



PSYCHIATRY

Magnetism against depression

An experimental technique shows itself to be efficient in the treatment of severe psychiatric disorders

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Ana Paula can hardly remember the last time she saw her mother smile. Since she suffered her first crisis of depression some 20 years ago, Maria spends sad days, lying on the sofa re-running thoughts that spring from a world that is forever grey. She has already tried all the types of known anti-depressants, but not one was capable of putting an end to her apathy that still accompanies her today and made her abandon her work in the family's business in the metropolitan region of São Paulo. Useful in the majority of cases, medicines, in the case of Maria, at best put off her next relapse. In a last chance attempt, some six months ago, the doctors had to resort to the application of electrical shocks to the patient's brain under a general anesthetic, electro-convulsion therapy, more commonly known as electroshock – a treatment considered to be one of the most efficient for the most serious cases, still stigmatized for

having been applied in a cruel manner and even as a torture technique against prisoners. This treatment can help to re-establish the normal working of the nerve cells, even though it generally causes a passing loss of memory, which can last from a few days to months.

Not even the electrical shocks worked, and in November Maria began therapy at the Psychiatry Institute of the University of Sao Paulo (IPq/USP) against depression that over the last few years has been awakening the interest of psychiatrists and neurologists throughout the world: repetitive Transcranial Magnetic Stimulation (rTMS), a sequence of intense magnetic pulses capable of stimulating or inhibiting the activity of nerve tissue. Until only a short time ago restricted exclusively to scientific experiments, the rTMS appears to produce the same effects as the electro-convulsive therapy in the treatment of depression: readjusts the working of determined regions of the central nervous system, but with less undesirable effects. USP's Psychiatry Institute released the use of rTMS for the treatment of depression in October of 2006, after the team led by the psychiatrist Marco Antonio Marcolin tested the method for almost six years against depression and as well as the treatment of chronic pain,



Cyclists, 1989, oil
on canvas by Iberê
Camargo: autonomy
and movement



Studies of Cyclists
series, 1990,
Iberê Camargo

some forms of hallucination common in schizophrenia and in the recovery of patients who had suffered a stroke.

Currently the institute is analyzing how to ask for the inclusion of rTMS on the list of procedures paid for by the Public Health System for the treatment of depression, with the object of offering it freely to a greater number of patients. Approved for this purpose only in Canada, Australia, New Zealand, Israel and some European countries, this therapy is still expensive: it costs R\$ 300 for each of the 20 applications necessary for the treatment of acute depression, a problem that one in every ten people can experience during their lifetime.

In general, one session per day is carried out for a month. Fifteen days after the start of treatment, Ana Paula had already noted the first signs of recovery of her mother. The dose of the anti-depressant, which Maria still took, dropped to a quarter of its initial value and . Marcolin's team began to remove the sedative that she used for sleeping. The application is truly peaceful. On the morning of the 6th of December, in a small room on the Institute's first floor, the psychiatrist Maria do Carmo Sartorelli brought a bobbin in the form of a figure of eight, about the size of an open hand, to the left side of the head of Maria who was seated in a reclining chair. Next she heard a series of rapid clicks for ten seconds. This was followed by 20 seconds of silence and then a new

sequence of pulses was shot off, the cycle being repeated a further 23 times. "My mother came out of the application speaking, and not quiet as before", recalls her daughter Ana Paula. "I was surprised by the change in her mood."

During each click, an electrical current of some milliseconds and of high intensity (up to 5,000 amperes) passes through the bobbin. The rapid sequence of on-off produces fluctuations in a magnetic field that crosses the cranium and generates a low intensity electric current in a specific area of the cortex, the brain's most external layer. In spite of being low, this electric current is sufficient to set off the transmission of a nerve pulse from one cell to another, explains the physicist Oswaldo Baffa Filho, from USP, Ribeirão Preto campus, who is carrying out research in this area.

Reprogramming neurons - Both the rTMS and the electroshock techniques function based on the same physical principle – the passage of electrical current through the encephalon, the grouping of structures of the central nervous system that includes the brain. But there are also important differences between these two resources. The main differences are the intensity and the coverage of the electric current applied to the central nervous system. Whilst the rTMS generates currents of a few millimeters in a restricted area of the brain, the electro-convulsive therapy produces currents around one thousand times higher, of up to 2 amperes, that traverse all of the encephalon and originate convulsions similar to those observed in epilepsy – patients do not feel the convulsions nor remember them because they spend all of their time anesthetized. Independent of the technique used, it is believed that this passage of electric current reprograms some nerve cell genes, making them take on their appropriate function, in the same way as the anti-depressant medicines.

In the treatment of depression, the rTMS's target is a region of the brain located on the left side of the head, at the side of the forehead and above the eyes. Here one can find the so-called dorsal lateral prefrontal cortex, a region the size of a coin associated to short term memory, logical thinking and the evaluation of the goals that are desired





to be attained. In general this region is found to be less active in patients with depression than with other normal people, independent of the origin of the problem – whether it is depression coming from genetic, hormonal or environmental factors.

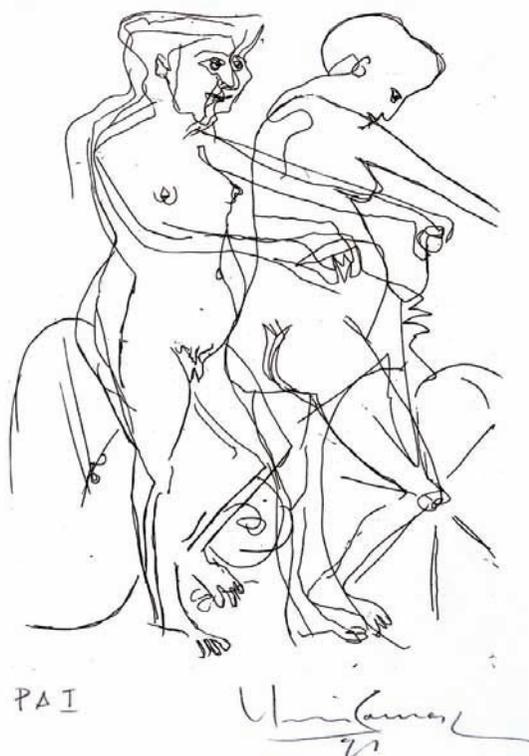
In the opinion of Marcolin, the patient who goes through the rTMS sessions, in general, feels nothing, although they can suffer from a slight headache or contractions on the scalp, which generally end as soon as the device is switched off. It was this almost total absence of side effects that caught Marcolin's attention almost ten years ago and gave him the motivation to change direction in his line of research. On seeing the results of his first experiments, he abandoned his specialization, namely the interactions between psychiatric drugs and other medicines, in order to investigate whether the rTMS technique would really be efficient in combating depression and other maladies that usually take away people's control of reason and control of their very own lives.

Besides the international experiments, two experiments carried out at USP have attested to these benefits and have helped to give a base to the Psychiatry Institute's decision to liberate the rTMS technique for the treatment of depression – especially for cases in which neither medicines nor psychological therapies any longer produce the desired effect. The most recent of these stud-

ies, published in December in the *International Journal of Neuropsychopharmacology*, shows that the rTMS technique is just as efficient as the electroconvulsive therapy for minimizing the signs of depression which do not yield, the so-called refractory depression. The psychiatrist Moacyr Rosa, a member of Marcolin's team, selected 42 patients between the ages of 18 and 65 years, all suffering from refractory depression, to receive one of the two possible treatments: rTMS or electroconvulsive therapy.

Randomly, Rosa treated half of this group with weekly sessions of rTMS for a month, whilst the other half went through 12 applications of electroconvulsive therapy for the same period. Throughout the study, researcher Rosa measured the degree of depression on three occasions by way of a scale that runs from 0 to 40 points – a point score below 7 indicates the absence of depression and above 22 confirms severe depression, the stage generally during which brutal changes of behavior occur: loss of sleep or contrary to this frequently oversleeping; exaggerated eating or almost total loss of appetite; disappearance of sexual desire and a common desire to commit suicide.

Other benefits - After the second week of treatment, the average point score of the participants of the two groups had gone down from 32 to almost 25. Fifteen days later the average severity was even lower, close to 15, a depression level considered moderate to slight. In a general manner, 40% of the patients who received electroconvulsive therapy and 50% of those who had undergone magnetic stimulation sessions responded well to therapy – for the doctors this means that they had reduced, by at least half, the signs of depression that they had shown at the start of the study. At the end of the research, 20% of the people in the former group and 10% in the latter group were no longer considered depressed. "The proportion of participants who improved is considered small, but one needs to remember that the cases that arrive at USP's Psychiatry Institute are always extremely serious", says Marcolin. The most important thing that this study demonstrated is that the rTMS produces improvement similar to that of the electroconvulsive therapy, which demands the application of a general anesthetic during each of the three sessions that take place weekly. This was a relevant effect but not the only one.





MIGUEL BOYAVAN

Application: the bobbin sets off an electric current of high intensity for milliseconds

Two years previously Marcolin's team had discovered another rTMS benefit: the stimulation of determined regions of the brain by means of magnetic and intense pulses accelerates the action of anti-depressant medicines. The psychiatrist Demetrio Ortega Rumi, from USP, prescribed to 46 patients with severe depression five weeks of therapy based on amitriptyline, one of the most efficient anti-depressants to reestablish the equilibrium of the messenger chemicals of the central nervous system, which, it is believed, are found at less than desirable levels in cases of depression. At the start of the second week, Rumi separated the study's patients into two groups: half received 20 sessions of rTMS and the remainder went on to have an equal number of inactive stimulant sessions, in which the bobbin positioned around their head made the same clicks, but did not generate any magnetic field – during the experiment none of the group members knew which treatment they were receiving.

The effect of the true stimulant was evident. Rumi had observed already during the first week that the intensity of the depression had decreased: going from 32 to around 20 points, on average, among those treated with an active bobbin, while in the other group the scale still marked profound depression – around 30 points. By the end of the fourth week almost all of the group members who had received the true stimulant had im-

proved considerably: half were no longer depressed and the remainder had only slight depression. Only 12% of the patients who underwent the simulated stimulation were free of the problem of using medicine, according to the results published in 2005 in the magazine *Biological Psychiatry*.

Before anti-depressants - At the University of Vita-Salute, in Milan, Italy, the team led by Dr. Raffaella Zanardi observed similar effects using the rTMS technique in patients treated with three other more modern anti-depressants: escitalopram and sertraline, which inhibit the recapture of the neurotransmitter serotonin, and venlafaxine, which prevents the recapture of serotonin and noradrenalin. In this study, detailed in a paper in the *Journal of Clinical Psychiatry* of December 2005, the participants who received applications of the true magnetic pulses improved more quickly than those treated with the inactive stimulant, although at the end of the study all of them no longer presented depression. "This data suggests that the magnetic stimulant anticipates the action of the anti-depressant, which in general takes between two to four weeks to produce the desired effect", says Marcolin.

Not everyone agrees with Marcolin. The more cautious believe that it is still too soon to release rTMS for the treatment of depression. Those who prefer to wait longer remember that, up until now,

the studies include a relatively small number of participants, from 40 to 60 patients, and the studies lasted only a few weeks. But this situation is beginning to change with the conclusion of studies with a greater number of patients.

At the beginning of December the psychiatrist Sarah Lisanby, from Columbia University and the New York State Psychiatric Institute, presented at the annual meeting of the American College of Neuropsychopharmacology the conclusion of a study of 301 patients with depression that she had followed at 24 centers in the United States, Canada and Australia. In this test, funded by Neuronetics, one of the companies that manufactures the rTMS equipment, the participants did not receive anti-depressants for four weeks and half were treated with trans-cranium magnetic stimulation, whilst the other half received false stimulation. The rates of improvement were more marked in the former group.

In Sarah's opinion, this data collaborates the effects of the anti-depressants of rTMS, comparable to those obtained with anti-depressant medicines in the treatment of patients with moderate depression and a certain resistance to medicines. "But this efficiency is still less than that obtained using electro-convulsive therapy", explains the psychiatrist, the head of the Brain Stimulation and Therapeutic Modulation Division of Columbia University, in Nova York. The result of this study served as the basis for a request for a re-evaluation of rTMS sent to the Food and Drug Administration (FDA), the American agency that regulates foods and medicines. At the end of January, specialists from the FDA should meet to evaluate the most recent evidence of safety and efficiency of rTMS, before deciding whether or not to approve its wide use in the United States, where it is still being used in an experimental fashion.

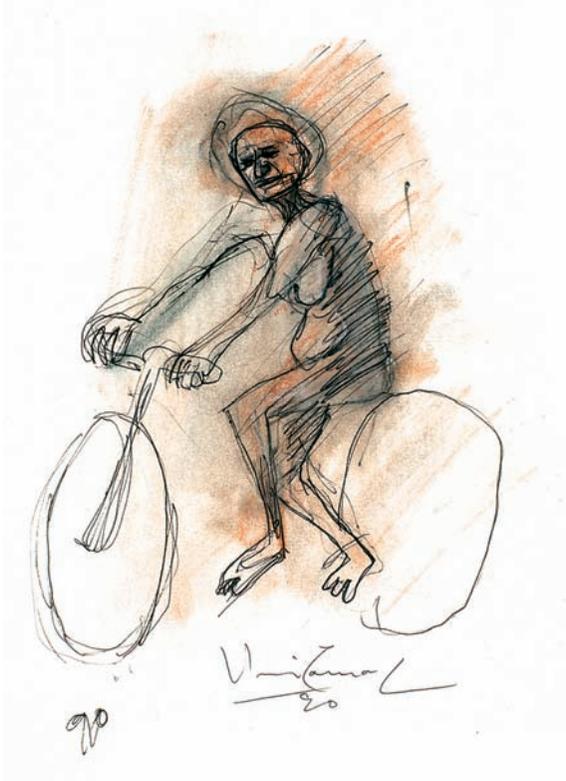
There is still a lot to investigate about the rTMS technique. The first experiments indicating its anti-depressive action were published by the neurologist Alvaro Pascual-Leone, from Harvard University, in the United States, only in 1996, a century after the French medical doctor and physicist Jacques-Arsène D'Arsonval had attempted for the first time to use magnetism to change the state of mood of a person. For now, it is

not known for certain if the dorsal lateral pre-frontal cortex is the region best indicated for the applications of rTMS or if other areas in the brain would produce better results. Also the intensity and frequency of the most suitable pulses is under discussion.

In the beginning the application of this technique causes some epileptic crises in people with depression who were healthy and had participated in the experiments. Adriana Conforto, from USP's Neurology Department, investigated, when at the University of Bern, Switzerland, the effect of different techniques to define the individual's sensitivity to this type of treatment, with a proposal to determine the specific, efficient and safe dosage for each person. The frequency and the intensity of the stimulation are another two parameters that define the safe use of this therapy. "The association of the techniques of neuronavigation and functional neuroimaging have great potential in the therapeutic use of trans-cranium magnetic stimulation in a safer and more efficient manner", comments Adriana.

In Ribeirão Preto, the physicists Oswaldo Baffa, Dráulio Araújo and André Cunha Perez are working with the neurologist João Leite to solve another problem: how to find the most suitable place on the head to position the rTMS bobbin. They are attempting to create a computer program that reads nuclear magnetic resonance images of the brain and helps in the positioning of the bobbin in a precise manner in areas such as the pre-frontal cortex.

"It's crucial that things be well carried out", commented researcher Pascual-Leone, from Harvard. "We're taking a lot of care of quality control, safety and the indication for its use" The team from the IPq in Sao Paulo is working on the development of directives that guide the applications of rTMS in order to maintain treatment, after the depression has been overcome. There is a long way to go, but it is promising, recalls the team led by the Spanish neurologist Jaime Kulisevsky, in a paper published in 2003 evaluating the use of rTMS for depression: "Many clinical treatments used today in psychiatry were developed slowly, by way of a process of initial enthusiastic approval and then almost disappearing, and, again, its broad and sensible clinical use". ■



The controversial electroshock

When the first electroshock was applied in 1938, well before the manufacture of medicines for psychiatry, the Italian doctors Ugo Cerletti and Lucio Bini believed that the inducing of cerebral convulsions similar to those observed in epilepsy would cure mental disorders because a person with epilepsy could not also suffer from schizophrenia. Later they discovered that this idea was false, but they had proven that electroshock, used under adequate conditions, could treat severe depression and other disorders such as schizophrenia.

Almost 70 years after having been applied for the first time, electroshock continues to be of the most controversial medical therapies of all time. But to compare the electroshock applied today in hospitals to that which was carried out at the start of the 1980s is the same thing as comparing current surgery techniques to those in which the good surgeons were those that

made their incisions as quickly as possible so that the patient did not feel pain.

Today the electroshock sessions are a long way from scenes in films such as *One Flew Over the Cuckoo's Nest*, in which the characters come out completely incapacitated after having been subjected to shocks much more intense than those of today – and without any anesthesia. Currently the doctors administer a general anesthesia and muscle relaxants before beginning treatment: a sequence of very short electrical shocks, lasting 1 to 2 milliseconds, which bring about a convulsion registered by means of an electroencephalograph. The anesthesia stops the patient from feeling pain and the relaxant avoids the contraction of the muscles during the convulsion, thus avoiding possible injuries. As well as these concerns, the patient who undergoes an electroshock receives oxygen and remains under cardiac monitoring.