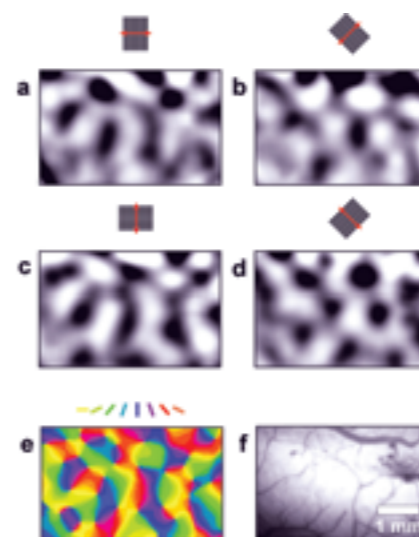


Not Every Stimulus Leaves an Impression

Sometimes we see things, but we don't perceive them. This is the fault of the brain's control centers that convert visual information into perception, as well as directing our visual attention. In this case, the nerve cells that receive visual input first may have received either incorrect feedback or no feedback at all. A group of scientists led by **RALF GALUSKE** at the **MAX PLANCK INSTITUTE FOR BRAIN RESEARCH** are investigating how the higher centers in the visual cortex work, and what role feedback plays in vision.

Say, why don't I ever get any vegetables here?" The patient sounded a bit annoyed during the daily ward round, three days after he had been transferred from intensive care to a regular ward. The doctors looked at each other in surprise. It seemed that the severe stroke had done more damage to the right brain hemisphere than they had initially thought: during the three days since the patient was able to eat solid food again, he certainly had been given vegetables.

"Apparently the patient's stroke had affected not only the brain regions that control motor functions, but also regions that are responsible for complex perception processes," says Ralf Galuske, one of the neurologists who many years ago had been involved in the treatment of the patient who complained about missing peas and carrots. Today, Galuske heads a research group at the Max Planck Institute for Brain Research in Frankfurt am Main. As is common with hospital food trays, the vegetables had been in a separate compartment on the left side of the plate. Due to the failure of a higher visual area in the right half of his cerebral cortex, the patient's vascular occlusion caused a phe-



Optically measured activity patterns in the primary visual cortex following stimulation with differently oriented gratings (a to d). Dark areas correspond to active regions, and light areas to inactive ones; (f) shows the area being examined, and (e) the color-coded orientation preference map.

higher area in the visual cortex, the man was not able to direct his attention to the missing food on his own. Only if the plate had been turned around would his lunch have been complete for him.

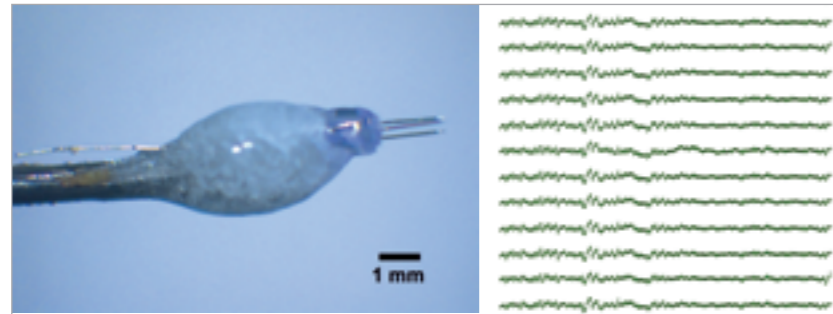
Seeing something but not perceiving it is a strange concept. For most people, seeing and perceiving are one and the same. Even brain researcher Galuske has difficulty explaining the difference. That may be further proof of just how much people depend on the sense of vision. It is similar to an everyday situation that we have all encountered at one time or another: you are looking for the salt in the kitchen and dig through all of the spice containers because you suspect that the salt shaker must be somewhere behind them. And you completely miss that it had been right in front of you (where you didn't expect it).

FEEDBACK FROM HIGHER REGIONS

"We do not see the world as it is, but as we believe it to be," says Ralf Galuske. Or to put it another way: our knowledge causes us to see the world with different eyes. Galuske and his team want to find out what happens inside the brain during this process.



ILLUSTRATION: GROSS/VISION



FINE SENSORS FOR WEAK SIGNALS

The microelectrodes (left) were developed by scientists in the Department of Neurophysiology at the Max Planck Institute for Brain Research. They are made up of three Teflon-insulated tungsten wires attached to a short Teflon tube and have a diameter of 25 micrometers each. The flexible wires can float with the movements of the brain tissue, and thus remain firmly attached at the recording site for months. The figure at right shows parallel field potential recordings of 16 different electrodes from the visual cortex over a period of about 10 seconds. The electrical activity shown is integrated over a tissue region of about 500 micrometers in diameter. The amplitude of the signals is in the range between 0.1 and 0.5 millivolts and must be amplified about 10,000-fold prior to digitalization. Given the appropriate filtering and processing of the recorded data, it would be no problem at all to break down individual action potentials in the field potentials.

“The traditional view was that signal processing occurs sequentially,” explains the researcher. The stimulus causes electrical activity in the retina, which is then directed across the optic nerves to the thalamus and pre-filtered before it continues on to the primary visual cortex and from there into higher centers – and then we see an image, or smell or feel something.

Previous anatomical studies already indicated that something about this concept couldn't be right. From the higher centers, with such names as PMLS and PLLS, strong pathways also go back into the primary regions of the visual cortex, such as areas 17 and 18. “Therefore, the incoming signals should somehow be influenced by signals fed back from higher centers,” says Galuske.

To understand the role of this feedback better, the Frankfurt-based Max Planck scientist and his colleagues are studying visual processing in cats. There were some very good reasons for the decision to use

vision and cats for this study: “Exploiting the visual system as a model makes it very easy to control which stimuli are presented, and in consequence, to trace their processing in the brain,” says the neuroscientist. On the one hand, he can take a very reductionist approach without losing sight of the big picture: while tracking the work of individual neurons, he can also observe the entire visual cortex.

MAN IS A VISUAL ANIMAL

On the other hand, he can also produce complex visual stimuli and still control them. “I find that more difficult with auditory stimuli,” says Galuske and adds: “As a person who is not trained in auditory science.” In researching the sense of vision, he has a plethora of findings on which to draw: “In the past 50 years, a huge scientific community has studied the sense of vision in carnivores and non-human primates.” Primates and especially humans are simply visual animals.

Of course, it is no coincidence that brain researchers study vision in these two animal groups. Non-human primates are our closest relatives, and vision plays a similarly important role in the life of predatory mammals, such as cats, as it does in man. “In other words, cats may rely on vision in a very similar manner to us.” With mice, we can't be quite so sure. As potential prey, they must first and foremost be able to hide, and thus rely on a pronounced sense of touch and smell that helps them find their way in the dark. “Predators such as carnivores, however, have a complex visual system so they can locate their prey at great distance without being noticed themselves,” says Ralf Galuske.

MOVING FENCES CAUSE CONFUSION

To explain what he means by simple and complex stimuli, the researcher points to a television screen at which the cats in the experiments are looking: “Examples of simple stimuli are vertical or horizontal black bars that move up or down, left or right against a white background.” Even simpler are clouds of dots. Because dots have no orientation, the only information they provide is the direction in which the cloud is moving.

More complex stimuli pose a true challenge for the sense of vision, even if their structure is essentially simple. “We just superimpose two grating patterns on top of each other, offset at a slight angle, and have them move in opposite directions,” says Ralf Galuske. He calls this a “plaid” stimulus. At first, these two patterns actually move on top of each other independently, one to the right, one to the left.

Then the upper pattern gradually becomes more transparent, and the image suddenly changes. The independently moving levels merge into

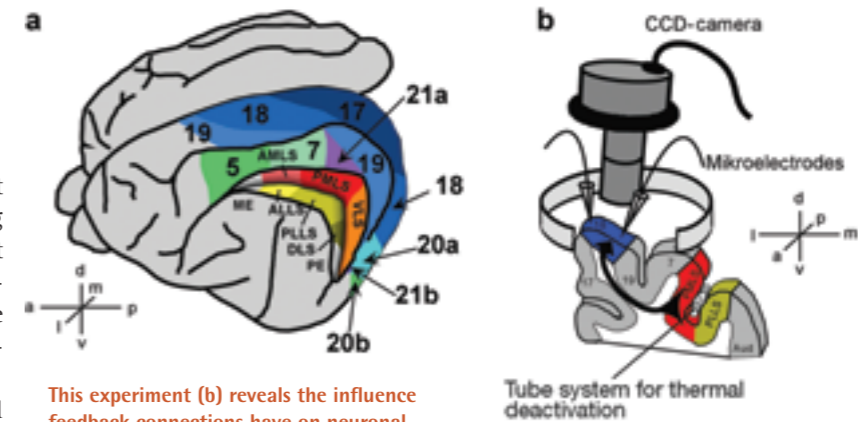
a unified pattern that is reminiscent of a lattice fence, but it isn't moving to either side, but upwards. Is that possible? Then the impression changes again and the two patterns move right and left again, as in the beginning. Amazing.

“This plaid stimulus is an optical illusion after all,” explains Galuske. The two superimposed gratings move toward the edges the entire time, even when it seems that a lattice fence moves upward. The only thing that really changes is the transparency of the upper grating. This makes the lower grating also visible at the point where they overlap. Before, they were hidden at those points by the bars lying on top of them.

Somehow the brain is impressed by that and suddenly perceives only one coherent stimulus moving upward. When the transparency disappears, the magic stops. Our perception jumps back to the two grating patterns moving on top of each other. Galuske can even manipulate this stimulus to such an extent that, under certain transparency conditions, without further changes, our perception continuously flips back and forth between the two possible interpretations.

“But the real issue now,” he says, “is that the individual neurons in the primary visual areas can't differentiate between the two alternative perceptions.” The optical illusion of the upward-moving lattice fence occurs only in the complete image. The neurons in the primary cortex see only a very small section of the whole picture and are thus confronted with the same contours in both cases.

“Nevertheless, we did find distinct activity patterns in the primary visual areas,” says Galuske. So something must have happened that combined the individual stimuli in such a way that another overall impression emerges. “We suspected that these differences are caused by



This experiment (b) reveals the influence feedback connections have on neuronal processing in the primary visual cortex. (a) shows the surface view of the cat cerebral cortex with the various visual areas. The microelectrodes are used for the electrophysiological measurement of neuronal activity, and the CCD camera above area 18 for optical measurement. The orientation of both images is indicated by the direction marker (l: lateral, m: medial, d: dorsal, v: ventral, a: anterior, p: posterior).

the feedback from the upper centers of the visual cortex. They house neurons that can integrate signals across very large areas of the visual field.”

To verify this hypothesis, the brain researchers watch the cat brain as it watches the gratings wandering across the television screen. Probably not terribly exciting for the cat, but all the more exciting for the research team. This can't be done, of course, by studying individual neurons in the ultrathin, stained section under the microscope. It requires the big picture, the systemic, external view of the whole complex in a living object.

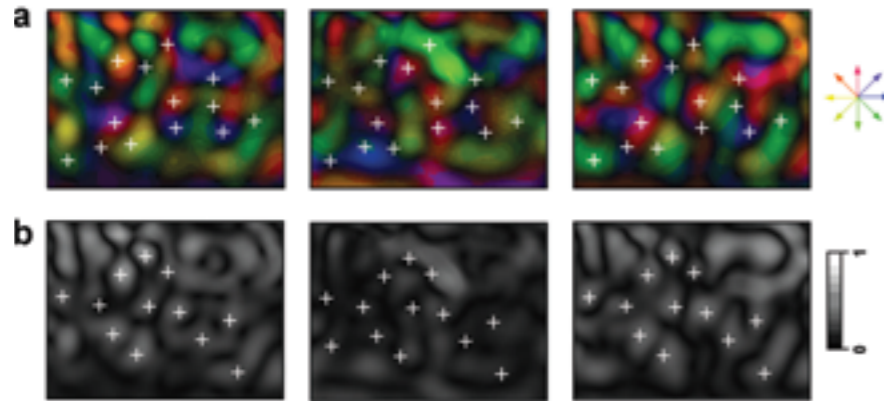
HOW OUR BRAIN GETS TRICKED

But not of the entire brain, either. It is just a small region of area 18 in the primary visual cortex, measuring about one-half to one centimeter in diameter. But even that means that the brain researcher records the activity of millions of nerve cells simultaneously. And “watching” can actually be taken very literally: in addition to traditional electrophysiological recordings, where the electrical activity of individual nerve cells is registered with extremely thin wires in the brain, Ralf Galuske and his colleagues rely primarily on an optical method.

“We don't record the activity of the nerve cells directly, but rather indirectly,” says the scientist. Working nerve cells require oxygen. It is transported to them – bound to the blood pigment hemoglobin – through tiny blood vessels. The researchers watch the activity of the cells in area 18 with a small camera through a window – measuring about two centimeters in diameter and covered with a glass plate – in the bone above the relevant region of the cerebral cortex.

The researchers exploit the fact that hemoglobin with and without oxygen absorbs red light differently. When the blood pigment has delivered its oxygen load to the cell, the blood absorbs far more red light than fresh, oxygen-rich blood. That is why regions in which nerve cells work hard and have greedily absorbed oxygen from the blood appear darker on the map than those where neurons are taking a break.

But Galuske and his team see even more than that. Neurons don't simply fire because something happens in front of the eye. Most neurons have a preference. Some react only to movements from right to left, while others prefer up and down. Some start to get jittery with horizontal bars, while others fire only for vertical bars. “Many nerve cells have a direction or orientation preference,



The PMLS is an area in the cortex that specializes in processing motion information. Deactivating this area has consequences for the representations and the neuronal activity in area 18: the color-coded direction maps (a) show that the allocation of the various direction-selective regions changes significantly during PMLS deactivation (center). The white crosses in the maps mark the same locations in each case; the assignment of the various colors to the different motion directions is pictured at the outside right. (b) shows the maps of the vector strength, each corresponding to the direction maps. Light areas correspond to high vector intensities, dark areas to low ones. Deactivating the PMLS (center map) significantly reduces the vector strength of the visually evoked responses.

and some are less selective,” says the researcher.

Depending on just what the neurobiologists are examining, they analyze the reactions to different stimuli in that part of the visual cortex in various maps – which are second to none among the great masterpieces of abstract painting. Black-and-white patterns visualize activity or a certain stimulus preference, while colorful superimpositions serve, for example, to recognize directional preferences across the entire region.

Thus, different color or black-and-white patterns show how the visual cortex processes the images when the cat watches a three-second television program with horizontal grating patterns, clouds of dots drifting to the right or left, or layers of gratings sliding on top of each other. All of this serves a single purpose: to find out what influence feedback from the higher visual centers PMLS and PLLS has on the lower-lying regions in the primary visual cortex, such as area 18. But to eliminate this influence,

one would have to observe area 18 and, at the same time, be able to switch the feedback on and off. And that is precisely what Ralf Galuske and his team managed to do.

The most direct method would be a lesion – that is, the removal of part of the nerve tissue. “That is very drastic, because the brain is highly traumatized afterwards,” says Galuske. One would have to wait awhile until the brain has recovered. If one waits too long, then it’s possible that the functions of the relevant region of the brain would have been taken over by another, and the malfunction thus already compensated for. “Then you see only the compensated state.”

NERVE CELLS PUT INTO AN ICY SLEEP

Another option would be pharmacological intervention. There are numerous substances that inhibit the activity of neurons and stop neuronal processes locally. “However, it is very difficult to employ these drugs so extensively that they block the

activity of an entire cortical area,” says Ralf Galuske. The amounts required could then exhibit undesirable effects at many other locations in the brain.

Bertram Payne and Stephen Lomber, two American colleagues from Boston University with whom the group in Frankfurt collaborates, supplied a technique that avoids these problems. “We do it thermally,” says Galuske. The researchers transferred the cortical area into a kind of hibernation for a short time. Freezing-cold methanol flows through a thin metal tube that is bow-shaped at the end. When it comes out of the dry ice, it has a temperature of minus 70 degrees Celsius.

In this way, the tissue is chilled to 3 to 5 degrees, and to 10 degrees in somewhat lower layers. “That is enough to hinder nerve cells from generating any more action potential.” The result is a neglect – as in the patient who overlooked his vegetables. In lab tests, the cat, too, then no longer perceived snacks on one side, although it had previously eaten them. When the researchers stop the cooling, the brain area recovers within minutes and again fires action potentials.

The comparison of the maps and data with and without neglect initially confirms what some researchers had already suspected: there are simple quantitative differences. Without feedback from the upper levels, the overall activity in area 18 drops. The maps appear pale where there had previously been strong black-and-white contrasts. “If that was the only thing that happened, it wouldn’t be particularly exciting. The feedback would merely have a gain-setting function,” explains Galuske. It would be nothing more than an amplifier in a stereo system, and the neglect would have an effect comparable to a turned-down volume knob.

But there is more happening: when the feedback is turned off, the activity patterns corresponding to the global perception of the fence no longer appear on the maps. Only the individual components of this complex stimulus are shown. Really exciting are the directional preferences. The dot clouds reveal that the cooling causes individual regions of area 18 to change their preference for certain directions of movement. That is far more than simply turning the volume knob up and down, and much rather as if a rock fan had given up his preferences and now also listens to Händel. “The feedback makes a true qualitative difference,” says the scientist.

KNOWLEDGE CHANGES HOW WE SEE THE WORLD

But optical examination under red light allows conclusions to be made only about entire populations of neurons. Electrophysiological recording with superfine wires is required to study individual neurons. And this shows that the feedback influences primarily those neurons in area 18 that are particularly direction-sensitive, while the other neurons that aren’t as selective are far less responsive to the feedback. “Feedback not only regulates the general intensity of the response, it controls very specific groups of neurons,” says Ralf Galuske. Even in the very early processing steps, the knowledge of the higher centers systematically changes our view of the world, as it were, and so appears to dictate, or at least facilitate, our interpretations.

The feedback can also help explain why we sometimes see things that aren’t there at all – like the optical illusion of the moving lattice fence. And at the same time, it can explain why we sometimes don’t see things even though they are right in front of our nose – like the salt shaker in the front row.

MARCUS ANHÄUSER