Three neuroscientists win the Biomedicine award

The BBVA Foundation Frontiers of Knowledge Award goes to the architects of optogenetics, which uses light to probe and modulate the workings of the brain

- Edward Boyden, Karl Deisseroth and Gero Miesenböck developed and refined a technique that employs light to activate and inactivate proteins in the brain cells, making it possible to modulate their activity with unprecedented precision
- Optogenetics is now a widely used tool being applied to elucidate functions like sleep, appetite and movement or reward circuits in addiction
- The awardees all emphasize the basic knowledge underpinning the technique, which, they say, will eventually yield new opportunities in the clinic

Madrid, January 26, 2016.- The BBVA Foundation Frontiers of Knowledge Award in Biomedicine goes in this eighth edition to neuroscientists Edward Boyden, Karl Deisseroth and Gero Miesenböck for the development of optogenetics, a method to study brain function with unprecedented resolution. In a bare five years, thousands of groups the world over have begun using optogenetics to investigate functions like sleep, appetite, decision-making, temporal perception or the creation of memories, and elucidate the mechanisms of conditions such as epilepsy, Parkinson's, depression and certain forms of blindness.

The beauty of optogenetics is that it allows the selective control of neural activity simply by applying light of the right wavelength. Before, the most widely used methods to study the living brain could modulate the activity of hundreds of thousands of neurons, but with little selectivity. With optogenetics, it is possible to act exclusively on neurons treated previously with light-sensitive proteins, according to the behavior being tested.

Ed Boyden, (Plano, Texas, United States, 1979), a professor at Massachusetts Institute of Technology, used the following simile in conversation yesterday, after hearing of the award: "If we imagine the brain as a computer, optogenetics is a key that allows us to send extremely precise commands. It is a tool whereby we can manipulate the brain with exquisite precision."

Stanford professor Karl Deisseroth, (Boston, United States, 1971), who as well as a neuroscientist is also a practicing psychiatrist, remarked yesterday that "the main application for optogenetics is basic research, the understanding of how the brain works." This knowledge, he believes, will unlock "all manner of advances in the clinic," although he is also at pains to stress that "no one is yet using the technique directly to treat patients."

Gero Miesenböck, (Braunau, Austria,1965), a professor at the University of Oxford (United Kingdom), recalled how he got the idea that would sow the seeds of optogenetics: "I was looking at how to visualize neural activity using light-sensitive proteins. And suddenly, one Saturday afternoon, the thought came to me: Wouldn't it be amazing not just to read the brain's activity but also to control it? Because in biology to understand a system you need to have it under precise control, and that wasn't possible in brain science."

A revolutionary technique that has found its way around the world

Optogenetics, in the words of the award citation, "has revolutionized the study of brain function and is now used by neuroscientists around the world." Understanding how our brains' circuitry works "would require the development of a technology that allowed the selective control of individual neurons without affecting the activity of others. Optogenetics is this technology: it allows the activation and inactivation of neurons in living animals, and therefore can be used to make causal links between the function of specific neural circuits and distinct behaviors."

Miesenböck conceived his idea at the end of the 1990s, but it was some years before he was able to give it shape. The breakthrough came thanks to his work with light-sensitive proteins, because optogenetics involves inserting these proteins into brain cells: illumination of the proteins causes the cells to change their status from excited to inhibited or viceversa.

The technique owes its precision to the use of genetics. Neuroscience has come on enormously in the past few decades in its identification of distinct neuronal populations according to the genes that they express. Optogenetics uses these genes to deliver the light-sensitive proteins to the target neurons via techniques borrowed from gene therapy: the genes of the light-sensitive protein and the target neurons are introduced into the genetic material of a virus, which is then injected into the brain region of interest.

In 2002, Miesenböck was the first to show that neural activity could be modulated by light. He began with cultured cells, but realized immediately that "this was a technology with immense transformative power."

His second "breakthrough" moment was in 2005, when he and postdoctoral assistant Susana Lima managed to employ the technique in a living organism, concretely a fruit fly. By activating just two of its hundreds of thousands of neurons, optogenetics triggered the response that made the insect fly away.

But Miesenböck's technique had major drawbacks: the proteins used caused only modest neural activation, and the process was unlikely to be suitable for large-scale application.

The key to a solution lay with Karl Deisseroth and Ed Boyden. Working together at Stanford in the year 2000, they were struck by a remark made by Francis Crick, one of the co-discoverers of DNA, to the effect that understanding the brain would require access to far more precise techniques. Deisseroth and Boyden thought long and hard about "how to use different forms of energy to manipulate brain cells," recalls Boyden. Like Miesenböck, they tried working with light-sensitive proteins, but without ever cracking the problem.

The two men returned to the fray in 2004, only this time using a protein recently isolated in a species of green alga, with far superior light responsiveness to those employed by Miesenböck.

"We were lucky enough to get hold of proteins that responded on the right temporal scale to study neural circuits," says Boyden.

Deisseroth and Boyden's paper appeared in 2005. Since then, the technique has undergone successive refinements, with proteins, for instance, that respond at different speeds or to different types of lights, extending the range of brain functions that can be studied.

It should be mentioned that none of the seminal papers in optogenetics enjoyed an easy passage. Miesenböck recalls that the reviewers of his first submission "completely missed the point"; something he ascribes to the fact that "innovative techniques always take time to filter through."

Boyden too recounts how after the 2005 paper, rejected in turn by *Science* and *Nature*, he was turned down for jobs by at least half of the institutions he applied to: "At the time neuroscientists were distrustful of neurotechnology."

The three laureates agree that the first priority is to understand more about the brain. And they give examples. Miesenböck has discovered a set of sleep-inducing neurons in flies, and is also exploring the process of decision-making. He has shown that "flies think more about the harder decisions, just like us".

Boyden is striving to perfect the technological aspects of optogenetics, but is also keen to mention the work of other groups: on neural circuits involved in aggressive behavior; on the creation of memories; and on the possibility of treating some forms of blindness by replacing damaged photoreceptors in the retina with light-sensitive proteins.

Deisseroth, finally, refers to research being done on the circuits involved in cocaine addiction.

They declare themselves confident that a better understanding of the neural circuits relevant to certain diseases will enable the development of finely targeted drugs that act directly and selectively on those circuits. A degree of precision in the treatment of mental or neurological disorders that goes far beyond what we can do today.

As to the ethical implications, Miesenböck is "not that concerned," and sees "no real difference" between this technique and other behavior-modifying methods such as drugs. Deisseroth, meantime, is convinced that this is a discussion "that will have to happen," but not in the short term since the use of optogenetics in humans remains for him a fairly distant prospect.

The winning nominations in the Biomedicine category were put forward by Juan Lerma, Director of the Instituto de Neurociencias, CSIC-Miguel Hernández University (Spain); Andrew D. Hamilton, Vice-Chancellor of the University of Oxford (United Kingdom) and Lloyd B. Minor, Dean of the School of Medicine at Stanford University (United States).

Bio notes

Edward Boyden (Plano, Texas, United States, 1979) completed his BS studies in physics and electrical engineering and computer science at Massachusetts Institute of Technology (MIT) before obtaining a PhD in neuroscience at Stanford University, where he worked alongside Karl Deisseroth. In 1996, he joined the research staff at MIT, where he remains to this day as professor of Biological Engineering and Brain and Cognitive Sciences. He leads the institution's Synthetic Neurobiology Group, developing tools that enable the systematic mapping and repair of the brain and other complex biological systems, and is also an investigator at the MIT McGovern Institute for Brain Research and associate professor at the MIT Media Lab. He has been co-director since 2014 of the MIT Center for Neurobiological Engineering.

Karl Deisseroth (Boston, Massachusetts, United States, 1971) studied biochemical sciences at Harvard than went on to complete an MD at Stanford, where he also obtained his PhD in neuroscience. After finishing his PhD dissertation, he opted for a residency in psychiatry, and today continues to combine patient consultations with a devotion to basic research. He has spent most of his career at Stanford University, where he is currently DH Chen Professor of Bioengineering and Professor of Psychiatry and Behavioral Sciences. He served on the committee behind the BRAIN Initiative launched by the Obama administration in April 2013 to "accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought."

Gero Miesenböck (Braunau, Austria, 1965) studied medicine at the University of Innsbruck, where he also obtained his PhD. During a three-month stay at the University of Umeå, Sweden (1989). he came across the work of American biochemist James E. Rothman (Nobel Prize in Medicine 2013). In 1992, he moved to New York to work with Rothman at the Memorial Sloan-Kettering Cancer Center. Following three years as an Associate Professor of Cell Biology at Yale University, in 2007 he joined the faculty of the University of Oxford, where he combines the post of Waynflete Professor of Physiology with the leadership of the Centre for Neural Circuits and Behaviour (CNBC), which he also founded.

About the BBVA Foundation Frontiers of Knowledge Awards

The BBVA Foundation promotes, funds and disseminates world-class scientific research and artistic creation, in the conviction that science, culture and knowledge hold the key to better opportunities for all world citizens. The Foundation designs and implements its programs in partnership with some of the leading scientific and cultural organizations in Spain and abroad, striving to identify and prioritize those projects with the power to significantly advance the frontiers of the known world.

The BBVA Foundation established its Frontiers of Knowledge Awards in 2008 to recognize the authors of outstanding contributions and radical advances in a broad range of scientific, technological and artistic areas congruent with the knowledge map of the late 20th and the 21st centuries, and others that address central challenges, such as climate change and development cooperation.

Their **eight categories** include classical areas like *Basic Sciences*, and other, more recent areas characteristic of our time, ranging from *Biomedicine, Information and Communication Technologies, Ecology and Conservation Biology, Climate Change* and *Economics, Finance and Management* to *Development Cooperation* and the innovative realm of artistic creation that is *Contemporary Music*.

The **juries** in each category are made up of leading international experts in their respective fields, who arrive at their decisions in a wholly independent manner, applying internationally recognized metrics of excellence. The BBVA Foundation is aided in the organization of the awards by the **Spanish National Research Council (CSIC)**. As well as designating each jury chair, the CSIC is responsible for appointing the technical evaluation committees that undertake an initial assessment of candidates and draw up a reasoned shortlist for the consideration of the juries.

CSIC technical committee members in the Biomedicine category were **Carmelo Bernabeu Quirante**, Research Professor at the Biological Research Center (CIB-CSIC), **Paola Bovolenta Nicolao**, Research Professor at the "Severo Ochoa" Molecular Biology Center (CBM-CSIC), **Dolores González Pacanowska**, Coordinator of the Biology and Biomedicine Area and Research Professor at the Institute of Parasitology and Biomedicine "López Neyra" (IPBLN-CSIC), **María Isabel Mérida de San Román**, Research Professor at the Spanish National Biotechnology

Center (CNB-CSIC), and **María Luisa Toribio García**, Research Professor at the "Severo Ochoa" Molecular Biology Center (CBM-CSIC).

Biomedicine jury

The jury in this category was chaired by **Angelika Schnieke**, Chair of Livestock Technology at Technische Universität München (TUM) (Germany) with **Óscar Marín**, Professor of Neurosciences and Director of the MRC Centre for Developmental Neurobiology at King's College London (United Kingdom) acting as secretary. Remaining members were **Dario Alessi**, Director of the MRC Protein Phosphorylation and Ubiquitylation Unit, in the School of Life Sciences at Dundee University (United Kingdom), **Robin Lovell-Badge**, Head of the Laboratory of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute (United Kingdom), **Ursula Ravens**, Senior Professor in the Department of Physiology in the Carl Gustav Carus Medical School of Technische Universität Dresden (TUD), and **Bruce Whitelaw**, Deputy Director and Head of the Developmental Biology Division at The Roslin Institute, a basic and translational research center belonging to the University of Edinburgh (United Kingdom).

Previous laureates

A list of laureates in previous editions is available on the following link:

http://www.fbbva.es/TLFU/tlfu/ing/microsites/premios/fronteras/galardonados/2015/index.jsp

UPCOMING AWARD ANNOUNCEMENTS

CATEGORY	DATE
Ecology and Conservation Biology	Tuesday, February 2, 2016
Contemporary Music	Tuesday, February 9, 2016
Economics, Finance and Management	Tuesday, February 16, 2016
Development Cooperation	Tuesday, February 23, 2016

LAUREATE'S FIRST DECLARATIONS AND IMAGES

A video recording of the new laureate's first interview on receiving news of the award is available from the Atlas FTP with the following name and coordinates:

Server: **213.0.38.61**

Username: **AgenciaAtlas4**

Password: **premios**

The name of the video is:

"PREMIO FRONTERAS DEL CONOCIMIENTO CATEGORÍA BIOMEDICINA PROF. GERO MIESENBÖCK Y PROF. EDWARD BOYDEN"

In the event of connection difficulties, please contact Alejandro Martín at ATLAS:

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