Storms of the body and soul

Crises of depression and euphoria cause chemical imbalances that may damage cells and accelerate aging of the body

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ILLUSTRATIONS EDUARDO SANGINETTI

Since 2009, psychiatrist Rodrigo Bressan and other researchers from the Federal University of São Paulo (Unifesp) have been monitoring a group of teenagers with a high risk of developing serious mental diseases, such as bipolar disorder and schizophrenia. These scientists would like to discover the appropriate moment to act before disease manifests itself and thus try to prevent these disease symptoms from becoming established. At the same time, they are trying to teach the teenagers and their families how to address stressful situations, which may trigger crises. Bressan and psychiatrists Elisa Brietzke and Ary Araripe Neto are tirelessly working to determine whether anti-inflammatory, antioxidant or neurotrophic compounds might protect brain cells and possibly reduce the risk of developing these mental diseases.

The strategy for protecting the brain with these and other compounds is based on the hypothesis that neurons and other brain cells suffer gradual damage from the initial onset of a disease episode, and some researchers even suspect that the damage may begin before these events are observed. Recent studies indicate that in these disturbances the brain produces harmful levels of certain compounds that upset the functioning of cells and may cause irreparable damage if they are left to persist, leading to a deterioration of the capacity to reason, plan and learn and even to permanent changes in mood. Furthermore, as the concentration of these substances increases, there is also a drop in the level of naturally produced neuroprotective compounds.

The idea that bipolar disorder and depression worsen with every attack may indicate the need for early diagnosis and intervention

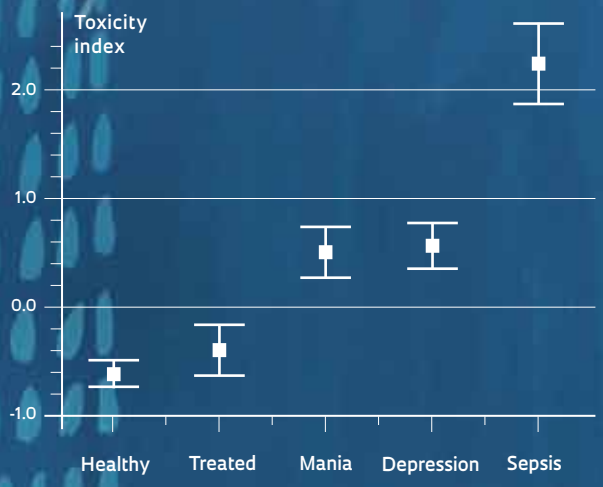
One of the researchers who helped to develop this hypothesis is the psychiatrist Flávio Kapczinski, a professor from the Federal University of Rio Grande do Sul (UFRGS) and coordinator of the National Institute of Science and Technology in Transactional Medicine. He is convinced that the dramatic evolution of serious cases of bipolar disorder and depression is the consequence of physiological alterations caused by the recurring crises.

Kapczinski believes that the crises that from time to time plague the mind also intoxicate the body. These crises are like chemical storms that unsettle the equilibrium of the brain microenvironment and release compounds that are carried via the blood throughout the body, occasionally leading to a degree of intoxication almost as serious as that in individuals with a generalized infection (sepsis). Repeated over years or even decades, these toxic avalanches, precipitated by outbreaks of depression or mania, produce slow and progressive wear in the brain and the entire body, thereby reducing the capacity for recovery and accelerating the aging process.

Kapczinski began to prepare this theoretical model based on experiments carried out by his team and by other groups that aimed to explain how and why depression and bipolar disorder,

Poisoned body

The graph below shows the average levels of toxic compounds in the blood that, in bouts of mania or depression, are increased in healthy or treated people and lower in people with sepsis



SOURCE KAPCZINSKI ET AL. / MOLECULAR PSYCHIATRY 2010

once established and not appropriately treated, follow a pattern of progressive deterioration that may culminate in early death due to cardiovascular problems and even cancer. According to the model, other diseases that apparently have nothing to do with what is happening in the brain might evolve as a result of these organic imbalances generated by severe episodes of depression and mania.

Initially presented in 2008 in Neuroscience and Behavioral Reviews, this hypothesis has gained international recognition. In the last year, Kapczinski's studies have been cited approximately one thousand times in other works. Australian psychiatrist Michael Berk, from the University of Melbourne, has been keeping track of this research and, with Kapczinski, has called this new model "neuroprogression."

"We know that these disorders are progressive, and this theoretical proposal explains why," says Berk. According to him, the interpretation that these diseases become worse with each additional attack may have a major impact on treatment because it indicates the need for diagnosis and early intervention and because it suggests that neuroprotective therapies may alleviate these negative effects.

"The idea has been launched," says Kapczinski. "Now, one can work to try to confirm or refute it." He knows that the model is bold and that it is necessary to gather more evidence to show that it represents the evolution of depression and bipolar disorder in an appropriate way. "We have enough work for the next two decades," says the researcher from UFRGS.

CONCEPT AND REALITY

According to some specialists, the concept of neuroprogression explains the clinical symptoms well, but one can question whether these biological alterations do in fact occur, as the evidence in support of this theory remains at an early stage. Brain images of patients indicate that there is a general reduction in the volume of some brain areas. But, most of the time, these images have been taken of the brains of patients of different ages who have suffered different quantities of mania and depression attacks. More consistent proof would require monitoring patients for several years and regularly examining them to assess the evolution of the problem.

Although it is far from being proven, this proposal is opening the way for a search for more specific and efficient therapies and for the development of strategies that enable the early identification of people at risk for developing these problems, as the team from Unifesp has been doing.

If this model is correct, it might help us to understand how a disease that first presents rela-

tively benign clinical symptoms can, in just a few years, lead to deterioration in the capacity to reason, plan and learn, as well as a permanent alteration in mood. Furthermore, these symptoms often escalate and prevent patients from leading a normal life, as Kapczinski and other doctors have frequently observed.

"This is one of the multiple progression mechanisms of the disease," says American psychiatrist Robert Post, an international authority on bipolar disturbance. "The clearest evidence [of what may be going on] is that the number of preceding episodes of depression or mania is related to the degree of cognitive dysfunction," says Post, with whom Kapczinski has been collaborating since 2008.

In an article published in May of this year in the Journal of Psychiatric Research, Post, Kapczinski and Jaclyn Fleming analyzed almost 200 pieces of work and found evidence that as cognitive dysfunction increases, changes in some regions of the brain intensify and treatment loses its efficiency as the number of crises and the duration of the disease increase. In the paper, the researchers recognize that it is impossible to know if these transformations are the cause or the consequence of the disease, although from a clinical point of view, they suggest that it would be prudent to start treatment as early as possible and maintain it for a longer period.

"According to this view, an attack of mania or depression can be looked at as being similar to a heart attack," says Elisa Brietzke, a former PhD student of Kapczinski. "All are acute events, but they result of alterations that were present in the organism long before." Given this interpretation, adds Araripe, "the objective of the treatment ceases to be merely the remission of the symptoms and becomes one of avoiding a relapse and helping to maintain functional capacity."

DAMAGE TO CELLS

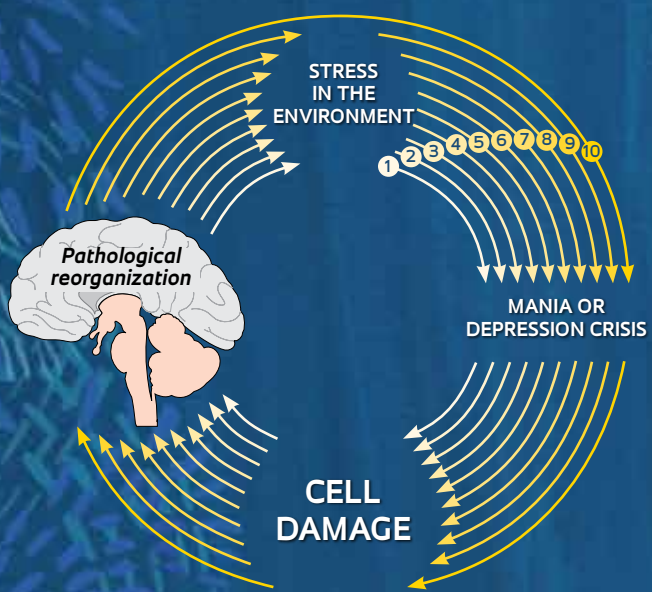
The model of the progression of mental diseases proposed by Kapczinski and his collaborators represents an advance in relation to previous models. The most widely accepted theoretical proposal considers mental disturbances to be the result of the interaction between the social, economic, psychological and cultural conditions in which the individual lives (the environmental factors) and their propensity to develop the problem, which is determined by their genetic characteristics.

This older approach was constructed a decade ago by psychologists Avshalom Caspi and Terrie Moffit, researchers at King's College, London, from the results of studies in which they monitored 1,037 children from the age of 3 to 26 years. In this work, they observed that certain alterations in the genes responsible for the production of chemical messages in the brain (neurotransmitters) increased the risk of an individual developing antisocial behavior or depression.

With the repetition of crises, cognitive dysfunction increases, brain alterations intensify and treatment loses its efficacy

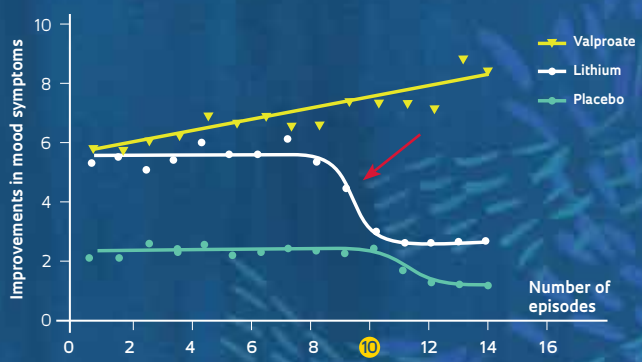
Vicious cycle

From the tenth mania or depression crisis, the bouts occur even in the absence of stress-provoking factors



RESPONSE TO TREATMENT

Patients with multiple episodes had the worst response to treatment, especially to lithium



As the disease progresses, the bouts of mania and depression may gain autonomy and become independent of the factors that triggered them

In addition to the influence of genes and environment, Kapczinski and his collaborators included a third element in the model: damage to cells in the brain and other organs caused by attacks of the psychiatric illness itself. These attacks generally begin as the response to a stressful event that may be intense and brief, such as an armed hold-up, or less dramatic but longer-lasting, like that experienced by someone who constantly works under pressure. Repeated many times, the episodes of mania or depression may end up undermining the capacity of the body to address new stressful events. "Our hypothesis is that the disease 'feeds' itself," says Kapczinski.

This proposal seems to provide a better explanation for the worsening of psychiatric disturbances, such as depression and bipolar disorder, when they are marked by successive crises. In these illnesses, the influence of environmental factors on the genetic propensity is fundamental for triggering the initial episodes of mania or depression. However, these factors become less important as the disease advances and the attacks become increasingly frequent and long-lasting (in some cases, even when medication is being used) and the intervals between them become shorter. Over time, generally from the tenth crisis on, the attacks gain autonomy and may become independent of the stressful conditions that previously triggered them (see the infographics on the next page).

CHEMICAL STORM

It has long been known that in every modest or intense episode of stress, caused by a real or imagined danger, the organism reacts by releasing the hormone cortisol. Produced by glands situated above the kidneys and released into the blood stream in small amounts and for a short time, cortisol increases the heartbeat, raises blood pressure and speeds up energy production. In short, it prepares the body to flee or confront dangerous situations. However, in high doses and for extended periods, as occurs before crises, cortisol begins to damage organs, including the brain (*see* Pesquisa FAPESP *129*).

Recently, researchers from the National Institute of Mental Health of the United States observed that in brain cells, especially neurons, high levels of cortisol damage the mitochondria, compartments in which the sugars from food are converted into energy. Damage to the mitochondria is certainly a problem, as they produce 85% of the energy that the cells consume to stay alive. Acting in an indirect manner, excess cortisol causes pores to form in the walls of the mitochondria, from which toxic compounds seep out, damaging lipids and proteins and altering the structure of the DNA within the nucleus of the cell. Moreover, this transformation activates mechanisms of apoptosis, or programmed cell death.

Using a technique that allows for an evaluation of thousands of proteins produced by the organism at a certain moment, Brazilian biologist Daniel Martins-de-Souza, a researcher at the Max Planck Institute for Psychiatry in Germany, also obtained evidence that the functioning of these organelles is altered in psychiatric diseases. Especially in depression, he found differences in the final phase of energy production, so-called oxidative phosphorylation or cell respiration, which occurs in the mitochondria.

The consequences of damage to the mitochondria are not restricted to cells, as the compounds they release reach the blood stream and activate defense system proteins that trigger inflammation, such as interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-alpha). When these factors reach the brain, they activate other biochemical reactions that cause additional neuronal death. According to Kapczinski, this process feeds cellular destruction, which is reinforced by another typical phenomenon of bipolar disturbance: the over-production of the neurotransmitter dopamine, which also activates apoptosis.

It was by measuring the levels of these compounds in the blood that Kapczinski's group identified a phenomenon to which little attention had previously been paid: the attacks cause systemic toxicity. According to Kapczinski, during the

episodes of mania and depression, the levels of compounds associated with inflammation were much higher in the blood of individuals with bipolar disorder; in some cases, these levels were similar to those detected in patients admitted to the intensive care unit with generalized infection (sepsis).

In rodents, it has already been shown that the toxicity that is observed in the blood corresponds to alterations in brain cells. However, this is yet to be proven in humans. "The best way to prove the toxic effects of these episodes would be an intervention to avoid the effects, followed by an evaluation of whether this intervention was capable of preventing the neurobiological alterations," says Post.

Most of the cells seem to survive this chemical storm even though they are damaged. Images evaluating brain function and microscopic examinations of postmortem brain tissue indicate that in mania or crises of depression, some regions lose 10% to 20% more neurons than under normal circumstances. According to psychiatrists and neurologists, this level of loss is insufficient to classify mood disturbances as neurodegenerative diseases. Both in bipolar disturbance as well as in depression, the biggest problem is that the neurons that survive do not remain whole; they apparently lose the projections called neurites, which connect them to other neurons.

Many brain researchers believe that it is the loss of neuronal connectivity that compromises the functioning of the brain regions most affected in mood disorders. The fact that these changes are subtle may explain why 100 years ago the German neuropathologist Alois Alzheimer, who first described the neuronal damage typical of the disease that bears his name, found no important alterations in the brains of people with depression (fostering the popular sentiment at the time that neuropathology embodied the death of psychiatrists). "Despite being subtle, these transformations are sufficient to cause a pathological reorganization of the brain," says Kapczinski.

The automatic transformations of the brain observed in illnesses affecting mood first became obvious approximately 10 years ago, when Grazyna Rajkowska and her group at the University of Mississippi found a reduction in the volume of the prefrontal cortex in patients with depression. The volume reduction in this area as well as in the region of the ventricles has been confirmed by imaging examinations in cases of bipolar disorder. Located in the front part of the brain, the prefrontal cortex is responsible for reasoning, decision-making and behavior control. This morphological alteration provides an explanation for why, with the advance of the disease, those who have bipolar disorder progressively lose their capacity to plan and learn. These people also become more impulsive and susceptible to emotions because there is a simultaneous increase in the volume of the amygdala, which coordinates the response to fear and negative emotions.

HYPOTHESIS IN FORMATION

In 1997, when he returned from completing his PhD in England and from an internship in Canada, Kapczinski began to collect evidence that a chemical storm installs itself in individuals who suffer from bipolar disorder. At the time, the group he led in the Laboratory of Molecular Psychiatry at UFRGS had noted that individuals with bipolar disorder, in addition to the psychological and cognitive alterations generally observed by psychiatrists, also had high levels of compounds in the blood indicative of brain cell damage and low levels of neuroprotective factors. "The molecules we study function like biomarkers [indicators of biological alterations] that allow us to distinguish if the disease is at an initial or advanced stage," says Kapczinski.

Identifying the stage of the disease is important for providing appropriate treatment, and Kapczinski thought his new hypothesis may help to improve the use of medication. There is evidence to suggest that controlling the disease immedi-

ately after the first episodes of depression or euphoria can preserve the recovery capacity of the patient and prevent psychological and cognitive degradation. Medications – mood stabilizers, antidepressants, antipsychotics and anticonvulsives, used alone or in combination – are generally effective in 80% of all cases of bipolar disorder and depression and have been proven to produce a neuroprotective effect, especially lithium, a cheap and efficient mood stabilizer that was once used to combat stress, gout and kidney stones.

Still, psychiatrists do not always manage to precisely administer the correct medication and dose at the first attempt. A recent North American study of 4,035 patients with bipolar disorder, undertaken by researchers at the Mount Sinai Medical School, found that in 40% of these patients, especially those with more serious depressive clinical symptoms, the illness was only brought under control when they took three or more medicines.

Kapczinski believes that these illnesses generally reach a much more difficult stage to control after the tenth crisis, which usually occurs approximately 10 years after the first manifestation of the disease. For this reason, psychiatrists believe that starting medication as early as possible is fundamental. It had already been observed that lithium, one of the most widely used medicines for treating bipolar disturbance, loses its effectiveness after the tenth attack (see graph on page 44).

Furthermore, individuals with mental disturbances normally wait to see a psychiatrist until long after the first signs of the disease appear, and years may pass until a specialist makes the correct diagnosis and prescribes suitable medication. In the case of bipolar disturbance, the period between the first manifestation of the problem and the start of treatment varies between 5 and 10 years, which is enough time for complications to arise at work, in family life and in relationships with friends, causing these patients to feel as if their lives are 'falling apart.'

With every crisis, the brain cells may suffer damage and lose some of their connections to other cells

THE PARTS AND THE WHOLE

When he was analyzing variations in the levels of these biomarkers in the blood, Kapczinski felt the need to seek a more comprehensive explanation that would allow him to associate the clinical signs of the disease with the physiological and anatomical alterations that could be detected in the brains of individuals suffering from mental disorders. Through this type of analysis, he sought to more effectively evaluate bipolar disorders, which affect approximately 1% of the population (but it is calculated that as many as 8% may have less serious forms), and another more common mood disorder – major or unipolar depression – which almost 15% of adults develop during their lifetime.

Kaczynski realized that he was not satisfied with what he had at hand when he received an invitation to present his group's results at an international symposium in the Barcelona Hospital Clinic in Spain in mid-2006. "We were missing the theoretical 'glue' showing how the data fit together," says Kapczinski.

He and his team had collected blood samples from people with bipolar disturbance during the periods in which they were experiencing extreme mood states, which can vary from intense sadness and low self-esteem to great vitality and energy, far beyond anything considered to be normal. Using a battery of tests, psychiatrist Angelo Miralha da Cunha, then at UFRGS, observed a phenom-

enon that was new to both depressive crises as well as manic episodes. He found that the levels of brain-derived neurotrophic factor (BDNF), with its neuroprotective action, were at least 25% lower in bipolar patients compared to individuals who did not experience the disorder or who kept it under control with the help of medication.

At the same time, Ana Cristina Andreazza and Elisa Brietzke, who were part of Kapczinski's team, detected higher rates of proteins indicative of inflammation, as well as higher levels of free radicals, highly reactive molecules with the potential to damage cells during periods of mood change. These data suggested that the blood may provide clues as to what was happening in the brain. However, at that time, it was impossible to know with any degree of certainty what those alterations meant or why they occurred.

THEORETICAL 'GLUE'

Kapczinski found the theoretical 'glue' he was looking for in the studies of American neuroscientist Bruce McEwen. In 2000, McEwen put forward the hypothesis that stressful situations oblige the organism to make adjustments to recover the stability it has lost. McEwen called this adaptation allostasis, a change that is necessary to re-establish equilibrium (homeostasis). He went on to suggest that, over time, there would be a price to pay for this adaptation, as it caused wear indicate that there is a general reduction in the volume of some brain areas the organism.

The theoretical proposals of psychiatrist Robert Post completed this idea. In the 1980s, Post had suggested that the clinical signs of bipolar disturbance would become more intense with each crisis as a consequence of the greater sensitivity of the brain circuits affected in previous episodes. The phenomenon, called 'kindling', had been discovered 20 years earlier by Graham Goddard, an English neuroscientist who studied epilepsy. During tests with rodents, Goddard found that low-intensity electrical stimuli, initially incapable of causing the animals any harm, began to trigger epileptic crises after they were repeated a few times, indicating increased brain sensitivity.

"Starting with these experiments, other authors began working on the idea that the brain learned to

Medication controls 80% of the cases of bipolar disturbance and depression, but patients often delay seeking treatment and doctors are not always successful in their first treatment attempt

become sick in other situations, especially in bipolar disorder," says neurophysiologist Luiz Eugenio Mello, from Unifesp. "According to this idea, modifications in the central nervous system, possibly at the level of the synapses [connections between brain cells], could transform a brain that was not very sick into one that was very sick," he explains.

Upon analyzing his data in light of the concept of allostasis and sensitization (later brought together in the concept of neuroprogression), Kapczinski found the link between what his group had observed and the alterations in the volume of certain brain areas that foreign teams had detected. This unification of concepts may also explain the origin of the clinical signs that are characteristic of these diseases and, furthermore, why people with bipolar disorder and depression have been shown to die 25 to 30 years earlier than people without psychiatric disorders. Moreover, a greater proportion of people with bipolar disorder and depression develop cancer and cardiovascular problems.

Influenced by neuroscientist Iván Izquierdo, Kapczinski did something that is rather uncommon in field of psychiatric research in Brazil: he formulated a theory to explain the development and consequences of psychiatric diseases. Like any attempt to reproduce reality from sparse data that can be identified and measured, the theoretical model conceived by the group from UFRGS is still being improved. Since its initial presentation in Barcelona, Kapczinski and his collaborators in Brazil, Australia, the United States and Spain have been working to improve this theoretical proposal and to verify that they are on the right track.

Kapczinski himself is testing his hypothesis by evaluating on mice the neuroprotective effect of a modified version of the antidepressant tianeptine, developed at UFRGS. He is also planning to examine chemical and cellular alterations in brain samples taken from patients with psychiatric diseases, which are kept in brain banks like the one psychiatrists Beny Lafer and Helena Brentani are currently organizing at the University of Sao Paulo Medical School. In another line of work, Lafer has recently started a clinical trial with supplements of the amino acid creatine, which are likely to improve the functioning of the mitochondria and may also increase cell protection.

Ana Cristina Andreazza, currently a researcher at the University of Toronto, is investigating the effects of malfunctioning mitochondria in brain cells. Her research suggests that an adequate diet rich in antioxidants may also help protect the brain.

"The hypothesis of neuroprogression represents an important model for explaining the progression of these diseases," comments Lafer, who is collaborating with the group from UFRGS. "There are other hypotheses based on genetics, which deal with the interactions between genes, the environment and inflammation, but no consensus has been reached." ■

The Projects

1 Postmortem stereological analysis of the main regions of the brain in individuals with affective bipolar disorder no. 09/51482-0; **2** Prevention of schizophrenia and bipolar disorder from neuroscience to the community: a multiphase, multimodal and translational platform for investigation and intervention no. 11/50740-5. **Modality 1** Regular Research Funding; **2** Thematic Grant/Pronex. **Coordinators 1** Beny Lafer – USP; **2** Rodrigo Affonseca Bressan – Unifesp. **Investment 1** R$ 130,249.30; **2** R$ 2,378,201.50

Scientific articles

1 KAPCZINSKI, F. *et al*. Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. **Neuroscience and Behavioral Reviews**. v. 32, p. 675-92. 2008.

2 BERK, M. *et al*. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. **Neuroscience and Behavioral Reviews**. v. 35, p. 804-17. 2011.