Method and Application of endogenous neurotransmitter regulation theory [1)]

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Abstract：

[Objective] Verification and application of the theory of brain cell activation.

[Methods] Applying Transcranial magnetoelectric encephalopathy treatment instrument to the treatment of Neurodegenerative disease. including but not limited to: Parkinson's disease and Alzheimer's disease.

[Results] Transcranial magnetoelectric encephalopathy treatment instrument， its double - center, randomized, double - blind clinical trial has been carried out at the national clinical trial base，it proves that the instrument is safe and effective. This instrument is especially suitable for the treatment of the following diseases: 1. It is suitable for the treatment of mild to moderate Parkinson's disease and can significantly improve resting tremor, rigidity, bradykinesia in patients with Parkinson's disease and other symptoms. 2. It is suitable for the treatment of mild and moderate Alzheimer's disease and vascular dementia and can improve the mental state, cognitive behavior and self-care ability of daily life. 3. It is suitable for the treatment of mild to moderate depression and can obviously improve the main symptoms of depression, sleep disorder, anxiety and so on. 4. It is suitable for the treatment of cerebral apoplexy sequelae, cerebrovascular dementia and brain atrophy,it can activate the brain cells in the state of inhibition and mobilize the potential energy of the brain.

[Conclusions] The theory of brain cell activation，It is applicable to encephalopathy and not limited to encephalopathy,according to this theory, the subject of "physical disease science" can be created.

Keywords： The theory of brain cell activation; Ca^{2+} channel; Transcranial magnetoelectric; Parkinson's disease; Alzheimer's disease

Brain science，being regarded as the last scientific tip of human beings, it is the "Pearl" in the crown of scientific research.Brain diseases, especially the neuron degenerative diseases such as Parkinson's disease and Alzheimer's disease, are the "most important" in brain science. They are recognized as a worldwide medical problem and are the goals that the academic world is dreaming of.

Parkinson's disease (PD), is closely related to the loss of dopaminergic neurons. There are about about 4000000 patients with Parkinson disease around the world, more than 2 million in China[1-3].At present, drugs can only control symptoms and do not cure the disease.Its increasingly prominent failure and adverse reactions have aroused widespread concern in the medical field[4,5]; The main methods for surgical treatment of Parkinson's disease are derogation, deep brain electrical stimulation and tissue cell transplantation.The destruction of the brain has not been advocated because of the irreversible damage to

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1)The project won the first prize of Heilongjiang Province Pharmaceutical Industry Science and Technology Progress Award

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the brain.Deep brain electrical stimulation requires the implantation of foreign bodies in the brain, and there is a strict standard of selection for the patients.Tissue cell transplantation is still in exploration[6].

Alzheimer's disease (AD), which is closely related to cholinergic neuron loss,It persecutes 35.6 million people worldwide and adds 4.6 million annually, up from 10 million in China alone.Since 1984.Glenner and Wong have isolated Aβ-amyloid from Senile plaque purification for more than 30 years now, AD pathogenesis is still not clear.There is not any truly effective drug birth yet[7,8]. Especially in the past two years, the research and development of chemical drugs once again in trouble, Global pharmaceutical giant Eli Lilly, Pfizer, Johnson & Johnson and others have announced the failure of drug development. In particular, Pfizer announced in early 2018 the closure of the development of a new drug research and development laboratory for Parkinson's disease and Alzheimer's disease, Dissolve the team of scientists, dismissed about 300 researchers,some scientists pointed out in this connection: "The amyloid hypothesis may mislead the research directions of brain scientists all over the world" [9].

At present, the status quo of brain science at home and abroad is rather chaotic,the results are severely fragmented, especially in dealing with degenerative diseases of neurons, there is no core theoretical support, can not form the main academic thought system and technology system, clinically lack of effective treatment of such diseases, drugs, the measures taken is “right medicine”, the serious side effects of chemical drugs in turn make the patient's condition more complicated and difficult. There is no doubt that the pathogenesis must be explored, however, it is of no use to patients who are currently suffering from encephalopathy.The top priority is to do that put forward the scientific hypothesis or theory that can play a strategic leading role in the direction of international brain science research, Invent or find techniques or methods that are effective in controlling or reversing the degenerative neurons that are developing, It is the correct idea of tackling the problem.

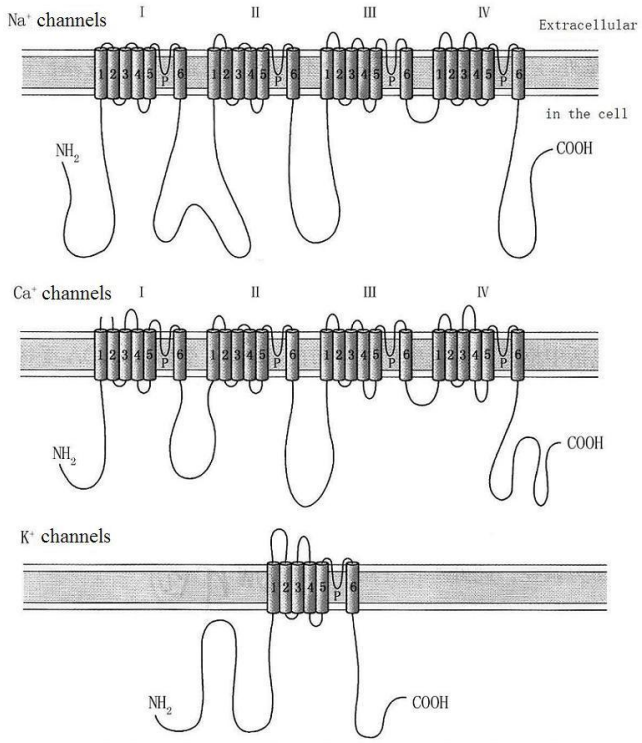
1 The theory of brain cell activation put forward

The theory of brain cell activation, can be understood as "endogenous neurotransmitter regulation theory" or "neural regulation theory",neurotransmitter neurons, which are thought to have degenerative changes, are basal exocytosis that maintains their basal metabolism before they die,it is a reversible process with normal neurons.The hypothesis that "activating brain cells is the key to the treatment of encephalopathy"[10] based on science and cell levels began in 1994, "The theory of brain cell activation" [9]published on the literature and molecular level is 2015.

The core of the theory of brain cell activation: PD, AD and other neurodegenerative diseases,it is closely related to the physical gated ion channels,available physical means to solve,activation of neurons is the key to treatment,voltage-gated Ca 2+ channels are the best targets for physical activation,the purpose is to induce Ca2 + influx trigger neuronal axon terminals synaptic vesicles to release neurotransmitters[9] .

The theory of brain cell activation, has made it clear that calcium channel is the best target of physical activation,pointed out the PD, AD and other neurodegenerative diseases treatment principles, methods and purposes, it clarified that the drug can not fundamentally treat the mechanism of neurodegenerative diseases, changed people's treatment of encephalopathy is mainly dependent on the concept of drugs and surgery,it provides the academic direction for the domestic and foreign scholars' brain science research.

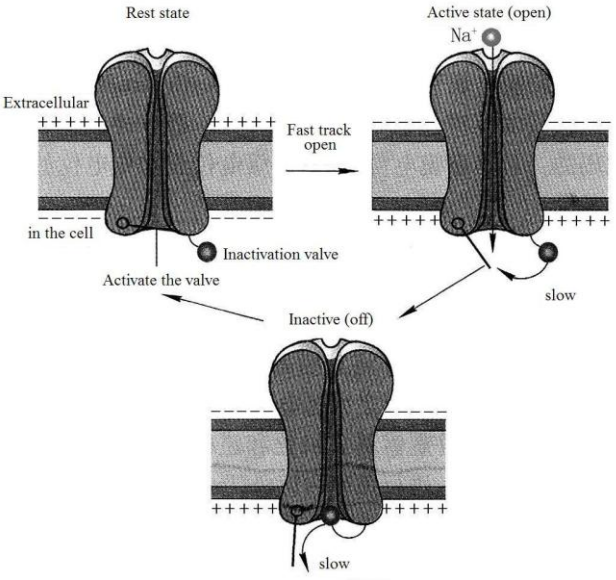
The theory of brain cell activation,supports the vesicle hypothesis[11]and the cholinergic hypothesis[11],questiones the amyloid hypothesis[12]and the Tau protein hypothesis[12] . It believes that the over-phosphorylation of Aβ-amyloid and Tau protein is hyperphosphorylated may be related to neuronal degenerative diseases,but not the main factor leading to degeneration of neurons (Figure 1, Figure 2).



Voltage-gated K^+ channels, voltage-gated Na^+ channels, and voltage-gated Ca^{2+} channels are all surrounded by four functional domains of a transmembrane protein. The four functional regions (Ⅰ, Ⅱ, Ⅲ, Ⅳ) in which Na^+ and Ca^{2+} hannels are formed are located in the same polypeptide chain, the four functional regions that form K^+ consist of four independent polypeptide chains. Each functional area consists of 6 transmembrane sequences, among them, the fourth transmembrane sequence may contain amino acid fragments with changes of voltage. The P-loop between the 5th and 6th transmembrane sequences is involved in the formation of pore walls in the channel.

(Quoted from Kandel ER, Schwartz JH, Jessell TM, Principles of Neuroscience. 4th ed. New York:McGraw-Hill, 2000.)

Figure 1 Main subunit structure of various voltage-gated ion channels



(Quoted form Kandel ER, Schwartz JH, Jessell TM, Principles of Neuroscience. 4th ed. New York:McGraw-Hill, 2000.)

Figure 2 Voltage gated channels open and closed

2 Neurotransmitter regulation method

The theory of brain cell activation, can be understood as "endogenous neurotransmitter regulation theory",this is relative to the neurotransmitters that neurons naturally produce and release to the synaptic cleft.The balance between brain excitability and inhibitory neurotransmitter activity maintains the normal function of the brain,the neurotransmitter released into the synaptic cleft obeys the constant hypothesis of internal environment[13-15] .

2.1 Propose technical ideas

Only for the typical degenerative neuron degeneration - PD, AD.

According to PD, AD and neurotransmitters dopamine, acetylcholine correspondence,using transcranial magnetic stimulation technology, physical means of voltage-gated Ca^{2+} channels activate dopaminergic neurons and cholinergic neurons.Such as PD → striatum → dopaminergic neurons → dopamine, AD → (striatum, cerebral cortex, hippocampus) → cholinergic neurons → acetylcholine. Because, dopaminergic neurons are mostly concentrated in the striatum, cholinergic neurons are mostly concentrated in the striatum, cerebral cortex, hippocampus[6,16].

⑴ Induction of Ca^{2+} influx triggers release of neurotransmitters in neurons

Gating of Ca^{2+} channels on the cell membrane is "voltage", neuron excitement only respond to electrical signals[17,18]. In different encephalopathies corresponding to different types of neurotransmitters in the main concentration area, find the best target area - Cerebral cortex function area, the best target - the nucleus, the best target - the cell membrane calcium channel. Transcranial electrical stimulation of the whole brain at the same time, transcranial magnetic and also strongly stimulate the functional areas of different encephalopathy, so strengthen the effect of transcranial.Human brain in the cerebrospinal fluid, in theory, if the cerebrospinal fluid is energized, the current will be evenly distributed in the brain, even though the skull is an insulator, as long as current is introduced into the brain through the ear, a whole brain stimulus is formed. Skull is high impedance, transcranial magnetic signals can pass through the skull and have a weak induction current in the brain, transcranial magnetic and transcranial complement each other, they activate neurons, they induce calcium influx, which triggers the release of neurotransmitters from the terminal synaptic vesicles of neurons, long-term use of it, can restore the production of neurons self-generation, the release of neurotransmitter function.

⑵ To ensure the excitability of synaptic cleft and inhibition of neurotransmitter balance

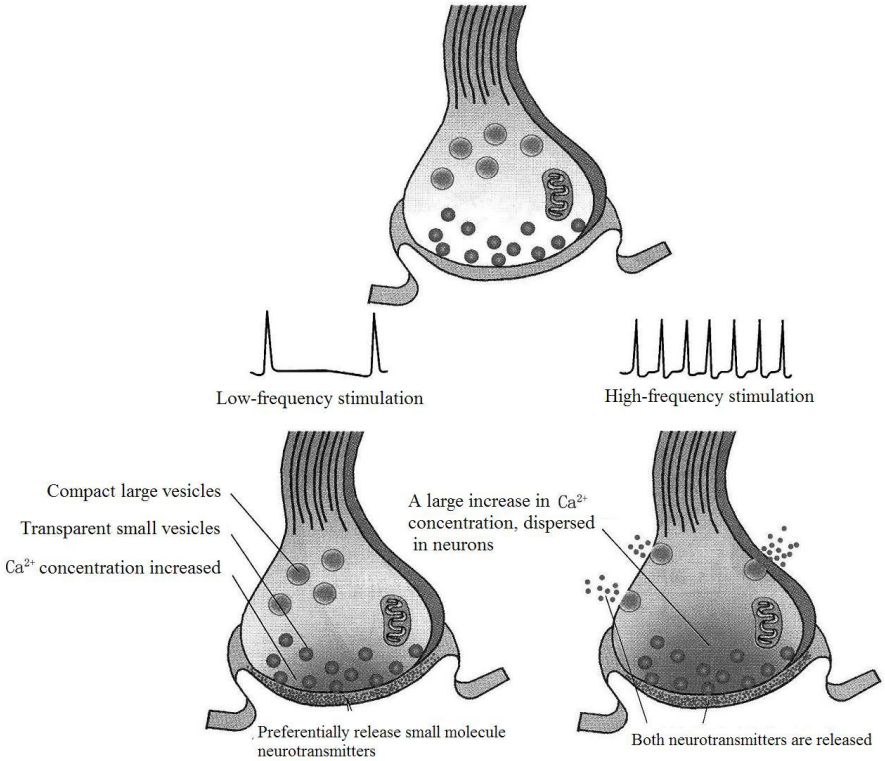
The balance between excitatory and inhibitory neurotransmitter activity maintains the normal function of the brain, the neurotransmitter released into the synaptic cleft obeys the constant hypothesis of internal environment, constant within the environment is not static, is based on a certain form of rhythm activity is constant. Transcranial magnetoelectric stimulation of excitement and inhibition of both neurons play a role, its role is two-way, in theory it stimulates all the neurons, but when it's role in the site, frequency, intensity different, the release of neurotransmitters are also different, for example, macrophages neurons are far and late to release from the cellular Ca^{2+} channel.When a neuron is in an inhibited state, it can be activated to excite it, when a neuron is excited, it can be effectively suppressed.

Regeneration of endogenous neurotransmitters, including vesicle packing, transport and anchoring, requires both process and time, calcium influx starts at the peak of action potential, it ends after the pre-synaptic membrane is fully repolarized, it makes the local area of calcium concentration from about 100nM resting state rapidly increased to greater than 10 ~ 100μM, the increase in calcium ion showed transient, the duration is about 400 ~ 500μs, time course corresponds to calcium current [19-21], synaptic vesicle fusion of molecular components require 1 to 5 calcium ions can trigger vesicle fusion or release. Synaptic neurotransmitter release at least divided into synchronous rapid release and asynchronous slow

release in two ways, the delay of synchronous release is very short (50 ~ 500μs), asynchronous slow release can last 1sor more[22,23] . EEG biological rhythm synthesis frequency of 8 ~ 13Hz, catecholamine neurotransmitters by enzymatic inactivation, vesicle recycling process takes time:if the frequency of 10Hz stimulation, usually tens of seconds to a few minutes [24].

There was no linear relationship between vesicle fusion rate and free calcium concentration, making synaptic vesicle fusion is extremely sensitive to changes in calcium concentration and is limited to a very narrow range of calcium concentration and a short period of time [25] . Neuronal membrane depolarization leads to channel activation, but activated to a certain extent, the channel is inactivated, it enters the state of no conductance, in the inactivated state, the voltage-gated channels are not activated anymore, even though the stimulus is still present or intense [6] . Therefore, the whole brain stimulation, may make the synaptic cleft excitement and inhibition of neurotransmitters appear instant imbalance, but will not lead to normal neurons uncontrolled release of neurotransmitters for a long time, for example, patients with PD may experience more transient jitter after using transcranial magnetoelectric stimulation, but calm will soon resume.

In fact the body's internal activity of the nerve are fluctuating, this is best illustrated by the feedback regulation in the hypothalamus-pituitary-gland axis [26,27] .Therefore, "Transcranial magnetoelectric stimulation technology" can also be understood as "endogenous neurotransmitter regulation technology" or "neural regulation technology" (shown in Figure 3).



as the picture shows，Neurons in low-frequency stimulation, the Ca^{2+} channel on the presynaptic membrane is open, Ca^{2+} concentration locally increased, peferentially release small-molecule neurotransmitters near the Ca^{2+} channel; In the high-frequency stimulation, In the high-frequency stimulation, a large number of Ca^{2+} into the neurons,Large and small molecule transmitter are released.
(Change from Purves D, Williams SM. Neuroscience. 2nd ed. Sunderland:Sinauer Associates Inc, 2001.)

Figure 3 Different neurotransmitters release probability is different

2.3 On the physical means

Magnetic stimulation[28] , magnetic twitch therapy, using time-varying magnetic field in vivo induced electric field and produce induced current; Electrical stimulation, that is, electroconvulsive therapy, beginning in the early nineties of last century. Because of inadequate treatment mechanisms and safety issues, magnetic twitch and electroconvulsive therapy are limited to the treatment of severe mental illness and chronic refractory pain, and are only allowed to be used by professionals in the clinical setting.

The technology search and literature search, internationally, the first application of transcranial electrical stimulation technology for the treatment of stroke sequelae, cerebrovascular dementia and brain atrophy and other neuronal ischemic encephalopathy, is the first author of this article invented transcranial computer functional rehabilitation apparatus, began in 1995.In 1994, his loved one suffered a brain stroke and invented a transcranial computer functional rehabilitation instrument;In 1995, the product obtained the national medical device product registration certificate;In 1996, access to national patents, the same year founded Harbin Aobo Medical Devices Co., Ltd., transcranial computer functional rehabilitation instrument to achieve the industrial application; In 1998, the author and clinical experts co-published the first application of transcranial electrical stimulation as the core technology for the treatment of encephalopathy clinical observation of the paper: brain function rehabilitation instrument (brain health instrument) on cerebral circulation and brain function [29] .

Developed successfully of transcranial electricity brain function rehabilitation treatment instrument for the transcranial magnetic stimulation technology research and application laid the technical foundation, it also provides academic directions for domestic and foreign scholars to study transcranial electrical stimulation technology. In the following 20 years, the first author conducted a long-term, in-depth and systematic exploration and practice from two aspects of the basic theoretical research and clinical practice of brain science, he proposed the theory of " The theory of brain cell activation", and in 2011 and 2014, he invented Parkinson therapy instrument[31,32], Alzheimer treatment instrument[31,33], depression (insomnia) treatment instrument[34,35] and other transcranial magnetic Computer series of rehabilitation treatment equipment, changed the past people's treatment of encephalopathy mainly rely on the concept of drugs and surgery, it provides a new way of physical treatment for the treatment of degenerative diseases of neurons.

2.3 Comparison of similar studies

Magnetic stimulator at home and abroad mainly round coil or 8-shaped coil-based, stimulation output is high-pressure low-frequency pulsed magnetic field, the actual output of 1 ~ 3T (Tesla) or even higher. The main results of the project using transcranial magnetic E-shaped coil is a multi-turn magnetic field generator, multi-point low-frequency alternating magnetic field, the actual output does not exceed 50 mT (milli-teres) , the target is the superficial cortex of the brain, the magnetic stimulation intensity reaching the target is 1 ~ 2G (Gauss) (1T = 10000G). Domestic and international electricity twitch therapy, began in the early nineties of last century, is a high voltage current, usually more than 90V; The main results of this project using transcranial electrical stimulation, low voltage weak current.

Monkey research shows that, as long as 1 ~ 2G (Gauss) magnetic stimulus is reached in the cerebral cortex, the threshold of hippocampus and motor cortex will be increased; When the cell membrane potential close to -40mV, Ca^{2+} channel opening probability began to significantly increase. Whether it is transcranial magnetic or transcranial electrical, neurons are the ultimate role of "electricity", the Ca^{2+} channel on the cell membrane gating way is also "electricity", therefore, neurons in the repressed state only respond to electrical signals.

The transcranial magnetic stimulation technology used in this project is a noninvasive noninvasive technique, it is weak magnetic micro-current stimulation, it is the second national medical equipment, its mechanism is clear, no side effects of safety, encephalopathy patients can be used in hospitals and families.

The main outcome of this project Alzheimer therapeutic apparatus, is original in the world, no similar products;Another major achievement of this project, Parkinson treatment instrument, is similar to, and comparable to, brain pacemakers in the United States.

American brain pacemaker, equivalent to human "brain pacemaker", it is an invasive deep brain stimulation, it can significantly improve and control tremor, rigidity, bradykinesia and other symptoms, its damage to the brain structure is reversible, does not affect the future to take other new treatment methods, the application of the theory of brain cell activation can explain its treatment mechanism. The main achievements of this project Parkinson treatment instrument, is a multi-point, multi-turn, multi-channel transcranial magnetic neuromodulation system, it is equivalent to people's "brain pacemaker in vitro", it is a non-invasive deep brain stimulation, it is suitable for mild to moderate Parkinson's disease, can significantly improve the resulting tremor, stiffness, bradykinesia and other symptoms, the theoretical basis is the theory of brain cell activation, divided into two types of medical and household, can enter the hospital into the family.

2.4 The main discovery, invention, innovation

Based on the above research background and academic achievements, the subject from theoretical discovery to technical invention and then series of industrial applications, has its own system, the main findings, inventions, innovations and contributions are summarized as follows:

Founded the brain cell activation theory, found that the voltage-gated Ca^{2+} channel is the best target of physical means to activate neurons, pointed out the PD, AD and other neurodegenerative diseases treatment principles, methods and purposes, clarified the mechanism by which drugs can not fundamentally treat such diseases;

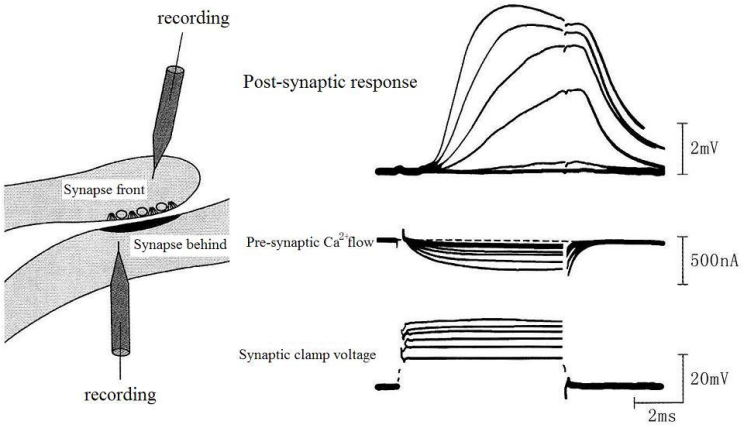
Invented transcranial magnetoelectric encephalopathy treatment instrument, established the transcranial magnetic stimulation of specific parts of the human brain caused by encephalopathy positive treatment time and space distribution, by changing the frequency, intensity and time of transcranial magnetic stimulation of specific parts of human head, the corresponding relationship of the regulation of endogenous neurotransmitter can be achieved;

Developed the Parkinson treatment instrument, Alzheimer treatment instrument and so on, transcranial magnetism encephalopathy series of rehabilitation equipment, the first application of transcranial magnetic stimulation for the treatment of PD, AD, break through the PD, AD treatment mainly depends on the limit ations of drugs and surgery, opened up a new means of treatment of neuronal degenerative diseases by phy sical means.

Transcranial magnetoelectric encephalopathy treatment instrument, is a multi-bit, multi-turn, multi-channel transcranial magnetic nerve stimulation system, includes head-mounted field effect caps and EEG generators. Of which: EEG analog generator, is a kind of brain cells can activate the instrument, the output of a special electrical signal to simulate the brain wave of healthy people, frequency and intensity, can be benign and weak electrical stimulation of neurons; Field effect cap, containing magnetic devices, for different types of brain diseases, choose the best target for human head.

Technical solutions: transcranial magnetoelectric generated by the three-dimensional superimposed alternating magnetic field and pulse current in the brain Co-acting on deep brain delivery of energy neurons, transcranial magnetic brain in a particular part of the formation of three-dimensional superimposed alternating magnetic field induced weak induction current, can direct the activation of cortical neurons; Transcranial electrical pathway in the basal ganglia neurons through the nucleus, the enhanced transcranial magnetic effect, transcranial magnetic and transcranial complement each other,

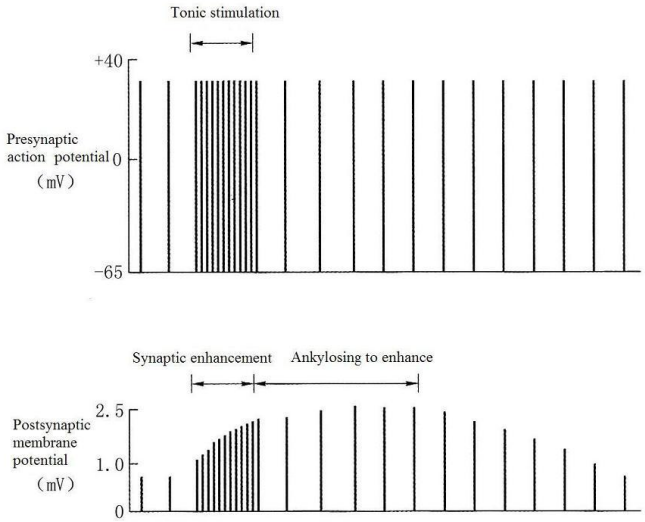
taking into account the fact that neurons transmit neurons and skull high impedance distribution of the facts (Figure 4, Figure 5).



The electrodes recorded the presynaptic and postsynaptic fibers of squid synapse respectively, TTX and TEA were added to the external fluid to block the voltage-gated Na^+ and K^+ channels, respectively. Under the premise that presynaptic cells can not produce action potentials, Given a progressive depolarization of presynaptic progression, in addition to recording a gradual corresponding increase in presynaptic Ca^{2+} flow, a correspondingly increased post-synaptic response can also be recorded. That neurotransmitter release is not the result of the opening of Na^+ or K^+ channels, but closely related to Ca^{2+} influx.

（cited from Kandel ER, Schwartz JH, Jessell TM, Principles of Neuroscience. 4th ed. New York:McGraw-Hill, 2000.）

Figure 4　Neurotransmitter release is the result of presynaptic terminal Ca^{2+} influx



As comparison, First give several presynaptic neurons 1Hz stimulation, induced presynaptic action potential, post-synaptic neurons can record postsynaptic potentials of about 1 mV. A series of 5 Hz tonic stimulation of presynaptic neurons within the ensuing few seconds, at the same time, a gradual increase in postsynaptic potential was recorded. When the presynaptic neuron stimulation frequency returned to 1Hz, the post-synaptic response is still maintained for some time enhanced response, that is, after strengthening, and then gradually reduced.

（Change from Kandel ER, Schwartz JH, Jessell TM, Principles of Neuroscience. 4th ed. New York:McGraw-Hill, 2000.）

Figure 5　Synaptic enhancement and post-ankylosing enhancement produced by tonic stimulation

3 Application of theory and method

From the hypothesis of encephalopathy treatment to the creation of "The theory of brain cell activation"; From Transcranial electrical stimulation from the invention of technology to form a transcranial magnetic core patented technology; From the development of the first brain rehabilitation therapy apparatus to develop a transcranial magnetic computer treatment of products, from practice to theory, to practice again. After more than 20 years, involved in the treatment of major diseases of neuronal degenerative diseases, ischemic encephalopathy, mental illness, a total of 4 countries registered medical device products, are independent intellectual property rights, all realized the industrialization.

3.1 Transcranial magnetoelectric encephalopathy treatment instrument (AOBO Parkinson treatment instrument)

The first registration is January 31, 2011, medical device product registration number : HEI SHI YAO JIAN (prospective) word 2011 No. 226001, scope: mild to moderate Parkinson's disease, can significantly improve the resulting tremor, stiffness, bradykinesia and other symptoms [36] .

Parkinson treatment instrument, select voltage-gated Ca^{2+} channel as the best target of transcranial magnetoelectric effect, the purpose is to induce Ca^{2+} influx trigger neuronal axon terminal synaptic vesicles release neurotransmitter, activation of dopaminergic neurons[6,9], break through the international treatment of PD mainly rely on drugs and surgical limitations, equivalent to human brain pacemaker, is another new way to treat PD.

Has been completed sci-tech novelty retrieval and Results identification, to fill gaps at home and abroad, transcranial magnetoelectricity technology in the field of physical therapy PD living in the international advanced level, for the world's first. Parkinson treatment instrument, has been listed as Heilongjiang Province key scientific and technological projects, ministry of Science and Technology Innovation Fund focus on supporting projects, committee of industry and information technolgy of heilongjiang province identified as the first key areas (sets) products, won the first prize of Heilongjiang Province Pharmaceutical Industry Science and Technology Progress Award, china Industry-University-Research Cooperation Innovation Award, the first prize of Heilongjiang Province Science and Technology Invention Award, is listed as Heilongjiang Province "Twelve Five" key to promote industrialization projects and biological industry in Heilongjiang Province structural adjustment projects.

3.2 Transcranial magnetoelectric encephalopathy treatment instrument (AOBO Alzheimer treatment instrument)

The first registration Date April 17, 2014, medical device product registration number : HEI SHI YAO JIAN XIE (prospective) word 2014 No. 2260036, scope: mild to moderate Alzheimer's disease, vascular dementia, the patient's mental state, cognitive behavior and ability to take care of themselves daily life better to improve the role of [33] .

Alzheimer treatment instrument, select voltage-gated Ca^{2+} channel as the best target of transcranial magnetoelectric effect, the purpose is to induce Ca^{2+} influx trigger neuronal axon terminal synaptic vesicles release neurotransmitter, activation of cholinergic neurons[9] , opened up new ways of treating AD by physical means.

Has been completed sci-tech novelty retrieval and Results identification, to fill gaps at home and abroad, transcranial magnetoelectricity technology in the field of physical therapy AD living in the international advanced level, for the world's first. Alzheimer treatment instrument, is Heilongjiang Province and Harbin City key scientific and technological projects, has been won the Harbin Science and Technology Progress Award,won the first prize of Heilongjiang Province Pharmaceutical Industry Science and Technology

Progress Award, is listed as Heilongjiang Province "Twelve Five" key to promote industrialization projects and biological industry in Heilongjiang Province structural adjustment projects.

3.3 Transcranial magnetoelectric depression(insomnia) treatment instrument

The first registration is January 31, 2011, medical device product registration number: HEI SHI YAO JIAN (prospective) word 2011 No. 226002, scope: mild to moderate depression, can significantly improve depression, sleep disorders, anxiety and other major symptoms[35] .

Transcranial magnetoelectric depression(insomnia) treatment instrument, select voltage-gated Ca^{2+} channel as the best target of transcranial magnetoelectric effect, the aim is to activate serotonergic neurons[9] .

Has been completed sci-tech novelty retrieval and identified provincial new product by Committee of industry and information technolgy of heilongjiang province, conclusion: To fill the gaps at home and abroad, the world's first, the core technology is in the international advanced levelin the field of depression treatment applications. Transcranial magnetoelectric depression(insomnia) treatment instrument, has been included in the 2011 national key new product development plan, the 2012 Torch Program project, won the eighth Heilongjiang Province outstanding new products first prize,the first prize of Heilongjiang Province Pharmaceutical Industry Science and Technology Progress Award, heilongjiang Province Science and Technology Award (invention class) first prize.

3.4 Transcranial electricity brain function rehabilitation treatment instrument

The first registration is December 4, 1995, medical device product registration number: HEI YI XIE ZHUN ZI (95) No. 227014, scope: stroke sequelae, cerebrovascular dementia and brain atrophy[29,30] .

Transcranial electricity brain function rehabilitation treatment instrument, select voltage-gated Ca^{2+} channel as the best target of transcranial effect, the goal is to save the dying neuron and activate the neuron in the repressed state[9,10].

Stroke, whether it is ischemic cerebrovascular disease or hemorrhagic cerebrovascular disease, Once into the sequelae, all belong to ischemic encephalopathy, such as brain atrophy or cerebrovascular dementia, the same treatment mechanism and AD, the method is similar: activation of energy-producing neurons is the key to treatment. Transcranial electricity brain function rehabilitation treatment instrument, activation of key areas of neuronal groups taking into account the whole brain stimulation, for stroke sequelae, cerebrovascular dementia and brain atrophy encephalopathy, for the treatment of ischemic encephalopathy has opened up a new way.

In 1995 through the Heilongjiang Province Food and Drug Administration organized the provincial scientific and technological achievements appraisal. Identification conclusion: The product to fill the gaps in the country, in the domestic and international advanced level of similar products.Transcranial electricity brain function rehabilitation treatment instrument, has successively been listed as a major scientific and technological project in Heilongjiang Province and a major science and technology industrialization project, National Torch Plan Project, National Science and Technology Enterprise Innovation Fund key support projects, Won China Invention Exhibition patent gold medal, Paris, France International Invention Expo Repin Repin Award, Heilongjiang Province, the first prize of scientific and technological benefit, Heilongjiang Province Science and Technology Award (invention class) first prize.

4 Discuss

Life sciences, especially neuroscience, have been studied to the very micro level, many biochemical results are obtained by physical means, the theory of brain cell activation is also based on the clinical practice of transcranial magnetic stimulation technology and the existing biochemical results derived a

conclusion. Regrettably, often when we treat various diseases, emphasize one and underestimate the other, few mentions physical means, or just locate it on adjuvant therapy, ignores the complementary relationship between physical and chemical means.

The theory of brain cell activation, suitable for encephalopathy is not limited to encephalopathy, based on this, you can create "Discipline of Physical Diseases." According to the gating of Ca^{2+} channels, the disease can be divided into physical diseases, chemical diseases and physical and chemical diseases, when the cell is in an inhibited state, it only responds to the electrical signal, when the cell is in an excited state, it is possible for the chemical to flatten it from the excited state to the normal state, but through physical means can be done, namely, the diseases that can be solved by drugs are also possible through physical means. The problems that drugs can not solve can be solved by physical means.

Simply from the cell inhibition and excitement to divide, Physical means with two-way adjustment, anyone who has a neurodegenerative disorder that is selectively degenerative, can belong to the physical gated Ca^{2+} channel disease, can try to be treated by physical means, such as schizophrenia, bipolar disorder, myasthenia gravis, Huntington's disease, epilepsy, pediatric cerebral palsy, autism, mental retardation, addiction, CO poisoning, pain, vegetative disease, coronary heart disease, diabetes, More than 20 kinds of major diseases.

In fact, physical means, especially transcranial magnetic stimulation technology, it has aroused the widespread concern of the world's scientists. In December 2016, a number of internationally renowned brain scientists jointly issued a long article on the well-known academic journal *Neuron*, giving high attention and affirmation to the emerging physical means of transcranial stimulation [37]. In June 2017, more than 10 scientists from a number of authoritative academic institutions such as Massachusetts Institute of Technology, Harvard Medical School, and Royal London Hospital conducted a basic experimental study on noninvasive transcranial low-frequency electrical stimulation. And in the "*Cell*" magazine published an article: "Transcranial low-frequency electrical stimulation technology is mature and reliable,It is recommended that you do not have to do the brain biochemical test for the brain, call for such an approach to be applied as soon as possible in the treatment of major human brain diseases, such as the treatment of PD, AD, stroke sequelae and the study of the human brain "[38].

In recent years, the object of rewards of international authoritative scientific and technological awards organizations have also begun to favor physical therapy, at the same time also attracted the attention of strategic investors. In 2014, inventors of brain pacemakers Mahlon DeLong and Alim Louis Benabid won the Lasker Award, the highest award in medical science in the United States. In 2013 and 2015, it won the Scientific Breakthrough Award again and again. GlaxoSmithKline invested heavily in 2013 to support research similar to the main results of this topic, in 2016, Neuronix Company of the United Kingdom combined transcranial magnetic stimulation and cognitive training, "Targeted Encephalopathy Area for Alzheimer's Disease", the treatment of mild to moderate Alzheimer's disease (AD) has a positive effect, approvals from the U.S. Food and Drug Administration (FDA) are being sought[39,40]. Bill Gates also said in 2017 that it will invest heavily in research on the physical therapy of PD and AD other than drug development.

Some people think that the amyloid hypothesis "Too big to fail", is it really? Method and Application of endogenous neurotransmitter regulation theory, once again reminded the industry professionals in the chemical synthesis at the same time do not ignore the physical means, the combination of physical means or the combination of physical and chemical means may be one of the most important research directions in the future for the total overcoming of neurodegenerative diseases in humans. In the face of 40 million

PD, AD patients and their families who are in pain, the face and interests of any organization must be unconditionally dropped!

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