B·DEBATE International Center for Scientific Debate BARCELONA

biocat | Obra Social "la Caixa"

Synopsis

EARLY LIFE EXPERIENCES

VULNERABILITY OR RESILIENCE?

ORGANIZED BY:

INc Institut de Neurociències

WITH THE COLLABORATION OF:

CORE SALUT MENTAL UAB

Vall d'Hebron Institut de Recerca VHIR

The Institute for the Study of Affective Neuroscience (ISAN)

CHILDHOOD STRESS:

NEGATIVE, POSITIVE…AND HEREDITARY?

Mental illness is oddly stigmatized in light of the numbers. It is so prevalent that, in one its widely-varied forms, it will affect approximately one in four people. And in economic terms, its repercussion will be greater than that of heart disease and even cancer.

More than half of all mental illnesses begin developing before adulthood. Although there are many different causes, scientists are increasingly looking to events that take place in childhood and adolescence. Does early stress lead to a greater risk of mental illness? There are many figures that say yes, but research is introducing unexpected new nuances. On one hand, a certain type of stress is beginning to be seen as positive, as it helps us adapt to adversity in adulthood. On the other, there are indications that the after effects of exposure to early traumatic experiences can be passed down to our children and even grandchildren through epigenetic mechanisms.

In order to discuss some of the most recent and important advances, several of the top international experts met on 25 and 26 October 2016 at the debate 'Early Life Experiences. Vulnerability or Resilience?' organized by B·Debate –an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate– and the Institut de Neurociències, with collaboration from the CORE in Mental Health of the Autonomous University of Barcelona, the Vall d'Hebron Research Institute and The Institute for the Study of Affective Neuroscience.

CONCLUSIONS

- **Negative stress in early stages of life** increases a person's chances of experiencing **depression, anxiety or psychosis, as well as non-mental illnesses** like some types of cardiovascular disease.
- Studies show that there may also be **positive stress**: making people more resilient and having benefits in adulthood.
- The exact routes and mechanisms behind adaptive stress aren't fully understood yet, but it seems important for it **to be perceived as controllable**.
- The consequences of negative stress **could be hereditary and passed down to the following generations**. If this were confirmed, it would be an epigenetic not genetic inheritance.

NEGATIVE STRESS: A TRIGGER FOR ILLNESS

"**Many violent offenders suffered a traumatic childhood experience**," explained Carmen Sandi, director of the Brain Mind Institute in Lausanne, Switzerland. In some way, "The brain exposed to fear and stress early on develops differently, takes different neural paths."

According to Roser Nadal, ICREA ACADEMIA professor at the Autonomous University of Barcelona Institut de Neurociències and one of the scientific leaders of this B·Debate, "**Negative stress is a proven risk factor that increases a person's chances of psychosis, anorexia, depression or anxiety. However, it also affects the immune and even cardiovascular systems**: the effects are not only mental."

For example, numerous studies have shown a connection between early trauma and psychosis, as explained Neus Barrantes, ICREA ACADEMIA professor at the Autonomous University of Barcelona. For example, the risk of developing schizophrenia is higher among racial minorities that are more isolated. And psychotic symptoms are seen considerably more in individuals that have suffered from abuse or bullying early on, quite a bit more than a traumatic accident. "It seems to play a secondary role in society, a subordinate position. It could be a unifying mechanism that would explain the environment's influence on developing psychosis," said Barrantes.

The great challenge lies in understanding the exact biological mechanisms that increase these risks. In the case of psychosis, there seems to be a dopamine imbalance, among other things, which affects what is known as the hypothalamic–pituitary–adrenal axis. This acts as a bridge for communications, connecting the brain and the adrenal glands, which produce the main stress hormone: cortisol. An early traumatic experience alters this in such a way that it tends to have an exaggerated, disproportionate reaction. This can even have an effect on brain organization.

This is one potential mechanism, but it is extremely complex. Among other players, **cell adhesion molecules** seem to have a key role. These molecules are important in binding neurons together correctly. "This is a therapeutic pathway that is opening up for the future," Sandi said.

In fact, understanding these mechanisms would also help explain why the results differ so greatly. For example, in Sandi's own research, "When we subject a group of lab rats to early stress, we always see that, on the whole, they tend to become more aggressive. But **individually, some of them don't change.**" Up to 30% seem to be able to better handle the tension, as they adapt and their corticosterone levels go back to normal. This seems to put a halt to the developmental deviation seen in their companions.

Deeper understanding of all of this –including improvements in research methods, which for many aren't as robust as they should be- would help fight what Barrantes calls "non-scientific nihilism," and could limit the social and psychological enrichment and help available to this type of patients. One of these fields of knowledge is the antithesis of what we've said so far, the other side of the coin: positive stress.

THE FIRST REVOLUTION: POSITIVE STRESS

"It is a revolutionary concept," said Nadal. "Depending on its intensity, how much control the child has over it, and the tools the family provides, **stress can have a positive, adaptive effect**. Clearly, **keeping children in a bubble doesn't do them any favors. It's a matter of balance**."

In order to apply this, "The key is understanding the mechanisms that make us more resilient and able to overcome adversity. It seems that better resilience comes from greater work memory and ability to anticipate the future. This is highly necessary in **a society that increasingly puts us in stressful situations**. However, the tools won't come from modifying one gene or one environmental situation. We don't know what they are yet, but we have some ideas."

These ideas, for now, mainly come from laboratory animals. One of the most remarkable has been known since 1956 and is called postnatal handling, as explained Albert Fernández, ICREA ACADEMIA professor at the Autonomous University of Barcelona. Then, the group led by psychologist Seymour Levine began a series of experiments in Chicago to assess the long-term effects of different early-life experiences. To do so, they put newborn rats into groups. One of them would stay with the rest of the litter and their mother, as normal. Those in another group, however, were put into separate cages on their own for several minutes every day for the first twenty days. Finally, a third group was separated from their mother for several hours each day. As expected, prolonged separation had negative long-term effects. **Nevertheless, the results from the short-term separation (handling) group were surprising.** Later on, these rats were more able to adapt and several additional studies have shown, in general, that they tend to react better to stress, be less anxious and even have better memories. (Although nuances and areas where it isn't as positive have also been added.)

This doesn't mean paternal care isn't fundamental. Other experiments with rats have also shown that the more affectionate mothers were with their offspring (measured in the number of times they lick them and known as "licking"), the less vulnerable they would be to stress as adults. There is even evidence in humans: maternal support in infancy is associated with greater volume of the child's hippocampus, a key region of the brain for memory and stress. In Israeli children living in war zones, the risk of posttraumatic stress was inversely proportional to the support and relationship they had with their mothers.

The issue, then, seems to be striking a delicate balance that gives enough affection without being overprotective. The theory, however, is complex. One of the new hypotheses pits the traditional view, which says that an accumulation of significant episodes of stress increases a person's chances of developing negative consequences in the future, against a new, complementary one: **episodes of stress in the early stages of life can help people face similar ones in adulthood. This is known as the "match-mismatch" theory**. It is so complex that the two

may overlap. As explained Mathias Schmidt, researcher at the Max Planck Institute of Psychiatry in Munich, "Some characteristics could follow different models in the same individual and even have a genetic background," which would make it difficult to apply a global model.

But these facts are extremely relevant. Not only for an individual but also for their descendants. This is the next (possible) revolution.

THE SECOND REVOLUTION: IS STRESS HEREDITARY?

The fact that important childhood trauma can change behavior practically for life implies that something has marked the individual's development, if not independently then in a complementary manner to their genetics. That something is **epigenetics**, the series of hereditary changes from one cell to its daughters that don't depend on the DNA sequence. But can epigenetic changes be passed on to our descendants? This question is still up for debate and cause for much skepticism, as it **contradicts some of Darwin's basic hypotheses**, but some indications of this have come specifically from studying stress. Here are some of them.

The group led by Kerry Ressler, professor at Harvard Medical School, had been studying some of these issues for years. "It was complicated, but we started from the observation that child abuse tends to be perpetuated generation after generation," he said. In 2014**, one of his papers went around the world**. In it, they used male mice *trained* to be afraid of a specific smell, acetophenone (similar to cherries). The revolution came when they discovered the first- and second-generation offspring of these mice were also afraid of this smell, but none of the other mice were. And it wasn't a behavior they had learned: it even happened when the mice were born through in vitro fertilization of other mothers and kept in separate cages.

How could this happen? Their hypothesis was that during the *training* process, the epigenetics of the gene that detects that smell had been altered: it had lost some methylation marks (a group of chemicals *stuck* to the DNA) that kept it downregulated. In fact, this loss was also seen in the descendants of these mice. The enigma was, how did the change survive the reset these epigenetic marks experience at fertilization? "We don't know," Ressler admits. "**For now, the mechanism is a great black box**."

Ressler's group isn't the only one studying these topics. Rachel Yehuda, professor of Psychiatry at Mount Sinai Hospital in New York, has been researching the possibility of posttraumatic stress being inheritable for years. She has published numerous articles on the **consequences of the suffering experienced by holocaust survivors** and their descendants. In these studies, she has shown that there is a persistent alteration in the hypothalamic–pituitary–adrenal axis that regulates response to stress both in those who experienced it directly and in their children, who are more depressed and anxious.

In any case, in interpreting these studies we must consider that there are many elements that could

distort the results, like for example a more complicated family environment. To get more evidence, "**We decided to study what happened to mothers who were pregnant on 9/11, during the attack on the Twin Towers**," explained Yehuda. The results showed that there was also an alteration in the axis, measured in cortisol levels in both mothers and babies at 7 months, particularly in those who had suffered posttraumatic stress.

Her latest research has also looked at the possible role of epigenetics. To do so, they studied methylation marks on the FKBP5 gene –one of the most studied marks in relation to stress- both in holocaust survivors and their adult children. The results show mutations in both groups, although there are subtle differences that will have to be confirmed in future studies.

This is one of the challenges still facing epigenetic studies: to understand the functional relevance of these mutations. Mathias Schmidt posed the question, "What is the threshold after which we can say they have a significant impact?"

And Isabelle Mansuy, professor at the Swiss Federal Institute of Technology Zurich answered, "There's no magic number."