VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

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Deep Brain Stimulation: An Emerging Technique in Treatment of Alzheimer's disease.

Estimulación cerebral profunda: una técnica emergente en el tratamiento de la enfermedad de Alzheimer.

Estimulação cerebral profunda: uma técnica emergente no tratamento da doença de Alzheimer.

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VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

ABSTRACT

Deep brain stimulation is a therapeutic method that has been studied in animal experiments and clinical trials in degenerative diseases and has a huge potential if applied to Alzheimer's disease. In this review, it is described the deep brain stimulation technique and the underlying physical principles. It is also listed some of the most relevant studies performed in this scope to better understand the mechanisms of stimulation performance in relation to the improvement of cognitive performance related mainly to memory, neurogenesis and improved glucose metabolism and reduced expression of disease-causing proteins and increased levels of acetylcholine.

Palabras clave: deep brain stimulation; Alzheimer's disease; neural stimulator; memory; neurogenesis; acetylcholine

RESUMEN

La estimulación cerebral profunda es un método terapéutico que se ha estudiado en experimentos con animales y ensayos clínicos en enfermedades degenerativas y tiene un enorme potencial si se aplica a la enfermedad de Alzheimer. En esta revisión, se describe la técnica de estimulación cerebral profunda y los principios físicos subyacentes. También se enumeran algunos de los estudios más relevantes realizados en este ámbito para comprender mejor los mecanismos de la estimulación en relación con la mejora del rendimiento cognitivo relacionados principalmente con la memoria, la neurogenesis y el incremento del metabolismo de la glucosa y la reducción de la expresión de proteínas causantes de enfermedades bien como el aumento de niveles de acetilcolina.

Keywords: estimulación cerebral profunda; enfermedad de Alzheimer; estimulador neural; memoria; neurogenesis; acetilcolina

RESUMO

A estimulação cerebral profunda é um método terapêutico que foi estudado em estudos com animais e ensaios clínicos em doenças degenerativas e apresenta um enorme potencial se aplicado à doença de Alzheimer. Nesta revisão é descrita a técnica de estimulação cerebral profunda e os princípios físicos subjacentes. São também enumerados alguns dos estudos mais relevantes realizados neste âmbito para melhor compreender os mecanismos de estimulação em relação à melhoria do desempenho cognitivo relacionado principalmente à memória, neurogénese e melhoria do metabolismo da glicose e redução da expressão de proteínas causadoras de doenças e aumento dos níveis de acetilcolina.

Palavras-chave: estimulação cerebral profunda; doença de Alzheimer; estimulador neural; memória; neurogénese; acetilcolina.

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly (older than 65 years) (Prince et al., 2015). Dementia corresponds to the loss of cognitive functioning (thoughts, memories and reasoning) and behavioural skills in such a way that it interferes with a person's daily life (American Psychiatric Association, 2013). AD is a degenerative and irreversible neurological disorder that progressively affects the function of memory, attention, concentration, language, thinking, among others, and as it progresses there is loss of ability to perform the simplest tasks (National Center for Health Statistics).

There are some authors (Hardy & Higgins, 1992), (Shankar et al., 2007) who defend the amyloid cascade theory as the main mechanism that is at the origin of the disease, wherein the disease is driven by the extracellular accumulation of the amyloid beta (Aβ) peptide and aggregation into senile plaques. Animal studies to determine which soluble Aβ forms cause synaptic loss in the hippocampus have been shown to be the oligomers that cause this effect from a cell pathway comprising NMDA-type glutamate receptors, calcineurin and cofilin (Shankar et al., 2007). The synaptic loss along this path leads to the induction of long-term depression (Mulkey, Endo, Shenolikar, & Malenka, 1994), (Cummings, Mulkey, Nicoll, & Malenka, 1996). Thus, synaptic dysfunction and loss, which is considered to be the strongest correlation of the level of cognitive decline observed in patients with AD (Terry et al., 1991), may be induced by low-number diffusible Aβ oligomers (Shankar et al., 2007), (Walsh et al., 2002).

While the intracellular accumulation of tau protein in neurofibrillary tangles arises as a consequence of the Aβ pathology (Grundke-Iqbal et al., 1986) but the way these two processes relate to synaptic degeneration is still unknown (Holtzman et al., 2000), (Stokin et al., 2005). When examining the synergy between Aβ and tau, i.e., to observe how Aβ senile plaque accumulation and synaptic loss occur in the presence of human tau, how tau contributes to Aβ-related pathology, and how Aβ influences non-mutant tau, recent experiences have achieved surprising results. Then the presence of human Aβ stimulated the tau propagation (Busciglio, Lorenzo, Yeh, & Yankner, 1995), increased the size of plaques, and intensified neuritic dystrophies (one of the types of senile plaques) (Meyer-Luehmann et al., 2008). In the presence of tau, there was an increase of Aβ in the synapses near the plaques than far from the plaques but the exaggerated expression of the human tau did not increase the amount of Aβ located near the synapses (Jackson et al., 2016). Therefore, the mouse endogenous tau is sufficient to cause the negative effects associated with Aβ (Roberson et al., 2007) and the important role that the endogenous tau can play in the neurotoxicity of tau and Aβ can occur mainly in the earliest stages of the illness (Jackson et al., 2016).

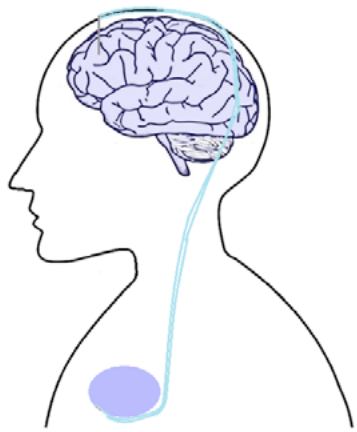

Figure 1. Deep Brain Stimulation system. Image authorship without copyright conflict.

Currently, there is no cure for Alzheimer's disease. However, there are some medications used to treat the symptoms of disease such as acetyl cholinesterase inhibitors that can temporarily improve or stabilize memory and thinking skills in some people by increasing the activity of the cholinergic brain network. Memantine is another medication used to prevent declines in memory and language which binds to NMDA receptors, blocking glutamate binding. Although none of these medications can stop or reverse the progress of the illness (National Institutes of Neurological Disorders and Stroke; National Institute on Aging, 2004).

Researchers have attempted to develop therapies not only for the treatment of Alzheimer's disease symptoms but also to address the underlying disease processes.

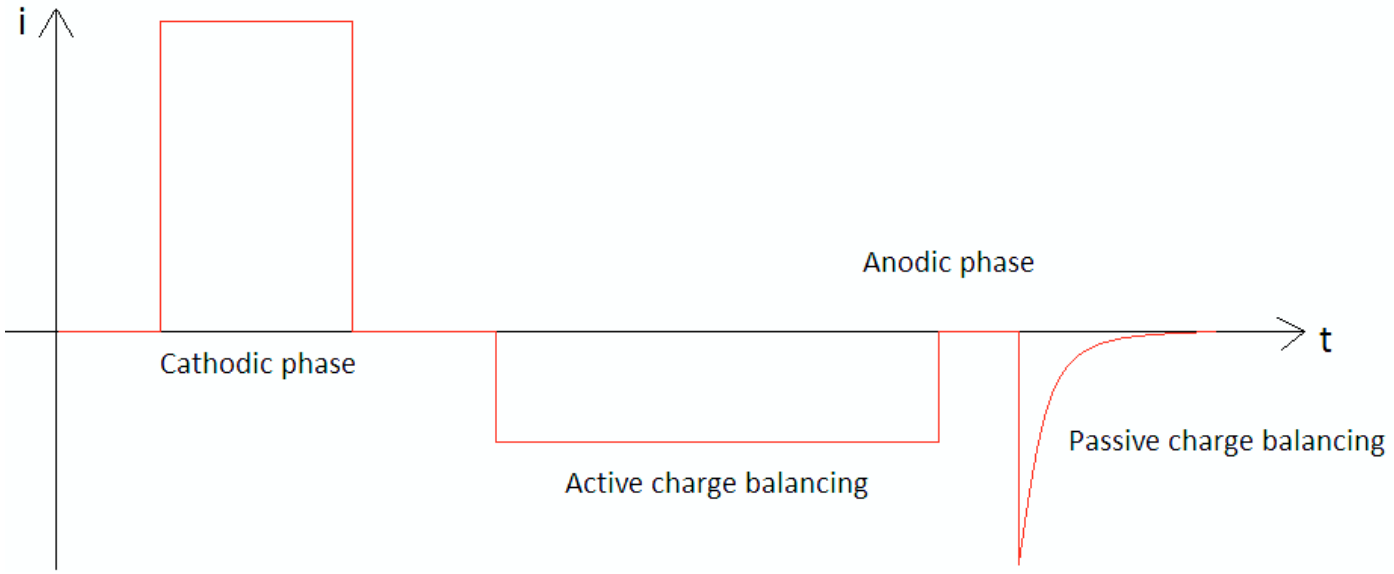

Figure 2. Typical waveform of DBS current stimulation with active and/or passive charge balancing. Adapted from the original without copyright conflict. (Kolbl et al., 2016)

Such interventions include: immunization therapy, drug therapies, cognitive training, physical activity and treatments used for cardiovascular disease, diabetes and other neurodegenerative diseases (National Institute on Aging, 2017).

One of the treatments that has been recently reported as likely to demonstrate beneficial effects in the treatment of Alzheimer's has been deep brain stimulation (DBS). DBS is an adaptive, reversible and effective neurosurgical treatment that was initially developed as a treatment of motor disorders, more specifically in Parkinson's disease (National Institute of Mental Health, 2017). Therefore, research has been carried out to test therapeutic targets under DBS (in animal studies and more recently in clinical trials) with the potential to delay the cognitive decline typically observed in AD patients (Arrieta-Cruz, Pavlides, & Pasinetti, 2010b; Hescham et al., 2015), to counteract the hallmark brain atrophy of the disease and increase the brain metabolism of glucose (Chamaa, Sweidan, Nahas, Saade, & Abou-Kheir, 2016; Sankar et al., 2015) and disaggregate and reduce the proteins that contribute to the pathology of AD and increase the levels of cholinergic neurotransmitters in the cerebral cortex (Gondard et al., 2015; Jeong et al., 2014).

The aim of this review is to describe the technique of deep brain stimulation and the advances made in its application to Alzheimer's disease, with special focus on its effects on memory function, brain structure, glucose metabolism by hippocampus, proteins involved in the pathogenesis of AD and neurotransmitter acetylcholine synthesis.

Description of the Deep Brain Stimulation Technique

The neural stimulation is a modulation technique of the nervous system's activity, used only when other therapies, such as drugs and physical rehabilitation, fail to provide a positive response to treatment of neurologic disorders (Laotaveerungrueng, Lahiji, Garverick, & Mehregany, 2010). Brain stimulation therapies involve activating or inhibiting the brain directly with electricity. The electricity can be given directly by electrodes implanted in the brain, or noninvasively through electrodes placed on the scalp. The electricity can also be induced by using magnetic fields applied to the head. While these types of therapies are less frequently used than medication and psychotherapies, they hold promise for treating certain mental disorders that do not respond to other treatments

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

(National Institute of Mental Health, 2017). The way axons response to extracellular electrical stimulation is based on three physical foundations: (1) axonal excitability depends on the diameter of the fibers, (2) there is a relation between the distance of the axons to the electrode and the current transmitted (EJ, 1996) and (3) the pulse strength is related to its duration (Ranck, 1975). A stimulation system consists of a stimulator which transmits the electrical signals to an electrode placed near the area of interest. The neural stimulator contains the energy source of the deep brain stimulation (DBS) system (see fig.1) and therefore it generates and controls the therapeutic stimulation. The electrodes and the neural stimulator are connected by a lead (Laotaveerungrueng et al., 2010). The electrodes of the traditional DBS systems have the shape of a ring and generate a substantially spherical electric field (Kühn & Volkmann, 2016). The DBS therapy uses constant voltage electrical pulses, where the current transferred to the tissue depends on the impedance between tissue and electrode (Gong et al., 2015). High-voltage and high-current pulses are required due to the high impedance of the tissue and the rather large target areas (Hemm et al., 2004). Pulse sequence usually consists of monophasic or biphasic configurations, defined by the amplitude (of the cathodic phase), frequency and pulse width (Yousif et al.,

2010). For movement disorders like Parkinson's disease, the stimulus needed have a 100-130 Hz frequency, 60-120 µs pulse width and 1-3.6 V or 0.2-2 mA amplitude (Volkmann, Moro, & Pahwa, 2006). The pulse width is determined by the terminology traditionally used as the duration of the stimulus pulse (Foutz & McIntyre, 2010). However, these parameters can vary slightly depending on the brain anatomy of each patient (Laotaveerungrueng et al., 2010).

In DBS devices are used biphasic pulses with rectangular and charge-balanced stimulus waveforms (see fig.2). Each stimulation cycle consists of a cathodic phase (also called the stimulus pulse) defined by the amplitude and width of the chosen pulse, an interphase interval and an anodic phase (also called the recharge pulse) to balance the injected charge, avoiding tissue or cellular damages from the accumulation of remaining charges (Foutz & McIntyre, 2010; Yousif et al., 2010). While tissue damage is reduced as a consequence of the anodic phase of the pulse, (Yousif et al., 2010) showed that both phases play an important role in modifying neuronal activities.

Some researchers have been proposing novel ways to improve the efficiency and/or selectivity of this stimulation technique (Foutz & McIntyre, 2010). Changing the duration of the pulse makes it possible to vary the amount of charge injected and the selectivity of DBS (Kühn & Volkmann, 2016). One of the main reasons for (for example) changing the stimulus waveform to a non-rectangular one was based on the assumption that it is capable of generating the appropriate neuronal response, causing the least possible tissue damage, while at the same time having lower energy needs (Sahin & Tie, 2007), (Foutz & McIntyre, 2010). Thus, the efficiency can be achieved from three goals: (1) increasing the battery life of implanted neural stimulators (Jezernik & Morari, 2005), (Wongsarnpigoon & Grill, 2010), (2) increasing the time between charges (with main application in rechargeable devices) (Foutz & McIntyre, 2010) and (3) reducing the volume of the stimulation implant (Foutz & McIntyre, 2010), (Wongsarnpigoon & Grill, 2010). *Foutz and McIntyre* (2010) compared situations of constant current stimulation with: (1) an electrode placed intracellularly, (2) an electrode with the origin located extracellularly and (3) an extracellular DBS electrode. In the DBS model, the current-controlled stimulus comes into contact with the electrode nib and propagates from it through an isotropic and homogeneous tissue medium. They still tested in neural models (so that the spontaneous brain activity that might occur did not interfere with the experiment) how the stimulus waveform affect the activation of either fibers of passage or local projection neurons. Each neuron was stimulated with each waveform (rectangular and different non-rectangular ones) and pulse width. The energy (E) of each cathodic phase was calculated by the equation 1 where Tc is the duration of the cathodic phase, I(t) is the current at that time, and Z(t) is the impedance (defined with the constant value of 1 kΩ).

The charge injected during the stimulus (Q) is calculated by the integral of the current during cathodic phase (see equation 2).

To optimize the waveform, it is essential consider not only the decrease of energy requirements but also the injected charge (Foutz & McIntyre, 2010). However, as there is a correlation between increased charge injection and tissue damage, the charge injection had to be limited by the equation 3 where D is charge density in $\mu C/cm^2$/ phase and Q is charge and is the limit for safe charge injection (1.38 µC/phase).

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

So that no damage is observed, k must have the constant value of 1.5. Since D = (IT) / A = Q / A, the above equation (equation 3) can be rearranged and expressed as in equation 4 where I is current, T is the duration of each phase of a two-phase pulse and A is the surface area of the electrode (Shannon, 1992).

According to the study of Foutz & McIntyre (2010), the DBS electrode changed the pulse width to larger values

Ecuacion 1

$$E= \int_0^{T_c} I^2(t)Z(t)dt\,,$$ (Foutz & McIntyre, 2010) (1)

relative to the other electrode types. This is synonymous that geometry of the electrode influences the pulse width (Foutz & McIntyre, 2010). Nevertheless, the effect

Ecuacion 2

$$Q= \int_0^{T_c} I(t)dt\,,$$ (Foutz & McIntyre, 2010) (2)

of considerably changing the waveform and thereby increasing the energy threshold seen for short pulse widths was reduced (Mortimer, Shealy, & Wheeler, 1970). Analyzing the safety of the waveforms, they realized that by stimulating narrow fibers with the DBS electrodes farther than 2.5 mm, the charge injection became an element to take into account. Smaller pulse widths safety stimulate such fibers. On the other hand, these have an

Ecuacion 3

$$k= \log(D)+\log(Q),$$ (Shannon, 1992) (3)

increased energy needs compared to stimulation without charge limitations (Foutz & McIntyre, 2010). However, it is not ensured that the decrease in the energy of the waveform at half its original value increases to twice the battery time (Anheim et al., 2007). Finally, although energy savings are an engineering goal, they are still

Ecuacion 4

$$K= \log\frac{(IT)}{A}+\log(IT),$$ (Shannon, 1992) (4)

dependent on the charge injection, and it is limited by its elicited effect on the surrounding tissues, which may compromise the possibility of improving the patients' lives (by not subjecting them to successive surgeries during the treatment to replace the stimulator battery) (Foutz & McIntyre, 2010).

The selectivity corresponds to the predisposition that DBS has to preferentially stimulate the intended neuronal components and can be improved if (for example) the geometry and polarity of the electrodes are changed (Butson & McIntyre, 2006), (Howell, Huynh, & Grill, 2015). This notion of stimulation adapted to the target neuronal elements is based on a feedback-controlled stimulation, that is, it can undergo an amplitude adjustment or be interrupted depending on the signal sensed uninterruptedly (this signal translates to the clinical condition of the patient) (Kühn & Volkmann, 2016). Howell et al (2015) had as objective to ramp up electrodes that increase the efficiency and simultaneously had a greater selectivity and to test them in a computational model and *in vivo*. The selectivity was achieved with the decrease of the sensitivity due to the inadequate position of the electrode, having as a consequence the reduction of the side effects. The electrode model was composed of a prototype in cylindrical form with three contact regions, wrapped by a certain (cubic) volume of brain tissue. In order for the electrode to behave as a perfect insulator, it was imposed a current density with a value of 0 A/mm^2. Electrode geometries were tested that could: (1) efficiently activate myelinated axons of passage, terminating axons and local neurons (Howell et al., 2015); (2) selectively activate the myelinated axons of passage orient parallel (to the electrode) in the direction of the z-axis instead of the myelinated axons of passage oriented perpendicular (to the electrode) in the direction of the x-axis or (3) selectively activate parallel terminating axons instead of the axons of passage (Howell et al., 2015), (Lehto et al., 2017). The diameter of the electrode had a significant influence on the construction of electrodes for efficient stimulation since its increase is related with a greater damage to the stimulated tissues. The efficiency was improved in part by the decrease in electrode impedance

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

(Wei & Grill, 2005), in part by its placing close to neuronal components. It was further concluded that there was an improvement in selectivity when multipolar configurations activated the neuronal components based on their orientation to the electrode. Contrary to expectations, there was no possible to find an electrode configuration that is equally efficient and selective to stimulate neuronal components. In addition, there is no ideal geometry or configuration that can be applied to all therapeutic targets of DBS (Howell et al., 2015).

Deep brain stimulation as safe and promising therapy in treatment of Alzheimer's disease

One of the first experiments carried out by some researchers on the DBS application as a modulation therapy of the symptoms of Alzheimer's disease arose after observing a phenomenon of recovery of some episodic memories of an obese patient when submitted to stimulation. This initial analysis allowed to deduce that it possible to reach the neuronal components underlying the memory-related neural functions, and hence to modulate their activity using fornix/hypothalamus-oriented stimulation (Hamani et al., 2008). From these inferences, two studies were carried out: a phase I trial with 6 patients (Laxton et al., 2010) and a phase II trial with 42 patients to investigate the safety and efficacy of DBS to treat dysfunctions of brain circuits linked to memory in AD (Lozano et al., 2016). The volunteer patients for these trials showed declines in these functions compatible with earlier and less severe stages of the disease. The reason for choosing patients with this profile was due to the supposition proposed by the authors that they would possess sufficient structural integrity and therefore there was reason to consider such an appropriate approach. Assuming that DBS could modify the activity of the circuits connected to the memory and, thus, to bring a potential benefit in patients of the initial stages of AD, the hypothesis was tested from the stimulation of the fornix/hypothalamus (Laxton et al., 2010), (Tsivilis et al., 2008). In fluoroscopy-guided surgery under the effect of local anaesthesia, the electrodes were implanted bilaterally in the awake patient, 2 mm anterior and above the vertical portion of the fornix, within the hypothalamus, with the most ventral contact lying 2 mm above the dorsal portion of the optic tract. After a first examination of the side effects caused by stimulation, the neurosurgeons linked the electrodes to the neural stimulator (also designed internal pulse generator). This had been implanted in the chest of the patient under the effect of general anaesthesia. The parameters chosen for each contact were: 130 Hz of frequency, pulse width of 90 μs and voltage continuously increased from 1 to a maximum value of 10V. However, due to the adverse sensations such as flushing, warmth and increased heart rate and blood pressure caused by voltage with values greater than 7V, these were adjusted to the range 3 to 3.5V (Laxton et al., 2010). The other parameters (frequency and pulse width) remained unchanged. To assess which brain regions evinced significant changes in their activity in response to stimulation, was used the method called standardized low-resolution electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002). To quantify brain glucose metabolism prior to the surgery (the baseline so as to have a comparison term) and with the stimulators functioning 1 month and 1 year after continuous DBS, PET (positron emission tomography) images were used with the glucose radiotracer. The clinical outcomes of the phase I trial (Laxton et al., 2010) showed cognitive differences (whose neuropsychological measures are expressed in the Alzheimer's Disease Assessment Scale,

Cognitive Subscale (Adas-Cog) (Rosen, Mohs, & Davis, 1984) and Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) scales) from patient to patient that can be understood as the existing variations in the severity of the illness and these relate to the functional integrity of the fornix/hypothalamus circuit (Stern et al., 1994) and in turn to the predisposition of such circuit to improve with DBS. The alterations in activity occurred so only in cerebral structures located ipsilateral to the stimulation side and demonstrated coherence with the activation by synapses of region downstream to the connectivity between fornix and hypothalamus (Laxton et al., 2010). There were an increase in glucose metabolism in regions typically more affected by AD (default mode network) (Raichle et al., 2001) and withal a decrease in glucose utilization for areas not affected by the disease (Smith et al., 2012). As before initiating, patients were taking acetyl cholinesterase inhibition medications, the authors (Laxton et al., 2010) hypothesized that metabolic outcomes were due to a long-lasting effect of these drugs in delaying the brain decline of glucose metabolism (Smith et al., 2009). However, given the nature of the study to be more focused on safety assessment rather than on efficacy of DBS, the authors concluded that the whole procedure including surgery and stimulation over the 1-year period was well tolerated and brought potential

ORIGINALES / ORIGINAL PAPERS
VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

benefits to reversing dysfunction in certain circuits and glucose metabolism (Laxton et al., 2010).

In the phase II trial (a double-blind clinical trial), to exclude the "placebo" effect included in it a control group whose patients were implanted with DBS electrodes but the stimulators were switched off. The patients were divided by age: the younger patients (less than 65) and the older patients (greater than 65). The younger patients showed a more marked cognitive decline, suggesting a greater severity of the brain pathology in comparison with the older patients or even if they had been misdiagnosed with AD (Lozano et al., 2016).

The normally chosen targets are part of the circuit of Papez (see fig.3), one of the main pathways of the limbic system and which is essentially involved in the function of memory, because it is degenerate in AD (Rajmohan & Mohandas, 2007).

Cognitive improvement

Most of the studies carried out in the application of DBS in the treatment of AD are based on DBS efficacy in mitigating learning and memory deficits in order to slow down the progress of the disease. Since cognitive decline is the most prominent symptom of the disease, researchers have done experiments to fill this effect and to delay this deterioration of memory by restoring it. For this, DBS have been applied to different brain targets that are closely related to memory function, among which: fornix (Gondard et al., 2015), (Ross et al., 2016), (Sankar et al., 2015), (Zhang, Zhang, Hu, Wu, & Zhang, 2015), midline thalamic nuclei (Arrieta-Cruz et al., 2010b), anterior nucleus of thalamus (Zhang et al., 2015), (Hescham et al., 2015), (Chamaa et al., 2016), entorhinal cortex (Hescham et al., 2015), (Zhang et al., 2015), Ca1 sub-region of hippocampus (Hescham et al., 2015), mammillothalamic tract (Hescham et al., 2015), dorsomedial portion of the ventromedial hypothalamic nucleus (Ying, Covalin, Judy, & Gomez-Pinilla, 2012), medial septal nucleus (Jeong et al., 2014) and ventral posterolateral thalamic nuclei (Chamaa et al., 2016), in order to test which brain region has a more beneficial therapeutic effect.

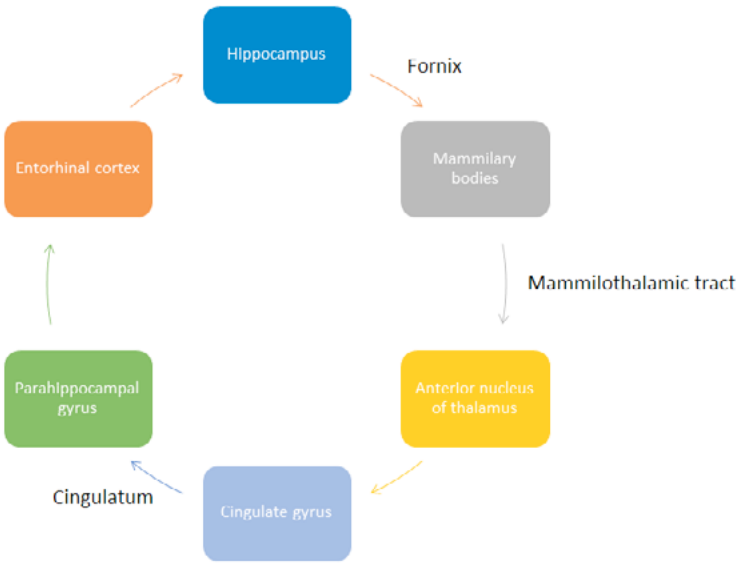

Figure 3. Circuit of Papez. General adaptation without copyright conflict. (Rajmohan & Mohandas, 2007)

Initially to test the hypothesis presented (Arrieta-Cruz et al., 2010b), in the pre-clinical phase in vivo were used rats that showed mutations in the gene coding for the amyloid precursor protein (APP), thus leading to an overexpression of the same protein. After bilateral stimulation of midline thalamic nuclei for 3 days, the animals' memory was evaluated from object recognition tasks in the so-called open field test and quantified by the recognition index. This value corresponds to a measure of the short-term memory and was calculated from the ratio between the time spent by the animal to explore the novel object and the sum of the times spent exploring the novel object and the familiar one. Mice with the mutated gene had shortterm memory shortfalls compared to wild-type mice. However, due to the stimulation, there were improvements in both memory acquisition and short-term memory (Arrieta-Cruz, Pavlides, & Pasinetti, 2010a).

Hescham et al (2015) tested DBS in animal models at different amplitudes (50 µA, 100 µA and 200 µA) and frequencies (10 Hz and 100 Hz), remained the pulse width constant at a value of 100 µs. To evaluate the behaviour of the rats, several tests were used: the object location task (measures of the spent), the open field test (Prut & Belzung, 2003) (measures of the distance travelled) and the

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

elevated zero maze (measures of the time spent), being the first two used in memory analysis and the latter for assessing anxiety. The placement of the electrodes did not cause histologic damage either when the stimulation was performed for Ca1 sub-region of hippocampus, anterior nucleus of thalamus and entorhinal cortex. The anterior nucleus of thalamus DBS showed exploration times of the objects similar to that of the control group (rats to which the electrodes were implanted but these did not undergo stimulation) in the object location test. In the open field test, the total distance travelled did not differ from that of the control group. In addition, adverse effects such as anxiety were not observed (Hescham et al., 2015). According to another study, whose stimulation parameters used were 500 µA, 130 Hz and 90 µs, it was reported that rats in the Morris water maze (Morris, 1984) were more able to memorize a platform location reference than those in the control group. But when presented to a novel object, the time spent to explore it did not show significant differences in relation to the control group. In spite of emphasizing the improvement of spatial recognition memory, the authors (Zhang et al., 2015) concluded that anterior nucleus of thalamus DBS did not show the best outcomes in spatial and recognition memory due to the fact that in the circuit of Papez, the anterior nucleus of thalamus connects with the hippocampus indirectly via the fornix and mammillary bodies pathway (Lovblad, Schaller, & Vargas, 2014). Similar results were observed in other research (Hamani, Stone, Garten, Lozano, & Winocur, 2011).

After the training session in the water maze, rats under stimulation of the entorhinal cortex spent more time in relation to the control group in the zone involving the escape platform, evidence of spatial memory enhancement (Zhang et al., 2015). In the novel object recognition test (an evaluation made on the premise that these small animals naturally tend to explore unfamiliar/ novel objects than the familiar ones) (Ennaceur, Neave, & Aggleton, 1997), the group significantly increased the value of the recognition index, that is, it showed an enhanced recognition memory in comparison with the control group as the anterior nucleus of thalamus group. As well as in the anterior nucleus of thalamus DBS, there were no indications of anxiety behaviours since the distance moved equalled that of the control group (Zhang et al., 2015). In another study carried out at the same target in the circuit of Papez, the same outcomes were observed in the object recognition task at a frequency of 10 Hz and amplitude of 200 µA. However, in the open field test initially indicated differences in the distance travelled between the DBS group and the control group, but they made an analysis after the conclusion of the test, from which they concluded that there were no relevant distance discrepancies. Taking into account its large area, the authors understood that the entorhinal cortex may not be the most suitable therapeutic target since the neural modulation is achieved through a single electrode (Hescham et al., 2015). Entorhinal cortex DBS influenced positively the spatial memory (Stone et al., 2011).

In relation to the therapeutic targets used for the application of DBS in AD or other dementia-related disease, fornix is usually chosen as the preferred area because it is the main tract to deliver signals from the hippocampus to the hypothalamus (Hescham, Lim, Jahanshahi, Blokland, & Temel, 2013). After the phase I trial, cited in Laxton et al. (2010), Shankar et al (2015) realised that only one patient had improved cognitive scores, different from that expected for an AD patient. Nevertheless, they failed to find a correlation between changes in hippocampal volume and cognitive outcomes. In the experiment carried out by Zhang et al (2015), the fornix DBS showed promising results similar to those of entorhinal cortex stimulation: significant improvement in the ability of the rats to retain a reference point, i.e., stimulation facilitated spatial memory development and auspicious outcomes in the object recognition task. Such observations are justified by direct neuronal connectivity that these brain regions (entorhinal cortex and fornix) have with the hippocampus in the circuit of Papez (Zhang et al., 2015). The hippocampus is activated due to the DBS of the fornix and so there is an increase of neurotrophic factors that play a very important part in the functions related to memory and learning (Gondard et al., 2015). Fornix DBS influences memory recall by increasing activity in some regions involved in memory retrieval (Lee, Fell, & Axmacher, 2013). In order not to damage the fibers constituting the fornix, cause of memory deficiencies, the DBS electrodes did not penetrate the bundle of fibers. *Ross et al* (2016) proposed a mechanism based on activation of the dopamine and glutamate receptors behind enhancements in cognition and memory recovery observed in AD patients who were given fornix stimulation. Responding to three fundamental questions: if the stimulation offers therapeutic benefits in memory functions, if it causes any adverse effect and what the

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

most appropriate parameters in the sense of having the desired therapeutic effect, other authors (Hescham, Lim, Jahanshahi, Steinbusch, et al., 2013) analysed the effects of DBS on animal models. Previously, the rats were injected with a substance named scopolamine that induces memory decline caused by the illness (Klinkenberg & Blokland, 2010). It being known that stimulating the limbic system, of which fornix is a part, may cause some adverse effects in the level of anxiety, a test was performed to evaluate the presence of these effects. But, as with the above studies, there were no significant differences in rats' behaviour between those under stimulation and the others in the control group. The stimulation parameters with a considerable improvement in the times spent exploring the unfamiliar object were 10 Hz + 200 μA and 100 Hz + 100 μA. Although both are efficient at improving memory performance, the 10 Hz has a disadvantage compared to the 100 Hz since the first requires higher currents (Hescham, Lim, Jahanshahi, Steinbusch, et al., 2013). A pilot clinical trial (Fontaine et al., 2013) was performed to one patient and this showed enhancements comparatively to cognitive decline hallmark of the disease.

In the Papez circuit, the Ca1 sub-region of the hippocampus receives the information related to the memory of the entorhinal cortex and transmits it through the fornix, thus being a brain area with potential to therapeutically benefit from DBS (Hescham, Lim, Jahanshahi, Blokland, et al., 2013). In a first analysis, no evidence was found on the behaviour of the rats of this effect, but a more in-depth analysis of the data after the experiment was completed showed a significant retrieval of memory under the conditions of 100 Hz, 100 μA and pulse width of 100 μs. This favouring of the formation and recall of recent episodic memory may be due to the fact that the stimulation was directed to a specific subfield of the hippocampus (Hescham et al., 2015).

Hescham et al (2015) also tested the stimulation of the mammillothalamic tract and compared it with other brain regions within the circuit of Papez such as the entorhinal cortex, the Ca1 sub-region of the hippocampus and the anterior nucleus of thalamus. In comparison to the control group, there were no changes in the memory restoration of mice under mammillothalamic tract DBS.

DBS was also applied to the dorsomedial portion of the ventromedial hypothalamic nucleus to study the plasticity of brain-derived neurotrophic factor (BDNF – a mediator of metabolism), and the authors came to the conclusion that the energy required to regulate this molecule confirms its influence on cognitive function (Ying et al., 2012).

Jeong et al (2014) stimulated the medial septal nucleus with a stimulation sequence of intermediate frequency (60Hz) to evaluate the ability of this therapy to reverse spatial memory declines induced by loss of cholinergic neurons (Winson, 1978). Data from the spatial memory test showed that the latency to reach the platform declined steadily as the training continued for all groups, indicating progressive learning of platform location. Since DBS mechanisms are not yet clear and there are no certainties about which are the most effective stimulation parameters, particularly regarding duration and location, there is a suggestion of the need for further testing in this area. On the other hand, it has been proposed that DBS applied to the medial septal nucleus positively affects spatial memory (Jeong et al*.,* 2014).

Neurogenesis and increased brain metabolism

The hippocampus corresponds to a brain region that belongs to the limbic system and that plays functions in the modulation of mood and memory, being known for its continuous neuronal regeneration (Deng, Aimone, & Gage, 2010). This hippocampal formation occurs in the subgranular zone of the dentate gyrus and is related to the connections that the hippocampus presents to the anterior nucleus of the thalamus (Altman & Das, 1965). For this reason, Chamaa et al (2016) applied DBS to the anterior nucleus of the thalamus of adult rodents in order to stimulate hippocampal neurogenesis. The stimulation was performed unilaterally in order to analyse differences in the DBS effects dependent on laterality and the rats were not under anaesthesia so that these factors (besides stress) did not interfere with the neurogenesis (Stratmann, Sall, May, Loepke, & Lee, 2010). After 3 days of stimulation, the rats were given an injection containing 5-bromo-2-deoxyuridine, a substance often used to detect proliferating cells in living tissues. The changes in neurogenesis that occurred as a reaction to the applied stimulation were analysed by imaging and quantified by the 3D quantitative microscopy technique called stereology. There was a greater amount of 5-bromo-2-deoxyuridine stained cells on the side of the subgranular zone of the dentate gyrus ipsilateral to the side of high-frequency stimulation in relation to the amount of cells found in the microscopy images performed on the contralateral side of the stimulation side and in the control group. Stimulation

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

of the anterior nucleus of thalamus significantly increased neurogenesis in the dentate gyrus ipsilateral to the side of stimulation, unlike the contralateral side which maintained neurogenesis at the same reference level as the control group (Chamaa et al., 2016), (Encinas, Hamani, Lozano, & Enikolopov, 2011). The differences in induction of neurogenesis were only at location level relative to the side of stimulation and not dependent on the animal sex since between males and females such differences were not noted. The authors (Chamaa et al., 2016) observed that there was a distinctive pattern based on the spatial distribution of neurogenesis in the subgranular zone of the dentate gyrus that made it possible to distinguish the levels of cells stained with 5-bromo-2-deoxyuridine. Thus, the rostral region showed a lower number of cells stained by 5-bromo2-deoxyuridine, i.e. it displayed a lower expression of 5-bromo-2-deoxyuridine, the intermediate region had a larger population of 5-bromo-2-deoxyuridine and the caudal region was the one with the highest number of 5-bromo-2-deoxyuridine positive cells compared to the other two regions. Thereby, the rostral region of the dentate gyrus indicated that it was not considerably affected by the stimulation applied. In other brain regions such as the neurogenic subventricular zone and the hilar zone, no appreciable discrepancies of the 5-bromo-2-deoxyuridine positive cell levels were observed between the stimulation group and the control group (Encinas et al., 2011), (Chamaa et al., 2016). In addition, they compared the results obtained from this experiment (anterior nucleus of the thalamus DBS) with the stimulation to a region that does not have direct connections with the hippocampus, the ventral posterolateral thalamic nucleus. The parameters used were the same as the type of electrodes but the neurogenesis remained unchanged at the same reference level of the control group (Chamaa et al., 2016). Toda, Hamani, Fawcett, Hutchison, & Lozano (2008) also reported restoration of hippocampal neurogenesis after stimulation applied to the anterior nucleus of thalamus.

After assessing the safety and efficacy of DBS applied to fornix in a phase I trial (Laxton et al., 2010), the authors hypothesized that the mechanism behind the slowing of cognitive decline was related to the plastic effects caused by stimulation within the memory circuit and in the whole brain. So they analysed changes in brain structure from brain magnetic resonance imaging of AD patients undergoing therapy in the aforementioned phase I trial and measured the volume of critical regions of the Papez circuit such as the hippocampus, fornix, and mammillary bodies to see if DBS made it possible to reverse the progressive neurodegeneration characteristic of the disease. In two of the six patients there was an increase in hippocampal volume as opposed to expected atrophy (Mormino et al., 2009). However, none of the other regions (fornix and mammillary bodies) showed enlargement despite the fact that these two patients presented the lowest atrophy rate of fornix and mammillary bodies. Both patients with increased hippocampal volume had an increase in hippocampal glucose metabolism, suggesting a trophic and structural effect underlying to hippocampal enlargement dependent on the ability of fornix DBS substantially enhance hippocampal metabolism. In response to stimulation, there was an increase in the volume of regions known to show atrophy in AD, such as right and left parahippocampal gyrus, right superior temporal gyrus, left inferior parietal lobe and bilateral precuneus, but also regions that are not usually affected by the illness, such as thalamus and superior frontal gyrus. The authors concluded that the latter observations were due to the proximity of these areas to implanted electrodes. Thus, Shankar et al (2015) concluded that DBS is capable of influencing brain structure and may slow or even reverse hippocampal atrophy in some patients suffering from a neurodegenerative disease since they have found evidence of structural neuroplasticity and a continuous neuroprotective effect of DBS on the Papez circuit. On the contrary, recent experiment has found no evidence of increased neurogenesis due to fornix stimulation (Hescham et al., 2017).

The brain, despite its small size, consumes a large amount of all the energy consumed by the body and thus metabolic energy significantly affects the regulation of essential brain functions such as cognitive functions (Gomez-Pinilla & Ying, 2010). Ying et al (2012) studied how hypothalamic stimulation could regulate the control of metabolism and synaptic plasticity in the hippocampus. For this, they used BDNF (an intermediate molecule between metabolism, synaptic plasticity and cognition) to evaluate both energy metabolism and plasticity involving the hypothalamus and hippocampus and divided the amount of energy consumed by the rats into mechanical energy related to physical activity and non-mechanical energy related to energy for the maintenance of basal activities (such as thermogenesis, neuronal function, ...). Stimulation at 50 Hz showed an increase in non-

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

mechanical energy consumption and BDNF, indicating that DBS causes an increase in the frequency-dependent metabolism applied.

According to Jeong et al (2014), the possible mechanism by which DBS could improve spatial memory is based on the neurogenesis of the hippocampus. In spite of neurogenesis of the adult hippocampus is limited to the subgranular zone of the dentate gyrus where new neurons are produced continuously throughout life, being that the neurogenesis is closely related to the memory dependent of the hippocampus. In the medial septal nucleus, neurons in healthy rats had intact cell bodies and dendrites structure. On the contrary, lesion, implementation and stimulation groups had appreciable injuries in the structures of the cell bodies and dendrites. Besides, a cholinergic neuron deficiency causes the reduction of the number of cells positive for a marker of adult neurogenesis in the subgranular zone of the dentate gyrus and hence in this region there is an increase in the number of apoptotic cells (Van der Borght et al., 2005).

Protein expression and cholinergic neurotransmitters

Arrieta-Cruz et al (2010b) applied DBS to midline thalamic region to investigate a new treatment method that had the ability to stop or regress the natural progression of AD. For the quantification of amyloid beta fragments (Aβ1-40 and Aβ1-42) performed an immunoassay using a colorimetric ELISA kit. The activity of α- and β-secretase was detected after the study and recording of electrical properties in cells performed in hippocampal sections. The secretase specific for the APP protein conjugated to the EDANS and DABCYL molecules was added to the brain samples. In the non-cleaved form of the APP protein, the fluorescence emissions from the EDANS molecule were suppressed by their proximity to the fraction of the DABCYL molecule. However, the APP protein when cleaved by the secretase makes possible a physical separation between the EDANS and DBCYL molecules, allowing the fluorescent signal to be observed. Thus, the enzymatic activity of the secretase is proportional to the fluorescent signal detected in the reaction. The authors reported that after high-frequency stimulation (at 50 Hz, 100 Hz and 200 Hz) there was an increase in α-secretase activity in mice containing the APP protein mutation. For the authors, there was a relationship between selective increase in the α-secretase activity and enhancement of synaptic transmission and shortterm potentiation verified upon high-frequency stimulation to isolated hippocampal sections of mice with the mutant APP protein. The improvement was nonetheless selective since it was not observed for the activity of β-secretase. In addition, stimulation altered the activity of the cellular secretase (the β-secretase) which plays a critical role in generating the amyloid beta peptide since the Aβ residue is derived from the cleavage of the APP protein by the β- and γ-secretase (Chishti et al., 2001). Because it is this peptide that derives from cleavage of the APP protein impairs the activity of the network by damaging synapses and destroying neurons. The FosB protein, a marker of neuronal activity was used to analyse neuronalfunctional-activation related to the applied stimulation. A pattern of FosB protein expression in the Ca1 sub-region of the hippocampus was observed, i.e. an increase in FosB protein expression in the Ca1 subregion of the hippocampus and in the dentate gyrus in response to DBS to midline thalamic nucleus. In conclusion, the therapeutic effect may occur through indirect mechanisms (improving cognitive status) or via direct mechanisms (modulating amyloid beta peptide accumulation in the brain) (Arrieta-Cruz et al., 2010b).

Taking into account that the gene c-Fos is expressed when the neurons transmit the information generating action potentials, Hescham et al (2015) structured the brain regions in relation to the memory processes based on the expression of this gene, with special focus on the medial prefrontal cortex and hippocampus. The rats to which stimulation to the Ca1 sub-region of the hippocampus were applied were the only ones that showed an increase in c-Fos gene expression in the cingulate cortex. But the authors also observed that c-Fos levels increased significantly in the infralimbic and prelimbic cortex both for the group of animals under DBS to the Ca1 sub region of the hippocampus and for the group under DBS to the mamilothalamic tract. While in the hippocampus more precisely in the Ca3 sub-region, there was an increase in c-Fos expression for the DBS groups to the entorhinal cortex and anterior nucleus of thalamus. Despite the outcomes, they failed to correlate the benefits of memory of the entorhinal cortex DBS with the selective neuronal activation that occurred in the hippocampus because they found no evidence that stimulation to this brain area caused alterations in neuronal activity either to the medial prefrontal cortex or to the hippocampus (Hescham et al., 2015).

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

In another study carried out about the alteration of protein expression in the hippocampus due to the high frequency stimulation applied to fornix, the authors evaluated the expression of certain proteins after different periods of time (1h, 2.5h, 5h, 25h) based on the following classification: (1) proteins that contribute to the pathology of AD, comprising tau, phosphorylated tau and APP, (2) neurotrophic factors including the BDNF, the glial cell line derived neurotrophic factor (GDNF) and the vascular endothelial growth factor (VEGF), and (3) synaptic markers of long-term potentiation and plasticity, including synaptophysin and growth associated protein 43 (GAP-43). In addition, they analysed the expression of the gene cFos that regulates neuronal excitability. The expression of the cFos neuronal activation marker increased only 2.5h after the stimulation since its level decreased to the reference level. This increase was expressive mainly in the dentate gyrus and Ca1 and Ca3 sub-regions of the hippocampus. Contrary to what was expected, the proteins involved in the molecular pathogenesis of the disease did not undergo significant changes in relation to the expression value of such proteins in the control group. But it was not possible to detect amyloid beta, since the mice were too young and therefore had insignificant concentrations of Aβ40 and Aβ-42. The neurotrophic factors BDNF and VEGF had the same expression pattern as the cFos gene: they increased expression level 2.5h after stimulation and meanwhile the value returned to the reference level. While the other neurotrophic factor analysed, GDNF, did not differ in expression values comparatively to those in the control group. There was an increase in the synaptic proteins GAP-43 and αsynuclein 1h and 2.5h after stimulation, the latter being (2.5h) the most marked increases. The expression of the synaptophysin protein also increased 2.5 hours after. In relation to chaperone proteins no effects on its expression were observed in the hippocampus. Thus, neurogenesis and memory improvement were measured by neurotrophic factors expression values and increased hippocampal volume by growth factors and synaptic proteins (Gondard et al., 2015).

The brain shows a loss of cholinergic neurons in the basal forebrain spanning the medial septal nucleus, reduced levels of acetylcholine, and a decrease in the acetylcholine synthesis enzyme in the cerebral cortex (Bierer et al., 2002). It is through acetylcholine, GABA and glutamate that the medial septal nucleus plays its role in regulating hippocampal activity. It decreased the number of immune-positive cells of choline acetyltransferase, which corroborates the effect of degeneration of cholinergic neurons in the basal forebrain. The activity of acetylcholine increased by a medial prefrontal cortex whereas in the hippocampus there were no differences compared to the normal group (Jeong et al., 2014).

The DBS applied to the central thalamus regulates a cortical network associated with the behaviour of skills and learning. Underlying the stimulation, Lin et al reported a possible molecular mechanism involving the activation of neuronal projections of the central thalamic lateral nucleus for the striated dopaminergic neurons and the regulation of the c-Fos, the dopamine receptor and the acetylcholine receptor of the striatum on the basis of modulation of the superior cognitive learning function (Lin et al., 2016).

Conclusion

Among all the targets addressed from the point of view of improving the symptoms described for AD, whether in improved cognitive decline, neurogenesis and brain metabolism of glucose and protein expression and cholinergic neurotransmitters, there was a pattern which was repeated: all these beneficial effects were somehow associated with the circuit of Papez. In relation to delaying cognitive impairment, the entorhinal cortex despite showing significant improvements is not the most appropriate due to its large area. The dorsomedial portion of the ventromedial hypothalamic nucleus, the medial septal nucleus and the Ca1 sub-region of the hippocampus had favourable outcomes. Such as fornix with the exception of this being a bundle of myelinated fibers having an appropriate and accessible size for neural modulation in rodents and humans. With regard to the improvement of neurogenesis and glucose metabolism by the hippocampus, both the anterior nucleus of thalamus, the dorsomedial portion of the ventromedial hypothalamic nucleus and the medial septal nucleus such as fornix have shown promising therapeutic results. However, with respect to fornix it was not possible to find a correlation between the presented neurogenesis and the clinical cognitive scores of the patients. The protein expression (tau, Aβ,..) was reduced as well as increased cholinergic neurotransmitters when DBS was applied to the following targets: the midline thalamic region, the Ca1 sub-region

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

of the hippocampus and the medial septal nucleus. The fornix did not have the expected effect due to the young age of the animals studied, this being a limitation of the experiment carried out for the fornix to evaluate the proteins and neurotransmitters involved in the pathology of the disease. Therefore, I suggest the use of older rats (or, in the limit, transgenic rats in order to mimic AD). In conclusion, fornix DBS is the most used in the AD treatment but more research is needed to better understand and decide which the most appropriate therapeutic targets are and which parameters of stimulation combine efficacy and safety in the application of this therapy. So that in the near future this can be successfully practiced for patients with AD and thus there is hope for a valuable and effective treatment for this neurodegenerative disease that is expected to reach more and more people around the world in the coming decades.

As well remembered by Oliveira (2010), the use of instrumental enrichment strategies should be at the forefront of intervention in Alzheimer's disease, and the propositions of the use of deep brain stimulation clearly fit in this new perspective that neuroscience, in clear consolidation on degenerative diseases, helps us, in a period of time that should raise our hope to look at these pathologies, as chronic and not as terminal (in a near future).

Parra-Bollânos, Fernández-Medina & Martínez-Restrepo (2014) stress the importance that this view of neurodegenerative disorders could improve in de quality of life of patients and caregivers.

Finally, in a very wise intervention, Polanco-Carrasco (2016) stress the importance to try to highlight, at this historic level of scientific knowledge, the weight that could help or even invite psychologists to learn and help on the incredible field of degenerative disorders, and in Alzheimer's Disease in particular.

List of abbreviations

Aβ – Amyloid Beta; AD – Alzheimer's Disease; Adas-Cog – Alzheimer's Disease Assessment Scale, Cognitive Subscale; APP – Amyloid Precursor Protein; BDNF – Brain-derived Neurotrophic Factor; DABCYL – 4-(dimethylaminoazo)benzene-4-carboxylic acid; DBS – Deep Brain Stimulation; EDANS – 5-((2-Aminoethyl)amino) naphthalene-1-sulfonic acid; ELISA – Enzyme-linked Immunosorbent Assay; GAP-43 – Growth Associated Protein 43; GDNF – Glial Cell Line-Derived Neurotrophic Factor; MMSE – Mini Mental State Examination; NMDA – N-methyl-D-aspartate; sLORETA – Standardized Low Resolution Brain Electromagnetic Tomography; VEGF – Vascular Endothelial Growth Factor.

Received: 04/07/2017
Accepted: 20/12/2017

VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202

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VOLUMEN 12. NÚMERO 1. ENE-ABR 2018. DOI: 10.7714/CNPS/12.1.202