



מכון ויצמן למדע

WEIZMANN INSTITUTE OF SCIENCE

Science *Tips*

Publications and Media Relations Department, Rehovot, Israel 76100 Tel: 972-8-934-3852 / 56 Fax: 972-8-934-4132
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Behind Closed Eyes

Even when our eyes are closed, the visual centers in our brain are humming with activity. Weizmann Institute scientists and others have shown in the last few years that the magnitude of sense-related activity in a brain that's disengaged from seeing, touching, etc., is quite similar to that of one exposed to a stimulus. New research at the Institute has now revealed details of that activity, explaining why, even though our sense centers are working, we don't experience sights or sounds when there's nothing coming in through our sensory organs.

The previous studies of Prof. Rafael Malach and research student Yuval Nir of the Neurobiology Department used functional magnetic resonance imaging (fMRI) to measure brain activity in active and resting states. But fMRI is an indirect measurement of brain activity; it can't catch the nuances of the pulses of electricity that characterize neuron activity.

Together with Prof. Itzhak Fried of the University of California at Los Angeles and a team at the EEG unit of the Tel Aviv Sourasky Medical Center, the researchers found a unique source of direct measurement of electrical activity in the brain: data collected from epilepsy patients who underwent

extensive testing, including measurement of neuronal pulses in various parts of their brain, in the course of diagnosis and treatment.

An analysis of this data showed conclusively that electrical activity does, indeed, take place even in the absence of stimuli. But the nature of the electrical activity differs if a person is experiencing a sensory event or undergoing its absence. In results that appeared recently in *Nature Neuroscience*, the scientists showed that during rest, brain activity consists of extremely slow fluctuations, as opposed to the short, quick bursts that typify a response associated with a sensory percept. This difference appears to be the reason we don't experience hallucinations or hear voices that aren't there during rest. The resting oscillations appear to be strongest when we sense nothing at all – during dream-free sleep.

The slow fluctuation pattern can be compared to a computer screen-saver. Though its function is still unclear, the researchers have a number of hypotheses. One possibility is that neurons, like certain philosophers, must "think" in order to be. Survival, therefore, is dependant on a constant state of activity. Another suggestion is that the minimal level of

activity enables a quick start when a stimulus eventually presents itself, something like a getaway car with the engine running. Nir: "In the old approach, the senses are "turned on" by the switch of an outside stimulus. This is giving way to a new paradigm in which the brain is constantly active, and stimuli change and shape that activity."

Malach: "The use of clinical data enabled us to solve a riddle of basic science in a way that would have been impossible with conventional methods. These findings could, in the future, become the basis of advanced diagnostic techniques." Such techniques might not necessarily require the cooperation of the patient, allowing them to be used, for instance on people in a coma or on young children. ■

Prof. Rafael Malach's research is supported by the Nella and Leon Benoziyo Center for Neurological Diseases; the Carl and Micaela Einhorn-Dominic Brain Research Institute; Ms. Vera Benedek, Israel; the Benjamin and Seema Pulier Charitable Foundation, Inc.; and Ms. Mary Helen Rowen, New York, NY. Prof. Malach is the incumbent of the Barbara and Morris Levinson Professorial Chair in Brain Research.

For the scientific paper, please see: <http://www.nature.com/neuro/journal/v11/n9/full/nn.2177.html>

Bacteria are Models of Efficiency

The bacterium *Escherichia coli*, one of the best-studied single-celled organisms around, is a master of industrial efficiency. This bacterium can

be thought of as a factory with just one product: itself. It exists to make copies of itself, and its business plan is to make them at the lowest possible cost, with the

greatest possible efficiency. Efficiency, in the case of a bacterium, can be defined by the energy and resources it uses to maintain its plant and produce new cells,

versus the time it expends on the task.

Dr. Tsvi Tlusty and research student Arbel Tadmor of the Physics of Complex Systems Department developed a mathematical model for evaluating the efficiency of these microscopic production plants. Their model, which recently appeared in the online journal *PLoS Computational Biology*, uses only five remarkably simple equations to check the efficiency of these complex factory systems.

The equations look at two components of the protein production process: ribosomes – the machinery in which proteins are produced – and RNA polymerase – an enzyme that copies the genetic code for protein production onto strands of messenger RNA for further translation into proteins. RNA polymerase is thus a sort of work

“supervisor” that keeps protein production running smoothly, checks the specs and sets the pace. The first equation assesses the production rate of the ribosomes themselves; the second the protein output of the ribosomes; the third the production of RNA polymerase.

The last two equations deal with how the cell assigns the available ribosomes and polymerases to the various tasks of creating other proteins, more ribosomes or more polymerases.

The theoretical model was tested in real bacteria. Do bacteria “weigh” the costs of constructing and maintaining their protein production machinery against the gains to be had from being able to produce more proteins in less time? What happens when a critical piece of equipment is in short supply, say a main ribosome protein? Tlusty and

Tadmor found that their model was able to accurately predict how an *E. coli* would change its production strategy to maximize efficiency following disruptions in the work flow caused by experimental changes to genes with important cellular functions.

What’s the optimum? The model predicts that a bacterium, for instance, should have seven genes for ribosome production. It turns out that that’s exactly the number an average *E. coli* cell has. Bacteria having five or nine get a much lower efficiency rating. Evolution, in other words, is a master efficiency expert for living factories, meeting any challenges that arise as production conditions change. ■

Dr. Tsvi Tlusty’s research is supported by the Clore Center for Biological Physics.

For the scientific paper, please see: <http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1000038>

Weizmann Institute Scientists Show

Extra Copies of a Gene Carry Extra Risk

Is more of a good thing better? A gene known as LIS1 is crucial for ensuring the proper placement of neurons in the developing brain. When an LIS1 gene is missing, brains fail to develop the characteristic folds; babies with lissencephaly or “smooth brain” are born severely mentally retarded. But new research by Prof. Orly Reiner of the Institute’s Molecular Genetics Department, which recently appeared in *Nature Genetics*, shows that having extra LIS1 genes can cause problems as well.

Reiner was the first to discover LIS1’s tie to lissencephaly, in 1993. Their latest study shows that it works by helping to determine polarity in the cell – how the various organelles are arranged inside the cell as well as where it connects to neighboring cells. Neurons alter their polarity several times during development, especially when they take on an elongated shape and migrate to new locations in the brain.

But what if, rather than too little, the body has too much LIS1? One of the surprises to come out of the recent spate of post-human-genome research is the number of genes that can be repeated or deleted in an individual’s genome. Most

extra copies of genes may be no more harmful than a computer backup disk, but scientists have been finding that some repeats can cause disease.

Research associate Dr. Tamar Sapir and lab technician Talia Levy, working in Reiner’s lab, developed a mouse model in which additional LIS1 protein was produced in the brain. The scientists found that the brains of these mice were a bit smaller than average. On closer inspection, they discovered a range of subtle changes in cell polarity and movement: Nuclei within the proliferating zone tended to move faster, but with less control; rates of cell death were higher; and various factors in the cell became more disordered.

Reiner then asked whether their findings might apply to humans. Together with Jim Lupski and Drs. Weimin Bi and Oleg A. Shchelochkov of Baylor College of Medicine in Houston, Texas, they searched through blood samples using a technique that matches a patient’s DNA with control DNA to identify additions or deletions in its sequence. They identified seven individuals with extra copies of either LIS1 or adjacent genes that are also involved in brain

development. All suffered developmental abnormalities. Two of the patients – children with a second LIS1 gene – had previously been diagnosed with failure to thrive and delayed development, and were found to have small brain sizes. A third, who had three copies of the gene, was mentally retarded and suffered from bone deformation as well.

Reiner: “Several brain diseases, including schizophrenia, epilepsy and autism, have been linked to faulty neuron migration, and recent research has hinted that some of these may involve variations in gene number. Our study is the first to demonstrate the effects of the duplication of a single gene in a mouse model and tie it to a new ‘copy number variation’ human disease.” ■

Prof. Orly Reiner’s research is supported by the Nella and Leon Benoziyo Center for Neurological Diseases; the Kekst Family Center for Medical Genetics; the David and Fela Shapell Family Center for Genetic Disorders Research; the PW-Iris Foundation; and the PW- Jani.M Research Fund. Prof. Reiner is the incumbent of the Bernstein-Mason Chair of Neurochemistry.

For the scientific paper, please see: <http://www.nature.com/ng/journal/v41/n2/pdf/ng.302.pdf>