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Sant Joan de Déu HOSPITAL MATERNOINFANTIL - UNIVERSITAT DE BARCELONA

Sant Joan de Déu Research Foundation

Sinopsi

CONNECTING THE GROWING BRAIN

UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION

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RECONNECTING THE GROWING BRAIN

FROM SYMPTOMS TO MECHANISMS

Children's brains are always growing and developing, but unfortunately this complex machine can also break down. Traditionally, pediatric neurology has addressed these problems according to the symptoms that cause them: epilepsy, mental retardation, autism and movement disorders, for example. However this approach isn't enough because the categories overlap and the symptoms are only the external manifestation of the underlying problem. Studying only these manifestations isn't normally enough to treat the problem.

In the words of Àngels García Cazorla, pediatric neurologist at Hospital Sant Joan de Déu Barcelona, we need "a little revolution in the way we approach, research and treat these disorders. The symptoms are important, but treatment must address the underlying mechanisms, not their consequences. And this is why we need to know what's really going on inside the brain."

In order to address and comment on all of these challenges and problems, to discuss the latest advances, some of the top experts in the world met for a session of B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate.

CONCLUSIONS:

- ✓ Neuropediatric diseases affect up to 20% of all children, but they have traditionally been researched less than those that affect adults.
- ✓ Research has been addressed improperly, focusing on symptoms, which in many cases overlap between diseases, and not the mechanisms. This has made it difficult to find treatments that are truly effective.
- ✓ We must study brain function from a microscopic and macroscopic point of view. From the synapses that connect neurons to the wiring that connects regions of the brain, what is known as connectome.
- ✓ Treatments being studied include drugs to lessen certain disabilities, like Down syndrome; gene therapy and even light-activated drugs.

LIMITATIONS OF NEUROLOGY IN CHILDREN

For Dr. García Cazorla, scientific leader of this B·Debate, "brain disorders in development are a very significant health problems that can affect up to 20% of all children, but historically they have been studied less than those in adults." Xavier Castellanos, childhood psychiatrist and professor at the New York University School of Medicine, believes this could be because "children don't vote and aren't in power, this could be why less money is invested in this type of research."

The errors that occur in the brain during childhood lead to a wide range of possible symptoms: epilepsy, disorders on the autism spectrum, movement disorders, mental disabilities, and more. García Cazorla says, "We've specialized in these, but basic neuroscience is growing, and that indicates that we are a bit disoriented, because the symptoms don't reflect the exact decision of functioning: a mutation may manifest as epilepsy in some cases but as a movement disorder in others." Or, as Castellanos puts it, "There are mutations that cause holoprosencephaly (serious malformation of the skull and face) in some children but only cause others to be missing a tooth. There are many factors involved."

This lack of knowledge regarding the real mechanisms behind the symptoms makes if extremely difficult to come up with truly curative treatments because the therapies address the consequences but not the cause. This is why García Cazorla advocates for "a little revolution in the way we approach, research and treat these disorders. The symptoms are important, but treatment must address the underlying mechanisms, not their consequences. And this is why we need to know what's really going on inside the brain." A revolution that is not free from difficulties, as it must necessarily be transversal, involving people from many different disciplines. "There is the chance that we will disconnect instead of connecting, but that's a risk worth taking," she says.

In order to truly understand what is happening, it is necessary to study how the brain communicates. One on hand, on the microscopic scale, in terms of synapses that connect neurons. And, on the other, on the macroscopic scale, to untangle the structure of the wiring and how it works. And, at the same time, to look towards possible solutions.

MICRO AND MACRO, FROM SYNAPSES TO CIRCUITS

“I’m very happy to come to the land of Ramon i Cajal and speak about the brain and its connectivity,” explained Sakkubai Naidu, podiatrist and neurologist at the Kennedy Krieger Institute in Baltimore, United States. “He said that neurons are contiguous, not continuous, and that they are dynamic.” The way in which they connect through contiguity is with synapses, and they have been proven to be extremely dynamic. For example, “activity promotes synapses, both in prenatal and postnatal life. And some of the first to mature are those in the sensory cortex: the ones babies need to hear and move their head to feed,” says Naidu.

There are many types of synapses in which various neurotransmitters participate and can be considered the keys to various locks in the brain. Some are excitatory and react to glutamate. Some are inhibitory and react to GABA, the target molecule in most anxiolytics. And some are modulatory, including dopamine, serotonin, adrenaline, etc. And each synapse has its own life cycle: formation, maturation, maintenance and, in many cases, elimination.

Synaptic disruptions lead to a wide range of symptoms and diseases, many of which overlap. Manju Kurian, pediatric neurologist at Great Ormond Street Hospital in London, proposes calling all of these disorders “synaptopathies”, to focus the study. This study is highly necessary but not at all easy. Its complexity can be seen in the fact that hundreds of proteins have been identified in each synapse and the disruption can happen in many different phases, including synthesis of neurotransmitters, their storage or recycling, transport, in the receptors that recognize them, etc.

Amidst this complexity, one of the targets being studied is what are known as neuroligins, a sort of “molecular adhesive” that helps neurons find each other and make the synapses. **Several of them are mutated in familiar forms of autism, and scientists speculate that they may be behind several behavioral disorders**. This idea was shared by Nils Brose, director of the Department of Molecular Neurobiology at the Max Planck Experimental Medicine Institute, in Germany. For Brose, "One hypothesis that would explain autism is that there is an neuronal imbalance between excitation and inhibition. Certain neuroligins affect the behavior of the GABA inhibitor, which may be a therapeutic target in the future.”

But if the little things are important, so are the big ones: the “wiring” that connects the different areas of the brain and, as a whole, has come to be known as the “connectome”. In order to visualize this, scientists use ever more sophisticated techniques, which according to co-founder of Mint Labs Paulo Rodrigues, "Allow us to see the networks and nodes, how one part of the brain is connected to another.” In fact, for Rodrigues “**the connectome emphasizes the concept that the brain is one large, complex system**.”

In terms of pediatrics, these tools “can allow doctors to see the developmental alterations and identify an opportunity/window in which to administer treatment.” One of these alterations is Attention Deficit Hyperactive Disorder (ADHD). Although in many cases it is difficult to firmly establish, Josep Antoni Ramos Quiroga, psychiatrist at the Hospital Vall d'Hebron Barcelona, estimates that nearly 6% of all children have this condition, and that it carries over into just over 3% of adults. Neuroimaging techniques have allowed us to identify that those with this condition have approximately 3% less grey matter, as well as other areas of the brain, and show asymmetrical brain maturing compared to other children.

For Xavier Castellanos, who also researches this disorder, ADHD “has a highly variable prognostic, generally acceptable, but with increased risk of accidents and normally less access to quality jobs.” Interested in the brain networks that cause it, Castellanos and his team use functional magnetic resonance to link the brain structure with its activity. This has led them to suggest that attention deficit in these individuals is the result of “a bad connection between the networks that are active at rest and those that act at the moment of execution. Neuronal activity at rest is giant, up to 60% of the total, but its biological meaning isn't understood yet.”

MODELS AND TREATMENTS: THE SEARCH FOR SOLUTIONS

Biomedical research is complex in itself, but studying what are known as synaptic diseases adds additional difficulties. On one hand, because many of the genes involved have pleiotropic effects, meaning that altering them can lead to different effects. And these effects, moreover, can overlap across different syndromes. And, on the other, because in general they are rare diseases, which makes it more difficult to do patient research. This is why “we need animal models,” says Soledad Alcántara, professor in the Department of Pathology at the University of Barcelona.

These models are generally mice, and they have their own difficulties. Their genetic makeup, obviously, isn't the same as that of humans and there are many factors that may "confuse" the results. This is why up to 80% of treatments that work on models may not work on patients. But advancing towards better understanding the mechanisms of the disease seems to be the only way forward. "Pharmaceutical companies have abandoned neuroscience," says Mara Dierssen, group leader at the Center for Genomic Regulation in Barcelona (CRG). In part this is "because mistakes have been made, like basing treatment on symptoms. It must be based on physiopathology, on the mechanisms of the disease."

Dierssen's main line of research concerns Down syndrome. Based on the idea of attacking the mechanisms, her group began to test a compound found in green tea that seems to reverse some of the symptoms. The compound wasn't chosen by chance: it is an inhibitor of the Dyrk1 protein, which in excess causes effects similar to Down syndrome in mice. The compound is undergoing clinical trials and, according to Dierssen, "seems to improve various aspects, including cognitive function." Even neuroimaging studies "indicate improved brain activity and connectivity."

Drugs are one treatment option, **but in the case of genetic diseases, another may be gene therapy**, treatments aimed at correcting or compensating for defective genes. In the case of neuropediatric diseases, according to Dierssen, most research focuses on Leber's congenital amaurosis, a disease of the retina that tends to cause congenital blindness. The problem with these therapies is that the new genes normally have to be administered through a virus, which can enter anywhere in the genome and cause it to malfunction. But **new techniques based on CRISPR technology will hopefully overcome these difficulties**.

There are even some seemingly futuristic options, like **controlling neuronal activity with light**. This is the goal of disciplines like optogenetics and optopharmacology. The former uses gene therapy to introduce genes normally from algae into the neurons and then control their activation or inhibition with blue or yellow light, respectively. Optopharmacology, if possible, goes even further. As Pau Gorostiza, ICREA professor at the Institute for Bioengineering of Catalonia (IBEC), explained, it consists of "using synthetic compounds that join with endogenous proteins in the body in a reversible manner." These compounds are normally derived from azobenzene, a molecule that folds when hit with light of different wavelengths. As they are found in specific proteins, they can be modulated with light and directed towards specific neurons. This will not only help study their function but also "has

therapeutic potential," says Gorostiza. For example, in better controlling neuronal activity, they could replace and improve the electro-stimulation therapies used for Parkinson and some serious cases of depression. Some even hope that they may be used for some types of autism like Rett syndrome, which is a serious disorder that affects girls and is due to a mutation in one gene. Experiments with mice involving electric stimulation have been able to lessen the symptoms of this condition, and Gorostiza doesn't doubt in saying that these treatments "may end up being replaced by light-activated drugs."