Electroconvulsive therapy in the Fourth Industrial Revolution (Review)

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Abstract. There are very few treatments in psychiatry, even in medicine, that have experienced longevity and effectiveness such as electroconvulsive therapy (ECT), despite the controversies and stigma that accompany it. The experience of the COVID-19 pandemic has highlighted the need to strengthen mental health systems in most countries, given that depression is one of the leading health problems and that there is an evident shortage of psychiatrists worldwide. The Fourth Industrial Revolution, has witnessed great progress in artificial intelligence (AI) technology, which opens up the possibility of its application both in the diagnosis and in the therapy of mental disorders. It is no exaggeration to suggest that tools such as AI, neuroimaging and blood tests will bring significant change to psychiatry in the coming years, but even so, treating severe mental disorders remains a challenge. The present review summarized the development of ECT over time, its application in clinical practice, neurobiological correlates and mechanisms of action and sheds light on the important place of ECT in the era of technological development, considering that ECT is still the most effective therapy for the treatment of severe mental disorders, especially depressive disorder.

Contents

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1. Introduction

In the modern world and the Fourth Industrial Revolution (4IR), depression is one of the leading health problems among young individuals and ~280 million individuals worldwide live with depression (1,2). Research that was conducted in 2021 and which examined the effect of the SARS CoV2 pandemic on mental health, covering 204 countries, indicated that individuals in areas that were more severely affected by the pandemic, women and younger age groups were at greater risk of depressive disorder (3).

The COVID-19 pandemic and its consequences have indicated the need to strengthen the mental health system in most countries, which is in line with the shortage of psychiatrists worldwide. It is estimated that in rich countries with high incomes, there are ~12 psychiatrists per 100,000 individuals and in low-income countries, ~0,1 psychiatrists per 100,000 individuals (4). With all the facts and data in mind, researchers and developers are developing artificial intelligence (AI) treatments that evoke feelings of emotional security precisely because of their accessibility and widespread sense of emotional safety due to their accessibility and widespread engagement.

The recent decades have witnessed great progress in AI technology (AI is increasingly a part of digital medicine), which opens up the possibility of applying AI both, in the diagnosis and therapy of mental disorders. The term 'artificial intelligence', which is defined as 'the science and engineering of making an intelligent machine' was first used by scientists John McCarthy, Marvin Minsky, Nathaniel Rochester and Claude Shannon in 1955 (5). The use of AI in mental health care is still limited, especially compared with the application of AI in radiology, oncology and ophthalmology (6,7). AI could play a key role in choosing the best antidepressant therapy for

a patient, in the sense that based on scans of brain activity, it can accurately predict whether an antidepressant will work. AI has enormous potential to define diagnosis in psychiatry and to help improve understanding of mental illness (8).

In the 4RI, there are a few treatments in psychiatry, even in medicine, for which one can state longevity and effectiveness in application as is the case with electroconvulsive therapy (ECT) (9,10). In the world since 1984, electric current has been delivered through a digital device (Somatics, LLC or MECTA LLC) and advances in technology have brought changes in ECT devices. ECT is still the most effective treatment for severe mental disorders, especially depressive disorders (11). Despite evidence of safety and effectiveness of ECT, applicability in practice is insufficient. The explanations for the possible discrepancy between real needs and application can be a misunderstanding on the part of the non-medical public as well insufficient number of ECT centers and psychiatrists who apply ECT. According to the latest research, the percentage of application of ECT therapy (rate of use) was 5.56 per 100,000 patients (12). In Serbia, ~54 patients receive ECT annually, that is, the rate of use is 0.05/100,000 (13).

2. A brief overview of the historical development and improvement of ECT

Until the 18th century, the field of psychiatry was limited to the classification of types of 'madness', and only in the mid-18th century did they begin to consider the classification of psychiatric disorders (14). It was in the 18th century, that Pinel removed the shackles and chains from the mentally ill at the Bicetre Psychiatric Hospital in Paris (15,16). Among the drugs used were bromides, chloral hydrate (19th century), hypnotic barbiturates (in 1903) along with somatic therapies treatments for severe mental illness, such as hydrotherapy, lobotomy and insulin coma until the appearance of antipsychotics and antidepressants (in 1950) (17).

Convulsive therapy was begun because of the belief that convulsions helped patients with schizophrenia and this too has its beginnings in the 16th century, when the Swiss physician Paracelsus was the first to induce seizures by giving oral doses of camphor. However, the first scientific account was given in the 18th century by Vienna's University physician Leopold von Auenbrugger, who reported the beneficial effects on 'mania vivorum' of seizures induced by oral camphor (18). However, it was only at the beginning of the 20th century that the Hungarian neuropathologist Ladislas Jozef Meduna (1934) started the era of convulsive therapy (believing that schizophrenia and epilepsy are antagonistic disorders), by means of an intramuscular injection of camphor for the treatment of catatonic schizophrenia. The procedure was performed on conscious patients (without the use of anesthesia and muscle relaxants), whereby the patient would lose consciousness during the attack and a frequent adverse effects (AE) of this procedure was the fracture of long bones (femur, spine), due to strong, uncontrolled muscle contractions. Due to this, there was a negative attitude of the public, as well as fear among patients and employees of institutions often used it to punish and soothe seriously ill patients (19,20).

The Italian neuropsychiatry professor Ugo Cerletti used metrazol (cardiazol) to induce convulsions (shock) in animals and his colleague Lucio Bini used electricity (electroshock; ECS) as a substitute for metrazol-induced convulsive therapy. Cerletti had the idea to use electric current to induce convulsions in individuals. In 1938, Cerletti and Bini began using ECT on patients and the results were significant after only 10 to 20 treatments. A year later, in 1939, ECT was introduced to treat mental disorders in the United States of America (20).

The trend of improving ECT started with the application of succinyl-choline (1951), the so-called modified ECT, which eliminated the most frequent AE, related fractures of long bones. Blatchley (1979) had improved the neurophysiological and biological aspects of neural refraction, which led to the replacement of the sinusoidal current (pulse width 8-10 msec) with a brief electric pulse (pulse width 0.5-1.5 msec) (21,22). Since 1990, there has been interest in the ultrabrief pulse waveform (pulse width 0.1-0.2 msec). By applying pulse stimulation, the current does not pass continuously and only part of the charge is released, with a sinusoidal current of the same strength (20,23).

The next step of improvement was the replacement of the location of the electrodes, after the bilateral [BL; namely bifrontal (BF) and bitemporal (BT)] placed electrodes, the unilateral position was also examined, on the right side (RUL), which led to a reduction of side effects in the cognitive sphere. In 2001, the American Psychiatric Association (APA) published its latest report, which emphasizes the importance of informed consent and the expanded role of ECT in modern medicine (23). The latest research indicates that RUL ECT is as effective as BT ECT, only on the condition that higher energy doses are used (24).

ECT application through modern ECT devices has a number of advantages compared with manual ECT application. The FDA approved the Somatics Thimatron ECT device (Somatics, LLC) on September 27, 1984. It is a free-standing, desktop medical electronic device and contains transformers, electronic displays, a printer and modular boards with microprocessors, memory chips, optical isolators and other electronic components. Upon switching on, it automatically performs its own integrity tests. It delivers a short pulsed square wave stimulus of constant current 0.9 Amp. Thymatron IV has all the functions of a sophisticated 4-channel digital electroencephalogram (EEG) machine, which allows the recording and analysis of EEG in patients, to measure slowing of frontal EEG and other EEG manifestations that reflect the effect and effectiveness of treatment. In addition to EEG, it is possible to monitor electromyography (EMG) and electrocardiography (ECG). The Thymatron IV device prints the patient's EEG, ECG, heart rate and EMG (on the arm on which the cuff is placed; myorelaxant dose not pass through that arm) during the treatment on a paper strip that comes out from the front panel of the device (Fig. 1) (23,25).

When it comes to the implementation of ECT in Serbia, it should be emphasized that in the period 1946-1975, there were several ECT centers. Due to various organizational difficulties, since the late 1990s, ECT has been applied continuously to this day only in the Clinic for Psychiatry, Military Medical Academy in Belgrade. In the 21st century, another ECT center was established in Serbia (Clinic for psychiatry, Clinical center Kragujevac). In Serbia, since 2001, ECT has been applied via the Thymatron IV device (SOMATICS, LLC), BT ECT, with

Thymatron System IV S/N: 43536
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% Energy Set	25%
Charge Delivered	125.4 mC
Current	0.90 A
Stimulus Duration	7.0 Sec
Frequency	20 Hz
Pulse Width	0.50 mSec
Static Impedance	1830 0hm
Dynamic Impedance	270 0hm
EEG Endpoint	18 Sec
EMG Endpoint	12 Sec
Base Heart Rate	129 b/m
Peak Heart Rate	113 b/m
Average Seizure Energy Index	25789.5 μV^2
Postictal Suppression Index	88.8%
Maximum Sustained Power	34411.0 μV^2
Time to Peak Power	12 Sec
Maximum Sustained Coherence	95.9%
Time to Peak Coherence	13 Sec

Figure 1. Printed record Thymatron IV device. Static Impedance (before ECT stimulation; range 300-3,000 Ω); Dynamic Impedance (during ECT stimulation; range 120-350 Ω); Peak Heart Rate (preferably 140-180 beats per minute; bpm); Average Seizure Energy Index (measures seizure intensity, i.e. a low intensity index reflects a strong seizure intensity); Postictal Suppression Index, (PSI; measures the percentage of reduction of the ictal EEG amplitude immediately after the end of the seizure; PSI ≥70%, ECT success indicator); Maximum Sustained Power (measures the maximum average ictal amplitude); Time to Peak Coherence, (latency from seizure onset to peak interhemispheric coherence); Maximum Sustain Coherence (synchronous participation of both hemispheres in the seizure, i.e. coherence between two EEG signals). ECT, electroconvulsive therapy; EEG, electroencephalogram.

the application of short-term general anesthesia (premedication; atropine, short-acting intravenous anesthetic; propofol, muscle relaxant; succinyl choline) and signed informed consent by the patient (26). When the patient is under general anesthesia and the fasciculations pass, the psychiatrist applies electrical stimulation via stimulus electrodes placed on both sides of the forehead in BT ECT (~2.5 cm above the mean value of the imaginary line drawn from the tragus), in accordance with data on efficiency BT vs. RUL (26).

3. The place of ECT in the treatment of mental disorders in the 4IR

Although ECT was started because of the belief that convulsions help patients with schizophrenia, ECT is the most effective therapy for the treatment of an affective disorder, namely a depressive episode in major depressive disorder (MDD) or depressive episode in bipolar affective disorder. In all previous studies, the effectiveness and superiority of ECT compared with antidepressant pharmacotherapy has been proven (11). The explanation for the weaker response to antidepressant therapy compared with ECT can perhaps be explained by the role of the cytochrome P-450, 2C19 (CYP2C19) enzyme, which is involved in the metabolism of most antidepressants. In CYP2C19 slow metabolizers, the reduction in the severity of depression was 36% less and the response rate was 75% lower compared with normal metabolizers (27).

The superiority of ECT refers both to the reduction of depression and to the speed of recovery; after 1 to 2 courses of ECT, a clinical improvement is noted. The response to ECT is between 80 and even 100%, while lower response rates of 50-60% have been recorded in treatment resistant patients and with RUL ECT (28).

Due to the availability and effectiveness of lithium, affective stabilizers and antipsychotics in the treatment of mania, primary treatment with ECT is rare today, although ECT is an effective treatment; ~80% of patients show improvement (29).

Patients with schizophrenia have a lower remission rate on ECT (5-10%), with a higher response if catatonia or affective symptoms are present (40-80%) (30). Characteristics of schizophrenia, such as positive symptoms with sudden or recent onset, catatonia or history of good response to ECT, predict a favorable response to ECT (31).

ECT is the therapy of choice in malignant neuroleptic syndrome (MNS) and is a vital indication for patients with MNS, considering that it can reduce hyperpyrexia, sweating and delirium, probably by modulating dopamine activity in the brain. The first effects are usually registered after the fourth course ECT in a series (32,33).

The APA reports that ECT has no absolute contraindications (CI), but that a risk/benefit analysis is necessary for each individual. The latest research indicates that pheochromocytoma and increased intracranial pressure with mass effect can be absolute contraindications for ECT; while relative CIs include increased intracranial pressure without mass effect, cardiovascular and cerebral conduction disorders (23,34).

Advances in technology have contributed to the fact that today AI is mostly used to treat depression. As aforementioned, Thymatron IV has the function of a 4-channel digital EEG machine, which is gaining importance considering that EEG is widely used to study mental disorders and given that it is non-invasive, portable, inexpensive and has a high temporal resolution. EEG-based deep learning techniques (deep learning is a class of machine learning algorithms that use multiple layers to progressively extract higher-level features from raw input) help in the early detection of patients with MDD, thus contributing to reducing the adverse effects of MDD. Investigation of the effectiveness of algorithms (Dimensional Convolutional Neural Network-DCNN; Long-Short Term Memory Networks-LSTM), evaluated on the basis of resting EEG data obtained from 30 healthy subjects and 34 patients with MDD, with 90-99.24% accuracy in distinguishing depressed patients from healthy controls (35).

In addition to diagnostic and predictive purposes, AI is also used for psychotherapeutic interventions, such as cognitive-behavioral therapy (Tess application, 'chatbots' Sara, Voebot and Visa). These applications work in the form of a virtual psychiatric examination, helping patients to identify emotions and thoughts, to learn improved functioning skills and reduce anxiety. Research from 2017, in which the average age of the subjects was 22.2±2.33, indicates that these applications can reduce symptoms of depression (36).

AI with an accuracy >70%, also distinguished healthy individuals from patients with psychotic disorders; AI can localize where incoherence occurs in speech and predict

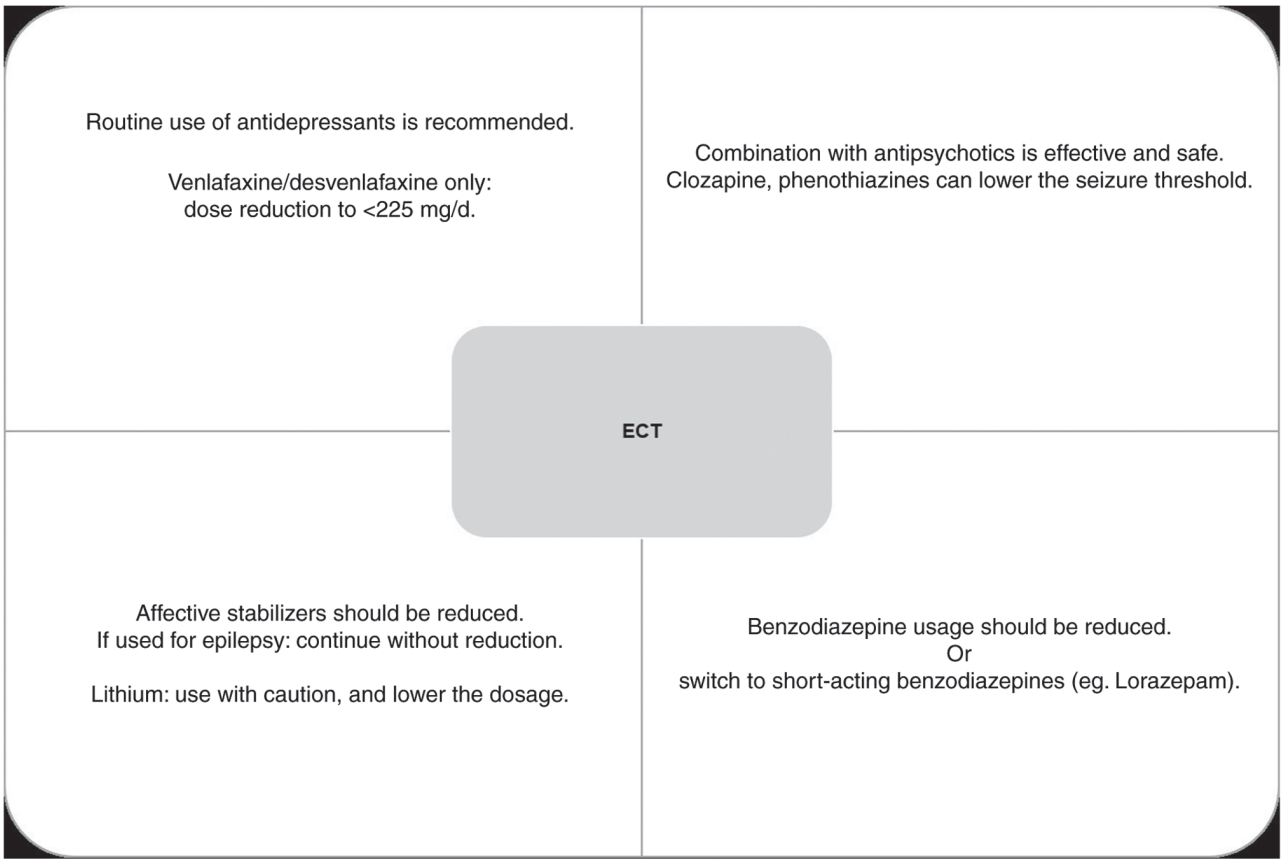

Figure 2. ECT and psychopharmacotherapy. ECT, electroconvulsive therapy.

levels of incoherence in psychotic patients compared with controls (37,38). Research shows that AI improves adherence to therapy in patients with schizophrenia (≤25%), quickly detects and predicts future nonadherence to therapy (39). Virtual reality therapy for 7 weeks in 19 patients with schizophrenia, during a 3-month follow-up period, helped to improve symptoms such as visual and auditory hallucinations, symptoms of depression and improvement of quality of life, especially in patients with treatment-resistant schizophrenia (40).

The functioning of AI is currently limited, but further accelerated progress is expected in the near future, which is especially important due to the recorded shortage of psychiatrists worldwide.

4. Pharmacotherapy and ECT

All medications taken by the patient should be recorded, due to their possible role in increasing morbidity or reducing the effectiveness of ECT. Although some clinicians discontinue psychopharmacotherapy before ECT, this is not always feasible due to the severity of mental disorder (Fig. 2).

Recent meta-analyses indicate a positive effect of ECT in combination with antidepressants in the treatment of depressive disorders. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors and monoamine oxidase inhibitors have shown efficacy in combination with ECT. In clinical practice, the routine use of antidepressants during ECT is recommended (41).

The combination of ECT and antipsychotics is effective in the treatment of schizophrenia and leads to a reduction of both positive and negative symptoms. The fastest response was recorded in the reduction of hallucinations, delusions and affective flattening. The combined therapy of ECT and antipsychotics leads to a significant decrease in the severity of symptoms in ≤60% of patients and also shortens the duration of the current episode (4:8 months) (42,43).

Concomitant use of lithium and ECT may increase the risk of cognitive deficits, delirium and spontaneous seizures. That is why greater caution and the use of lower doses of lithium (if the combination cannot be avoided) is required. In a randomized study, a combination of lithium and high-dose, ultrabrief pulse RUL ECT was shown to be superior to pharmacotherapy, with a relapse rate of <15% at a 6-month follow-up period (44,45).

Affective stabilizers and benzodiazepines should be reduced as much as possible, given that they increase the seizure threshold and can negatively affect the effectiveness of ECT. Not all affective stabilizers have equal effects in increase the seizure threshold, e.g. lamotrigine increases the seizure threshold the least (46,47).

5. Side effects of ECT

General somatic complaints (headache, nausea, muscle pain) are frequent AE of ECT. However, a high level of animosity when it comes to ECT, especially among the medical public, is the prejudice that ECT leads to cognitive impairment. Memory

is special, even sacred for individuals, because it defines one's sense of self and identity. Therefore if ECT can interfere with one's personal memories, even just temporarily or to a lesser extent, it puts it in a special class among medical procedures.

What happens to cognition in depression and psychotic disorders? Cognitive functions are impaired in severe mental disorders. One of the diagnostic criteria for diagnosing depression is impairment of cognitive functions and when it comes to psychotic disorders, this deficit is found in negative symptoms. Magnetic Resonance Imaging (MRI) studies have found that ECT leads to neuroplasticity and reconnections of neural circuits, rather than brain damage (48-50).

Only in recent years in 4IR, have methodologically improved studies appeared, which use computerized neuropsychological tests to monitor cognition during ECT, the results of which are of great importance for both researchers and clinicians (51-55). The advantages of Cambridge Neuropsychological Test Automated Battery (CANTAB), compared with other pencil-and-paper neuropsychological tests, are that it detects and differentiates frontal from temporal and amygdalo-hippocampal dysfunction, is sensitive to deficits related to depression, parallel forms of tests (thus the effect is avoided of learning during repeated testing in test-retest situations). It is suitable for testing both younger and older subjects, it is simple, quick to perform (the subjects have a positive attitude towards it) and the testing methods are culturally and linguistically independent (51).

The results of research conducted in recent years in the world, but also in Serbia, using reliable methods of testing cognition (e.g., CANTAB), indicate that the deficit of cognitive functions, which is associated with the acute phase of depression, improves during ECT treatment of depression and reduction of the severity of depression. Improvements were recorded in the domain of visual memory and learning [Paired Associates Learning (PAL)] and initial thinking time for problem solving (one of the executive functions). In other subdomains of memory no deteriorations are observed in connection with ECT (51-55).

The improvement of PAL (sensitive to the function of the medial temporal lobe) and executive functions (sensitive to the function of the prefrontal cortex) can be interpreted as part of the overall mood improvement, but this is not the only possible explanation. It should be borne in mind that the dorsal hippocampus contains mechanisms that support visual memory and learning and that this is precisely the area of the brain where neurogenesis occurs, thus supporting the theory of neurotrophic effects of ECT, especially in the medial temporal lobe (56).

6. Mechanism of action of ECT

Decades of research have clarified the molecular basis of ECT action. The research also included a preclinical (animal) model of experimental ECT, the so-called electroconvulsive shock and clinical studies. Also reviewed was research conducted using EEG, Positron Emission Tomography, Single-Photon Emission Computed Tomography and functional MRI.

During the last decade, much has been learned about the molecular basis of ECT action. Several hypotheses have been put forward about the mechanism of the antidepressant effect of ECT: Stimulation of neurogenesis, restoration of hippocampus volume, modulation of neurotransmitter and hormone levels, changes in angiogenesis and cerebral circulation, changes in gene expression, immune system and functional connectivity (57,58).

When it comes to ECT and neurogenesis, it should be emphasized that in the hippocampus, plasticity is not limited to synaptic plasticity, but also includes cellular plasticity, that is, neurogenesis increases the number of immature neurons and can increase the excitability of the hippocampus and its connection with the limbic system. Antidepressants, e.g. SSRIs, work mainly to increase active neuronal precursors. It is assumed that ECT activates the 'silenced' neural precursors from their 'resting phase' into a proliferative state, thereby increasing the amount of active stem cells that generate new precursor cells. New neurons generated following ECT do not differ in fate or phenotype compared with neurons obtained under physiological conditions and they integrate into existing networks of neurons and form appropriate synapses. ECT induces neuroplastic processes in the hippocampus and amygdala, i.e., it increases the volume of the hippocampus and amygdala, which are associated with the decrease of depression symptoms (57,58).

Research on animal models (ECS) has markedly contributed to increasing the knowledge of ECT influence on neurotrophic factors (59). ECS increases the concentration of brain derived neurotrophic factor (BDNF) protein and the expression of vascular endothelial growth factor (VEGF) in hippocampus in rats, as well as the concentration of nerve growth factor (NGF) in several limbic areas (60-62). Additionally, a significant increase in hippocampal BDNF has been noticed after a repeat ECS in the second and third week of rat age, as well as an increase in fibroblast growth factor 2 (FGF-2) after the third week of rat age in the rhinal cortex, which suggests a possible maturation of neurotrophic factors on repeated ECS (63). On the other hand, clinical research has shown that ECT increases BDNF and VEGF serum levels, as well as baseline NGF levels (60,64-68). The lack of statistically significant difference between NGF levels following the first and the last ECT may be explained by the sample of therapy resistant schizophrenia patients, given the previous findings of increased NGF in patients with depression and schizophrenia (66,67). Namely, baseline levels of NGF increased consistently following ECT in the group of patients suffering from depression, while in patients with schizophrenia it increased only following the first four ECTs (67). ECT also increases FGF2, but definitive evidence explaining its role in mediating the effects of ECT is still lacking (58,68). BDNF plays an important role in the maintenance and survival of neural functions and in neuroplasticity. Depressed patients have lower levels of BDNF compared with controls and BDNF levels increased markedly only in patients who responded to ECT and this increase was maintained even one month after ECT (64).

ECT reduces the global functional connectivity of neurons, especially in the dorsolateral prefrontal cortex, as well as the regional connectivity of neurons in the dorsomedial prefrontal cortex. Global functional connectivity is a quantitative parameter that reveals the extent to which a certain part of the brain

is connected to other parts of the brain. Pathological 'hyper-connectivity' between intracortical and corticolimbic circuits is an important aspect of depressive disorders (69).

There are an increasing number of research results linking inflammation with depression in somatically healthy subjects (70-72). In patients with depression, elevated serum levels were measured: proteins of the acute phase of inflammation (C-reactive protein), cytokines of inflammation (IL-6 and TNF-α), as well as type 1 immune response cytokines (INF-γ); while anti-inflammatory cytokines (type 2 immune response), IL-4 and IL-10, are markedly lower in patients with depression. ECT reduces these differences, leads to changes in the activity of the immune system and increases the level of anti-inflammatory cytokines, especially IL-10 (73).

7. Conclusions and perspectives

Modern, digitized ECT is still the most controversial therapy in psychiatry. Almost all the controversy surrounding ECT originates from sources of information about this therapy, which are actually anecdotal representations of ECT in movies and books and are not supported by evidence. Scientific research related to ECT generally begins with the fact that it is the most effective therapy for the treatment of severe mental disorders, especially severe depression.

The reason for emphasizing the effectiveness of ECT may lie in the need to remind the medical and psychiatric public that ECT is part of modern psychiatry. The antidepressant effectiveness of ECT is very high and antidepressant drugs or other depression treatments (e.g. transcranial magnetic stimulation) cannot yet be compared with ECT. ECT can save the life of patients who are severely suicidal, malnourished from depression, or have catatonic mutism. Therefore the important question is not whether ECT is good or bad, but whether it can help individuals who truly need it; ECT is not only an effective treatment, but in some cases the best we currently have.

On the other hand, it is not an exaggeration to suggest that the 4RI provided the most powerful tool so far for the advancement of brain science at the level of human systems and especially psychiatry. Structural and functional correlates of numerous mental disorders have been identified, providing a significant basis for a major step forward towards daily use for diagnosis, prediction of response to treatment and monitoring of therapeutic interventions. Tools such as AI, neuroimaging and blood tests will bring significant change to psychiatry in the coming years, but that treating the most severe mental problems will continue to be a challenge.

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Authors' contribution

ZS conceived the study and revised the manuscript. ZS, KS, VTO, ZG and APĆ participated in the writing of the manuscript. ZS and KS reviewed the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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