in French, English, and German.

To gain first-hand experience with contemplative practice, I enrolled in a two-week Seshin retreat in the Black Forest. This experience consisted of sitting in front of a white wall, counting breaths, for eight hours per day. We were not allowed to talk or have eye contact throughout the whole retreat. It was a mind-boggling experience, and it clearly did something to my brain. After a few days, interocular rivalry slowed down so much when I was sitting that I could observe change in eye dominance, and when watching the ant hills on my lonely promenades, I found that I could use my dorsal and ventral stream simultaneously; that is, I saw both the global flow of

[10] See https://www.mindandlife.org/.

[11] Earlier, I had briefly met Matthieu Ricard in London at a small workshop on the relationship between science and contemplative practices, organized by my daughters Tania and Nathalie.

motion as well as the tiny ants in intricate detail. Later I learned that expert meditators can deliberately induce such states of nonfocused attention.[12] After the retreat, I returned to my normal routine. My coworkers, who had not known of the retreat, told me months later how puzzled they were about my (admittedly transient) transformation into a patient and calm person.

More Decisions

After the move to Frankfurt, I thought that life would not challenge me with further bifurcations, but I was wrong. In subsequent years, I received three tempting offers to return to Munich: the first to succeed my former mentor, Lux, who retired in 1992 as the director of neurophysiology at the MPI for Psychiatry in Martinsried; the other two were to serve as president of the Max Planck Society.

My decision to not return to my former institute was reached out of solidarity for the institute in Frankfurt, along with the gut feeling that I should not tread in my own footsteps again. The decision to decline the presidency of the Max Planck Society was much more difficult. I felt a strong obligation to give back to the society that had supported me throughout my career, yet I was unable to sever my ties with research. You see, unlike other scientific societies, the presidency of the Max Planck Society is a full-time administrative position, one accompanied by the cessation of a person's research career. The request, made for the sake of continuity, involved service for two terms (each lasting six years), which would have precluded a return to science. The first call came much too early and, for this reason, it was out of the question. However, the second call would have brought me close to retirement age, which at that time was 65.

I seriously considered accepting the second call and tried to work out a way to accept it. My only request was that a solution be found to permit me to stay involved with my research, by retaining, for example, a small lab. My rationale was twofold: I reasoned that my future interactions with politicians as well as my scientist colleagues would be much easier if I was still recognized as a scientist. I also felt that I needed to resolve various lines of enquiry before completing my scientific career. My request, however, could not be met by the society, as it would have necessitated a redefinition of the presidency with an accompanying change to its constitution. So, again, I declined.

A Serendipitous Finding and the Beginning of a New Research Line

Because we had observed both in vivo and in vitro that synaptic modifications could be induced rapidly and reversibly, we wondered whether we could

[12] In a little study performed much later on expert meditators, we were able to confirm that they had much better control of attention than the control group (van Leeuwen et al. 2012).

trace these changes in vivo by recording from the same set of neurons while kittens underwent variable regimes of monocular deprivation and reverse occlusion. If feasible, this would allow us to determine the time constants of activity-dependent disconnection and reconnection of inputs to cortical cells as well as to find out whether cortical cells maintained their orientation preference while the thalamic afferents went through a cycle of suppression and recovery. We needed, however, a method that would allow us to record single-cell responses over several days in kittens at the peak of their critical period. I built the same microconnectors that I had used for the chronic EEG recordings during my thesis, but this time replaced the silver ball electrodes with Teflon-coated platinum-iridium microwires. These were inserted in the visual cortex, affixed with tissue glue, and then left floating in a well filled with silicon oil and covered by a layer of bone cement. In this way, we could record repeatedly, over many days, from awake, gently restrained kittens and map the changes in receptive field properties by presenting whole-field moving gratings to the two eyes. These experiments were performed with Laurence Mioche, a PhD student (Mioche and Singer 1988, 1989). We found that disconnection in the deprived eye is rapid and close to complete within eight hours; it did not matter whether monocular exposure was continuous or whether kittens were allowed to have brief naps between exposures. By contrast, recovery after reverse occlusion was slow: it took a few days, including a phase during which cells became entirely unresponsive to either eye. We also observed that after the cells had become reconnected to the initially deprived eye, they exhibited the same orientation preference as before, a finding that we later replicated with optical recordings of intrinsic signals (Gödecke et al. 1997). This suggested that once maps are formed, neurons inherit their selectivity from the embedding network and select appropriate inputs via a Hebbian mechanism.

These experiments led to a most serendipitous finding that changed my research for decades to come: One morning, in late 1985, after I plugged in the connector, no spikes were visible. Endeavoring to discover whether there was a problem with the connections or whether the wire tips were simply remote from cells, I switched off the high-pass filters to see whether field potentials were still being recorded, heard a purring noise, and saw large-amplitude, surprisingly regular oscillations on the scope in the range of 40 Hz. A quick check showed that these oscillations were neither related to the periodicity of the drifting grating that the kitten was staring at nor to the mains. They were induced by visual stimulation but must have been generated by the brain. In addition, they were synchronized across the different wires, some of which were several millimeters apart. I knew that similar oscillations had been described in the olfactory bulb of rabbits while they were sniffing (Freeman 1978). I took a Polaroid screen shot, wrote on it "the visual sniff," and taped it on the rack, where it remained for several months. I replicated this finding on another monocularly deprived kitten that had spikes on the leads and observed that spiking activity was synchronized to these oscillations, the amplitude of the oscillations reflected ocular dominance, their amplitude was largest for orientations that corresponded to the preference of the cells recorded from the respective leads, and oscillations together with the associated bursts of firing were synchronized across leads that happened to be in columns with similar preferences. My first thought was that we could henceforth use this analogue signal—which later became popular as the local field potential (LFP)—instead of spikes to assess the activity of local groups of neurons because it reflected so well the filtered multiunit activity. This would make it possible to record simultaneously from as many sites as desired and thus circumvent the problem of having to fish around for neurons—the main challenge in these chronic experiments.

My second thought was that these synchronous oscillations might provide a solution to the "binding problem." Over the years, I had had close contact with Christoph von der Malsburg and was aware of his work on the cocktail party effect. He had proposed that segmentation might be achieved by exploiting the temporal parsing of utterances of different speakers. At that time I was unaware of Milner's suggestions, published a decade earlier (Milner 1974), that the binding problem could be solved by synchrony. According to my intuition, it was highly plausible, for several reasons, that the brain could use temporal contiguity to encode semantic relations. First, there was the trivial evidence that temporally contingent events in the outer world are bound together. This implies that synchronously arriving signals are bound. In our previous psychophysical experiments (Wilson and Singer 1981; Altmann et al. 1986), we had observed that simultaneously presented visual stimuli were interpreted as belonging together. Second, we had ample evidence from the developmental studies that correlated activity is used as signature for the identification and selective association of inputs that convey semantically related information. In these cases, correlations were induced by contingencies in the outer world, but I reasoned that the brain could use the same mechanism to encode internally generated relations. All that would be required would be to impose temporal structure on self-generated activity and to synchronize those responses bound for further processing. Because the observed oscillations imposed temporal structure on the spike trains and apparently could become synchronized over large distances, I became excited at having discovered an important principle. The readout of correlated firing did not appear to be a problem because we had seen, in all experiments on synaptic plasticity, how well cells differentiated between synchronous and temporally dispersed inputs, both for the transmission of signals as well as for the selective association of inputs through LTP and LTD. If synaptic plasticity followed the Hebbian principle—and all our evidence supported the notion that the polarity of synaptic modifications depended on the degree of correlations—then there seemed to be only two solutions: Either the brain uses temporal correlations among discharges as a signature of relatedness all the time (in which case it has to impose temporal structure on responses that are not timed by external stimuli) or it has to use an entirely different strategy for the detection, encoding, and storage of relations among signals that lack temporal structure. I much preferred the first hypothesis as the more parsimonious.

A few months after the discovery of the “visual sniff,” Charles Gray joined the lab in early 1986 as a postdoc, wishing to participate in plasticity experiments. He arrived from J. E. Skinner’s lab in Houston, TX, where he had studied the modulation of oscillatory activity in the rabbit olfactory bulb by efferent pathways and developed a few simple programs for time-series analysis, such as auto- and cross-correlations. I showed Gray the “visual sniff” and we decided to analyze this phenomenon in greater depth rather than concentrate on plasticity. In a sense, the sniff-related oscillations in the olfactory bulb had the same effect as our oscillations—both imposed a precise temporal structure on sustained responses to stimuli that were continuous.

Peter König, Andreas Engel, and Thomas Schillen joined the lab soon thereafter and all of us became increasingly fascinated by the rich phenomenology of these stimulus-induced oscillations. Particularly exciting was the fact that synchronization probability was not a fixed property of a given cell pair; it depended on stimulus configurations that corresponded to certain simple Gestalt criteria for perceptual grouping. It was clear that we were not looking at trivial synchrony caused by common input but instead were observing the result of dynamic network interactions. We all shared the feeling that we were onto something potentially very important, and we wanted to nail it down carefully before presenting our results in a high-impact publication. We submitted the first results on the gamma oscillations showing the tight correlation between LFPs and spike responses to the *Proceedings of the National Academy of Sciences* (PNAS) in early 2008 and engaged in an extremely time-consuming review process, as the reviewers did not share our enthusiasm. Still, we did not want to go public by publishing in a fast-track journal, so we persevered with the reviewers. The first public communication of our results came at the Second International Brain Research Organization (IBRO) Conference in Budapest in summer 1987. We did, however, present our findings at an in-house symposium in autumn 1986 to which colleagues from neighboring universities were invited, as was our institution’s practice.

Another Stolen Moment, Backlash, and Resultant Tenacity

One of the guests at this in-house symposium was a colleague from Marburg. As we learned later from one of his coworkers, this colleague decided on the spot to repeat our experiments but insisted that his plan be kept secret. Because he was using the Thomas multidrive to determine receptive fields in the visual cortex of cats with reverse correlation, he was able to rapidly obtain data from multisite recordings, and this data was similar to ours. At the next European Conference for Visual Perception (ECVP), he presented a poster that looked so similar to what we had presented at our in-house symposium that I believed, from a distance, it to be ours. I turned to Gray, who was attending as well, to ask why he had gone ahead without discussing the matter with the group. Equally surprised to see the poster, Gray replied, “Have a look, it is not ours.”

In addition to the poster, we learned that our colleague had contacted the editor of *Biological Cybernetics* to obtain fast publication of his results, which ended up being published in December 1988 without reference to the IBRO abstract (Eckhorn et al. 1988). Because of the extensive review process, our first publication came out in *PNAS* in March 1989 (Gray and Singer 1989), at about the same time as the second paper on the feature selectivity of intercolumnar spike synchronization that we had submitted to *Nature* and that was processed much faster (Gray et al. 1989).

To say that we felt betrayed by a colleague, whom we trusted, is to put it mildly. Although there was satisfaction to be had in knowing that our results were reproducible, the whole incident left us speechless. Whether the community was less sensitive to such ethical misconduct is difficult to posit at this stage. For our part, we refrained from going public with details, but witnessed how it took several years before the scientific community became aware of the sequence of events.

The discovery of these dynamic synchronization phenomena, summarized in a first review in 1993 (Singer 1993) has been the source of occasional sleep deprivation, even to this day. I vividly remember attending a social of the vision club at an SfN conference in San Diego, where an otherwise-dear colleague had projected a slide taken from the first publication in *Nature*—PowerPoint had yet to hit the scene—after marking “bullshit” on it with a red felt pen. Later, at another SfN conference in Washington, DC, I was invited to participate in a symposium that had been organized by skeptics to provide a platform for the articulation of counterarguments; here, the oscillations and the associated synchrony were typified as the “exhaust fumes” of the brain that completely lacked all function.

I cannot emphasize enough that further pursuit of our research on oscillations and synchrony would not have been possible had we not enjoyed the freedom granted by the Max Planck Society to follow research agendas that are controversial and far from mainstream. It is unlikely that we would have received the necessary support from extramural funding sources.

Until today, the pendulum of opinions keeps swinging. Although the basic phenomena—once considered artifacts or to be irreproducible—have now been replicated, even in the labs of our most skeptical colleagues, the interpretations of their significance for processing and memory still diverge considerably. One of the primary reasons is that it is very difficult to come up with causal evidence, because these dynamic phenomena are an *emergent* property of network interactions: they are highly dynamic, nonstationary, and difficult to manipulate in isolation without interfering with other variables (e.g., the discharge rate of neurons). This should not come as a surprise to anyone: The situation is hardly any different for other theories that are based mainly on correlative evidence. Apart from the trivial argument that spikes are necessary for computations and can convey rate-coded information, only a handful of studies at best have shown, in a causal way, that modulating discharge rates influence perception or action (e.g., see Salzman et al. 1992; Brecht et al. 2004).

As time went on, I slowly faded out the developmental studies and in vitro work, except when we saw a possibility to use these approaches to search for a putative role of timing relations and correlations (Leonards et al. 1996). My lab became known as a place where multisite recording techniques were applied to analyze temporal relations among the responses of distributed neurons in search of temporal coding strategies. This attracted students interested in dynamics and, after a while, the whole lab engaged in this new line of research. This phase is intimately related to the work of Andreas Engel, Peter König, Pascal Fries, Pieter Roelfsema, Andreas Kreiter, Winrich Freiwald, Matthias Munk, Danko Nikolic, and Sergio Neuenschwander, all of whom took care of electrophysiology; Thomas Schillen, Sonja Grün, Gordon Pipa, Raul Muresan, and Michael Wibral, with their focus on mathematical methods and models; and David Linden, Peter Uhlhaas, and Lucia Melloni with their studies on healthy human subjects and patients—as well as the students each had supervised. Novel methods were developed for the analysis of dynamic variables in parallel recordings of LFPs and spike trains; time-frequency plots were introduced; and we ventured forth to confirm the existence of the phenomena that we had discovered in kittens, cats, and awake monkeys using noninvasive methods: first EEG and then later magnetoencephalography (MEG) in human subjects. Highlights from this exiting phase include the following demonstrations:

1. Synchronization probability reflects Gestalt rules for perceptual binding (Gray et al. 1989; Castelo-Branco et al. 2000).
2. Perceptual phenomena not accountable by rate modulations, such as amblyopia (Roelfsema et al. 1994), binocular rivalry (Fries et al. 1997), and brightness contrast (Biederlack et al. 2006), correlate well with changes in synchrony.
3. Synchrony can be established over long distances between the hemispheres (Engel et al. 1991a), between areas 17 and 18, as well as between the suprasylvian cortex and the tectum (Engel et al. 1991b).
4. Synchrony among cortical areas enhances their impact on tectal neurons (Brecht et al. 1998).

5. Cats trained to perform a visual detection task synchronize oscillations between the visual, parietal, somatosensory, and motor cortex in anticipation of the task with zero phase lag in the beta-frequency range (Roelfsema et al. 1997).
6. Small changes in the synchronicity of dual stimuli applied to the tectum alter the trajectory of eye movements: synchronous activity was interpreted by downstream oculomotor centers to have been evoked from a single large object, whereas asynchronous responses were interpreted as evoked by two independent objects (Brecht et al. 2004).
7. Basic findings in cats are reproducible in area MT and IT in awake-behaving monkeys (Kreiter and Singer 1996).
8. Gamma oscillations and synchrony are exquisitely state dependent, reduce rate variability, and are modulated by attention and expectancy both in cat and monkey (Munk et al. 1996; Herculano-Houzel et al. 1999; Lima et al. 2011).
9. In slices, the switch between LTP and LTD depend on the precise phase relation between oscillatory pre- and postsynaptic responses (Wespatat et al. 2004).
10. Cognitive functions in human subjects, such as conscious processing, are associated with topographically specific modulations of power and coherence of gamma oscillations (Melloni et al. 2007).
11. Measures of power and coherence of oscillations reveal abnormalities in patients suffering from schizophrenia and autism spectrum disorder and correlate with the severity of the syndromes (Uhlhaas and Singer 2010).
12. Analysis of coherence revealed major rearrangements of functional networks in late adolescence, the period in life when numerous psychiatric diseases become clinically manifest (Uhlhaas et al. 2009).

All this evidence supports the notion that oscillatory patterning of neuronal responses, and the option to synchronize them, is exploited by the brain (a) to encode semantic relations through temporal contiguity, as required for distributed coding; (b) to enhance the impact of responses for response selection and propagation; and (c) to dynamically bind subsystems into cooperating functional networks.

The Reception of Temporal Codes

The first labs to take up the idea that synchrony could play a role in the association of neuron groups into functionally coherent ensembles or networks were those applying EEG and later MEG measurements (e.g., Tallon-Baudry in Lyon, Varela in Paris, Pfurtscheller in Salzburg, and Hari in Helsinki). The likely reason for this is that these measurements are genuinely multisite; they selectively capture activity that is synchronized and oscillatory.

Electrophysiologists who applied multisite unit recordings and were interested in oscillations were working on the hippocampus (e.g., McNaughton et al. 1983; Wilson and McNaughton 1993) because of the conspicuous theta rhythm that was suspected to play a role both in coding through phase shifting of discharges (Bragin et al. 1995; Huxter et al. 2003) and in mediating synaptic plasticity by increasing cooperativity through synchronization. A natural interest in dynamics was shared by colleagues working in the auditory system because phase, frequency, and temporal codes are integral features of the stimulus domain. In addition, the documentation of the extreme precision with which the inferior olive neurons detect coincidence of inputs between the two ears for the location of sound sources and the precise timing relations between neurons that control birdsong rendered auditory physiologists much more sensitive to timing issues and temporal relations among neuronal responses than our colleagues in the field of vision. Commonalities were found with colleagues working on pattern generators in the motor system, such as Sten Grillner (Grillner et al. 1991) and Eve Marder (1988), or on dynamic coding in the olfactory system, such as Gilles Laurent (Wehr and Laurent 1996). Thus, although we continued to use the visual cortex as our prime model, we began to lose touch with the vision community as greater points of convergence were achieved with colleagues who studied other model systems. I regretted this development and still wonder why it happened.

The BOLD Phase

In 1995, Rainer Goebel joined us as a postdoc to pursue a specific interest in the binding by synchrony hypothesis. He had developed a simulated multilayer neuronal network that exploited this strategy, won a prestigious prize for scientific computing for this modeling work, and now wanted to get closer to data. His arrival coincided with the first demonstration of the BOLD signal by Belliveau (Belliveau et al. 1991). Hans Hacker, the head of the neuroradiology department on the medical campus in Frankfurt-Niederrad, had a 1.5 Tesla machine (one of the first in Germany) and had obtained visually evoked BOLD responses in collaboration with Francesco Di Salle and Fabrizio Esposito, from Italy. Our labs began to collaborate. Goebel soon realized that this field would require sophisticated software for postprocessing. Because of his ingenious programming abilities, he took on the challenge and developed the Brain Voyager—a program package, now in use worldwide, for which he and the department held the copyright license for many years. With this powerful tool at hand, we were able to look into the brains of humans and, in particular, patients. Even though the BOLD signal was way too slow to assess the dynamics that my lab was pursuing, we expanded this line of research for several reasons. First, Brain Voyager offered us a methodological advance over other groups, and Goebel and his coworkers (especially Lars Muckli, who succeeded Goebel after he left for Maastricht) were eager to exploit it. Second, the option to localize whole functional networks was tempting and could help us constrain conclusions derived from EEG and later MEG measurements. Third, it afforded us the opportunity to interact with clinicians and resume work with patients, work that I had abandoned after moving to Frankfurt.

Coordinated initially by Goebel and later Muckli, the fMRI projects soon became a highly visible branch of my lab's activities, complementing in many ways the animal experiments. However, they were obviously not suited to directly address dynamics at the time scales that were of primary interest. Still, with the introduction of event-related fMRI, a substantial number of fascinating questions could be addressed related to the dynamic formation of functional networks, cross-modal integration, predictive coding, interhemispheric binding, and binocular rivalry. We implemented the technology required for fMRI studies in monkeys and used this option to analyze functions of prestriatal cortical areas.

Expanding Horizons

European Neuroscience

When I first entered neuroscience, Europe was a continent marked by cultural and linguistic boundaries. Scientific journals (e.g., *Experimental Brain Research* and *Pflügers Archive*) accepted papers in German and at European conferences talks often were given in a speaker's native tongue. The first concerted effort toward integration happened in 1968, when the European Brain and Behavior Society (EBBS) was established by Konrad Akert and Larry Weiskrantz. I joined EBBS early on and served for many years as its secretary. Over time, EBBS attracted a growing number of disciplines, and many national neuroscience societies were founded. This created the need for a larger umbrella organization, and thus the European Neuroscience Association (ENA) was established to unite these groups. ENA had a hard time keeping pace with the newly founded SfN in the United States, which grew faster and at times attracted more European participants to its annual meeting than the ENA was able to do. To strengthen the ENA and increase visibility of European neuroscience, four members of the ENA executive council—Michel Cuenod, Per Andersen, Anders Björklund, and myself—met in Sils Maria, Switzerland in 1987 to establish the *European Journal of Neuroscience* (initially published by the Oxford University Press, under the editorial direction of Ray Guillery, followed by Michel Cuenod and Berry Everitt, before going over to Blackwell).

Even then, the desired integration was lacking. Thus, during my presidency of the ENA in 1994, plans were set in motion to dissolve the ENA and replace it with a federation of national organizations (Singer 1994;

Abbott 1998). Formalized in 1998, the Federation of European Neuroscience Societies (FENS) established practices to unite the individual national societies. The decision was made to convene the main meeting every second year in July (to avoid conflicts with the annual SfN conference) and to provide ample room for annual meetings within the national societies. Since then, attendance at the FENS biannual meeting has increased steadily, and it has become an important platform for European neuroscientists.

Social Conflicts

Throughout my career, I have attempted to meet the ethical and philosophical implications of neuroscience, and its role in society head-on through active engagement with students, the public, the media, and colleagues from the other areas of science (in particular, the humanities). As a scientist, I believe this obligation is mine, as Helmut Schmidt emphasized in his address to the general assembly of the Max Planck Society in 1977:

> In a democratic society, lucidity and transparency in science and research is a moral obligation—one needed to propel society forward. It is not the moral obligation of the 60 million citizens to retrieve such knowledge, but rather the moral obligation of the scientist and researcher to bring knowledge to citizens.

Numerous public lectures have exposed the challenges and pleasure of discussing state-of-the-art brain research with laypeople. My activities and best of intentions, however, landed me almost immediately in trouble with animal rights activists, who targeted me *pars pro toto*, not the least because of the involvement of kittens (and later monkeys) in my research.

Through various discussions with my critics, I realized how little the public actually understood about the reality of research; in particular, how indispensable animal experiments were to basic research. In an attempt to rectify this, I intensified my public activities and penned a cover-page article for the *feuilleton* (arts and literary) section of the *Frankfurter Allgemeine Zeitung*, one of the most-read, serious daily newspapers in Germany. My activities did not accomplish their intended goal, but they did strike key neuralgic nodes in some, for my private life was suddenly subjected to heightened dimensions of aggression. A smear campaign was ignited that, to this day, has waxed and waned to varying degrees, marked by a repertoire of public mobbing, personal menaces, nightly telephone stalking, graffiti, and the like. At times, I have required police protection, postal packages have needed to be opened at the police office, routes to work constantly altered, and escort has been required at public events. Once I brought legal charges against a group of activists whom I could identify, but the state attorney advised me to retract the case out of fear that the ensuing publicity would stir up even more trouble.

My former student, Andreas Kreiter, suffered far more than this: Animal rights activists succeeded in blocking ethical approval of his work by government authorities. This forced Andreas to defend his right to conduct science through legal means and necessitated numerous court proceedings. His fight did a great service to all of science, one that cannot be acknowledged or emphasized nearly enough, and he has won every legal battle. But instead of bringing about a resolution, this has served only to expose him even further, exacting a heavy price on Kreiter and his family.

Germany lags behind other countries, especially the United Kingdom and the United States, with regard to public outreach activities in the defense of basic research. I sincerely hope that this will change, now that the major science organizations have decided to take concerted action to counter the excesses of radical antivivisectionists. In spite of my personal experience, and those of my colleagues, however, I remain convinced that rational arguments and transparency are effective and offer the following to lend weight to such optimism.

A few years ago I was invited to give a public talk in Stuttgart, and because a protest had been announced, I was escorted to the hall by police. Rather than entering through the backstage door, as advised by the police, I insisted on using the main entrance and took the opportunity to speak to the few dozen protesters who had gathered in front, inviting them to attend the lecture. They readily agreed and accompanied me inside, as did the police. Before giving my talk, I held a vote among the audience to determine whether science should be the first topic of discussion followed by ethics, or the other way round. The majority opted for science first, and so I began. Once my talk was over, a most lively discussion on ethics ensued, lasting until around midnight. My role during this portion was to moderate the discussion between the protesters and the rest of the audience. At the end of the evening, a woman came up to the stage to express how impressed she was by the evening's discussion. A few months later, I learned that this woman had passed away and that she had donated a few million euros to the MPI of Brain Research in Frankfurt, which was then turned over to the Max Planck Society. The lawyer who handled her will told me that she initially had given this sum to an animal rights group, but had changed her mind, and will, after attending that public talk in Stuttgart.

Another source of conflict has been, and still is, the naturalistic or reductionist approach taken by the neurosciences to explain the origin and nature of mental phenomena. In 2003, during a keynote lecture to an International Congress of Philosophy in Essen, Germany, I presented commonly accepted concepts on the organization of the brain and spoke about distributed processing, nonlocal representations, and self-organization. At the end, I posed questions related to the difficulties involved in identifying an "observer" or "decider" in the brain as well as in defining a singular convergence center as the seat of the intentional "Self." I used evolutionary arguments to support the notion that neuronal processes are highly conserved and that the known laws of nature seem to suffice to account not only for the functions of simple but also of highly evolved nervous systems. Then, I left it up to the audience to discern what this all meant for concepts of top-down causation, free will, and ontological dualism.

Although what followed was entirely unexpected, it did reveal how deeply my worldview and self-understanding was influenced by my immersion in the neuroscience community, and how much this deviated from that of the audience. With few exceptions, these were analytical philosophers of the mind with Anglo-Saxon backgrounds, I discovered that the majority of philosophers in the lecture hall were either explicit or clandestine ontological dualists. They perceived my keynote lecture to be a frontal attack on human dignity, and most of my arguments were discarded as category error—a killer argument with which I would be confronted time and again over the ensuing years. A journalist from the *Frankfurter Allgemeine Zeitung* was in the audience and subsequently initiated a series of front-page articles in the *feuilleton*, wherein contributors were invited to disqualify my views. I was portrayed as an 18th-century *homme machine* mechanic, an epigone of La Mettrie. Some of the writers accused me of preparing the grounds for anarchy and the collapse of our legal system, sacrificing the precious achievements of enlightened humanism or, if they were of a particular religious persuasion, of violating basic religious tenets. The arguments were simple: no free will → no responsibility → no guilt → no sanctions → anarchy. A conservative fraction of the federal parliament even queried the Vatican, demanding to know how a scientist who propagated such heretical views could possibly be a member of the Pontifical Academy of Sciences.

Once again I reached out, attempting to explain that a naturalistic view of brain functions is compatible with responsibility, attribution of authorship, sanction of norm violations, and educational programs that utilize reward and punishment to change behavioral dispositions. Countless conferences and public debates were organized around the topic, and it has taken years to resolve the bulk of these misunderstandings. A positive aspect of this controversy was that it nurtured interest in a deeper understanding of the consequences of neurobiological insights for conceptions of humanity and the legal system. Seen in retrospect, some of the conflicts could have been avoided had clearer definitions been used to describe the ontological status of neuronal mechanisms, the emergent cognitive functions, and the social realities that came into existence through cultural evolution. Phenomena such as free will, intentionality, responsibility, guilt, justice, and fairness are perceived as realities, but they cannot be deduced from the cognitive functions of individual brains. Unlike the primary sensations, these phenomena exist only after cognitive agents begin to exchange their experiences and integrate the observations of the respective other in their own self-model. This emergence of new qualities still can be accounted for without having to take a dualistic stance, but this requires, for its analysis, an extension of the methods that we apply for the analysis of the functions of individual brains. As the social neurosciences begin to pursue this extended strategy, social realities may, with all likelihood, become amenable to naturalistic interpretations. This time, however, the *explananda* are phenomena that the humanities have been exploring for centuries. Thus, there is hope that any present distrustfulness will give way to cooperation.

Because most of these fascinating issues arose through interactions with German colleagues in the humanities, philosophy, and jurisprudence, they were conducted primarily in German. Thus, most of these lively debates passed unrecognized outside German-speaking countries. I am aware of similar discourse in other countries. Given the idealistic tradition of German philosophy and psychology, the debate was, and to some extent still is, particularly polarized in this country.

The Creation of New Institutes

The research pursued by my lab to analyze integrative functions of the brain necessitated state-of-the-art technology and this need set into motion a series of events that changed the scientific landscape of Frankfurt. Interested in investigating similar research questions in animals, healthy persons, and patients, we prepared a concept paper together with our colleagues from the clinical departments of psychiatry, neurology, and neuroradiology that outlined a multidisciplinary undertaking and approach. This concept was awarded a competitive grant from the German Ministry of Science and Technology and, together with substantial financial backing from the Max Planck Society, led to the establishment of an imaging center on the medical campus in Frankfurt-Niederrad. The Land of Hesse financed the construction of a dedicated building, and on May 7, 2004, the Brain Imaging Center[13] opened, equipped with two 3T scanners and (shortly thereafter) a MEG machine. Two full professors, Ralph Deichmann and Michael Wibral, were recruited to coordinate methodological advances in the MRI and the MEG units, respectively. Since its establishment, the Brain Imaging Center has provided advanced noninvasive imaging technology to a multitude of researchers and has developed an extensive multidisciplinary network in support of transinstitutional cooperation and scientific exchange.

The production of complex, high-dimensional data sets, however, increased the need for competency in theoretical disciplines. Although my lab had always included colleagues trained in these disciplines, they were

[13] See http://www.kgu.de/bic/.

somewhat lonely voyagers in a foreign environment—one dominated by experimentalists. Aware of similar needs in other biological disciplines, I submitted a proposal to the *VolkswagenStiftung* and, after international evaluation, received funding for an endowed chair in computational neuroscience at the Goethe University. As we moved forward to fill the chair, however, a most unusual problem arose: Neither the biological nor theoretical disciplines at the university were prepared to accommodate such a chair. The former argued that such a person would lack knowledge in biology, while the latter maintained that someone interested in biological problems would not be competent in math or physics. To get past this hurdle, I teamed up with Walter Greiner, a highly respected theoretical physicist at the university who was interested in strengthening theory in particle physics. Over time, and in multiple consultations with the president of the Goethe University, Rudolph Steinberg, and one of the vice presidents, Horst Stöcker, we developed a plan that envisioned an institute of theorists working on different animate and inanimate model systems, but sharing interests in complex systems with nonlinear dynamics.

Using the project proposal evaluated by the Volkswagen Foundation as a calling card, we initiated a fund-raising campaign. In October 2003, after about 5 million euros were secured, we founded the Frankfurt Institute for Advanced Studies (FIAS). This institute has a unique status: It is a nonprofit organization that is administratively attached to the university, and it runs an interdisciplinary graduate school. Because of the support of its many donors and supporters, the FIAS is thriving. It has its own dedicated building on the Riedberg campus,[14] engages about 120 scientists from 28 countries, and interacts closely with the data-producing experimental institutes throughout Frankfurt. The theoreticians working in my department have a second desk at the FIAS and are able to interact and share advanced theoretical and computational methods with their peers. The lonely voyagers are no longer alone.

Scientific Fairy Tales

On March 9, 2006, while at a Juan March conference in Madrid, I was sitting in a tapas bar celebrating my 63rd birthday when my cell phone rang. To my surprise, the caller was not Francine or my daughters, but rather Thomas Strüngmann, the twin brother of Andreas, who I knew from my mentoring days at *Schloss Neubeuern*. Thomas called to ask whether I would be interested in establishing a research institute on their behalf. Having recently

[14] Located at the northern edge of Frankfurt, the Riedberg is home to a natural science campus that contains departments of the Goethe University, the Frankfurt Institute for Advanced Studies, the Max Planck Institute for Biophysics, the Max Planck Institute for Brain Research, and various independent research groups.

sold their pharmaceutical company, Hexal, the two brothers were interested in giving back to science as a way of acknowledging the contributions that science had played in enabling their own success. For this purpose, they offered me 100 million euros.

Their generous offer, completely unexpected, set off myriad thoughts and caused me to return home quite perplexed. My first instinct was to secure an endowment for the FIAS, since at that time it was working with a capital fund of 30,000 euros. This, however, was not an option, because Andreas and Thomas Strüngmann wanted a new institute with a strong experimental base.

Exploring various possibilities, I began to calculate what it would take to establish an institute similar to mine at Max Planck. Soon it became obvious that an endowment of 100 million euros would not generate enough interest to run an institute with the critical mass required for excellence and international competitiveness. Without hesitation, Andreas and Thomas Strüngmann doubled the endowment, and now concrete steps were required.

I reasoned that such an institute could be successful—both in terms of science as well as in meeting the expectations of the donors—only if it were embedded within a research organization of high reputation, such as the Max Planck Society. Thus, I began deliberations with Barbara Bludau (secretary general of the Society) and Herbert Jäckle (MPI vice president responsible for institutes within the biomedical section). The goal was to establish this new institute under the umbrella of the Max Planck Society and to adopt its well-established instruments for governance, recruitment of directors, quality control, and definition of scientific priorities, but to finance all institutional running costs through the interest generated by the endowment. Unexplored territory was encountered on all levels: Legal issues had to be resolved, because Max Planck is supported by public money. Issues regarding autonomy needed to be discussed and clarified between the donors and Max Planck authorities. And once feasibility had been established, I needed to gain approval from the administrative and scientific boards of the Max Planck Society, as well as permission from its president, Peter Gruss, and Senate.

On more than one occasion, efforts were thrown back to square one, and often I doubted whether a solution could be found. Thanks, however, to the incredible engagement and goodwill on the part of all parties, success was achieved. Named after the donors' father, the Ernst Strüngmann Institute for Neuroscience in Cooperation with Max Planck Society (ESI) was established on September 12, 2008, with the status of a nonprofit organization with limited liability.

A competitive search process followed and, in 2009, Pascal Fries was nominated by the Senate of the Max Planck Society to be ESI's first director. Once Fries accepted, I stepped down from my role as founding director.

In 2011, after officially retiring from the MPI for Brain Research, I was named by ESI's Board of Trustees as a Senior Fellow at ESI. At the same time the Max Planck Society granted me some support for an emeritus lab. This generous support offers me the opportunity to continue some of my research and to stay connected to the world of science.

Commensurate with the retirement of the directors from the old MPI for Brain Research in Frankfurt-Niederrad—Heinz Wässle, Heinrich Betz, and myself—the Max Planck Society decided to relocate the institute to the Riedberg campus to coincide with the appointment of new directors, Gilles Laurent and Erin Schuman. This move necessitated, however, a new building for the institute. Laurent and Schuman chose to begin their tenure in interim offices on the Riedberg to be close to the construction. Their decision opened up space in the old institute, thus enabling Fries and the newly recruited principal investigators of independent junior groups to begin work immediately.

Writing these lines from my office in Frankfurt-Niederrad, I look out over a massive construction site now under way to create new space for ESI. The construction of the ESI science complex is due to the efforts and support of Roland Koch, minister president of the state of Hesse (1999–2010). During the early stages of negotiations to establish ESI, locations in both Frankfurt and Munich were considered. Keen to secure ESI in Frankfurt, Roland Koch offered to help us refurbish the old MPI building if we founded ESI in Frankfurt. Expecting a few million euros for this purpose, the state of Hesse offered ESI 30 million euros to establish its working quarters, and we look forward to moving into the new complex in 2017.

This brief description of the Strüngmann brothers' charisma and passion for science would be incomplete without mentioning yet another incredible and generous act. In 2004, the Dahlem Workshops—a unique and prestigious form of scientific discourse that was established in 1974 as a five-year project of the *Stifterverband für die Deutsche Wissenschaft*, with Silke Bernhard as its founding director—became mired in problems at the *Freie Universität Berlin* (which assumed its administration in 1990). I was familiar with Dahlem, having been invited as a young postdoc to one of its first neuroscience workshops in 1977, "Function and Formation of Neural Systems," chaired by Gunther Stent. The experience was truly eye-opening: for an entire week, I discussed and debated with the most distinguished neuroscientists of that time and remember, with great fondness, my interactions with Eric Kandel, Gerald Westheimer, David Hubel, Torsten Wiesel, Pasko Rakic, and Pat Goldman. Ever since, I have been an aficionado of the Dahlem Workshops. In 1987, I organized one together with Pasko on the "Neurobiology of Neocortex" (Rakic and Singer 1988), and I was in the process of proposing another theme with Christoph Engel (on conscious versus subconscious decision making) when the crisis came to light.

Many efforts were attempted to secure this revered conference series. For my part, I approached the Berlin-Brandenburg Academy of Sciences, of which I am founding member, as well as the Max Planck Society, but neither was able to help. Thus, in 2006 (not long after the Madrid telephone call), I turned to Andreas and Thomas Strüngmann to see whether they would be interested in rescuing this jewel. They immediately agreed and so I approached Julia Lupp (successor to Silke Bernhard) to ask whether she was ready to move to Frankfurt. After a short latency, I received an overwhelming "yes." Julia's commitment to this forum cannot be esteemed high enough as the preparation of these special meetings, the editing of the proceedings, and in particular the guidance of the scientists during the study week require not only a deep understanding of the dynamics of scientific discourse but also a good deal of charismatic authority.

As an institutional harbor, I anchored the institute within the FIAS because of its special status, and because ESI did not yet exist. And on October 1, 2006, Julia began the work necessary to reestablish the philosophy and approach to scientific discourse that had been lost in Berlin. Named after the brothers' father, the Ernst Strüngmann Forum[15] took off like a phoenix rising from the ashes. Since then, it has embedded itself within the scientific community, earning the reputation as the place where intellectual dead ends are overcome, where new ways of conceptualizing issues are grasped, and where future collaborations are created. To cultivate communication among past participants in the neuroscience community, we hold an annual social at SfN. And once the new ESI complex has been completed, the Ernst Strüngmann Forum will join us in Frankfurt-Niederrad to continue its work.

The Accompanying Love Story

In fairy tales, we expect that protagonists will have to master challenges and overcome twists of fate along the way. Often, a love story weaves itself in and out as the plot develops. Thus, it will probably come as no surprise to learn that our fairy tales involve an episode of thwarted love and happy resolution, albeit on an extended timeframe. With gratitude, and humility, let me explain.

During the first year of my university studies in Munich, I often would return to my boarding school at Schloss Neubeuern during academic breaks to serve as a mentor to younger students. In one of my groups was a young boy by the name of Thomas Strüngmann, who must have been about 14 or 15 years old at the time. One day, Thomas confided to me that he was completely in love with a girl from his class. The girl's mother, however, did

[15] See http://www.esforum.de/.

not approve of this innocent liaison and was refusing all weekend invitations to the teenagers' respective homes. Suffering desperately as a result, he turned to me for advice. On his behalf, I wrote a letter to his mother—longhand, of course, in the very best cursive, as would be expected—and met with her to speak about the matter. Through my intervention, she changed her mind and the problem reached a happy ending.

In all honesty, that day in the tapas bar, I would not have been able to recall this incident for it did not occupy a prominent place in my 63-year-old memory. For Thomas Strüngmann, however, it was a poignant experience—one that he related to me much later, after Madrid. He obviously had not forgotten.

Epilogue

Writing this has afforded me the opportunity to reflect comprehensively on my past, and I wish to thank wholeheartedly those who invited me to do so. It made me realize the irreversible passage of time as well as the curious role that hazards and fortuity have played in determining the decisive bifurcations in my life's trajectory. The eminent support that I have received from my family, teachers, mentors, friends, and colleagues is humbling, for without it, most of what I am now able to report would never have happened.

There is this deep and undirected feeling of gratitude to still be around. It is natural to lose relatives and friends over the course of a long lifetime, but some of them departed far too early: Creutzfeldt was just about to harvest what he had sown, Sireteanu was in the midst of consolidating a chair at the Goethe University's faculty of psychology when she left us, and Varela was up to something grand as he was taken away. All three left loving partners, children not yet autonomous, and students who were at the beginning of their careers.

This cursory account of my life would be ever so incomplete without acknowledging my family. Our two daughters, both fiercely determined to never get even close to their parents' professions, failed miserably in this respect. Nathalie, who began her career introducing French contemporary composers to German radio listeners, accepted a chair for "experimental radio" at the Bauhaus University in Weimar and promoted me to the rank of grandfather, a role that I deeply cherish. Tania is now a director at the MPI for Human Cognitive and Brain Sciences in Leipzig. Since her institute is part of the humanities, we rarely meet at Max Planck section meetings but do, on occasion, get invited to the same conferences and enjoy it when colleagues discover that we know each other fairly well. The two girls—monozygotic twins, as we found out through DNA sequencing when they were 30—have always been, and still are, an inexhaustible source of wonderment and surprise. Above all is the overwhelming sense of gratitude that I owe to Francine: her cultivated attitude, caring insistence about the truly important issues, and way of embracing the totality of life ensure that I never forget that there is a life beyond science.

Creutzfeldt used to warn that one should "never let your department get too big." Although neither of us quite succeeded, we did try to create a setting designed to spur young researchers on their way to independence. The value of a mentor is immeasurable, as is the return that one derives from working with young minds.

Since my initial foray into neuroscience, more than 45 years have passed. The finesse of our methods has increased dramatically over this time, as has our awareness of the mind-boggling complexity of the brain. The really big questions, however, have not changed, and in lucid moments, I feel further away from understanding them than I thought I was whenever a question seemed to be resolved. Fortunately, thanks to my association with ESI, I am able to continue the journey. I find it highly gratifying to work again with a small, devoted group of enthusiastic colleagues. The freedom to pursue knowledge, without the need to administer a large department or serve as managing director of a whole institute, is new. And I embrace this next stage with élan and renewed commitment.

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