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Article

Intracranial Self-Stimulation and Memory in Rats: A Sistematic Review

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ABSTRACT

Background: Intracranial self-stimulation (ICSS) is a technique by which rats press a lever to stimulate their brains through an electrode chronically implanted in brain reward areas. Currently only two laboratories in the world, one in India and one in Spain, are intensively studying the effect of this kind of deep brain stimulation on learning and memory. This paper will present the main findings. **Methods:** Different groups of young and old healthy and brain-damaged rats with electrodes implanted in the medial forebrain bundle received a treatment of ICSS after being trained in several paradigms of implicit and explicit learning. Memory was tested over short and long-term periods. Structural and molecular post-mortem analyses of their brains were examined in relation to memory results. **Results:** ICSS enhances implicit and explicit memory, especially in animals showing poor performance in the learning tasks, such as brain-damaged subjects. At the structural and molecular level, ICSS enhances size and dendritic arborization and promotes neurogenesis in specific hippocampal areas. ICSS also regulates the expression of genes related to learning and memory. **Conclusions:** Through activating reward and neural plasticity mechanisms, ICSS in the medial forebrain bundle is a promising technique for memory-enhancing treatments.

Autoestimulación Eléctrica Intracraneal y Memoria en Ratas: una Revisión Sistemática

Palabras clave:
Autoestimulación eléctrica intracraneal
Potenciación de la memoria
Haz prosencefálico medial
Refuerzo
Plasticidad sináptica
Estimulación cerebral profunda

RESUMEN

Antecedentes: La autoestimulación eléctrica intracraneal (AEIC) es un tipo de estimulación cerebral profunda autoadministrada a través de un electrodo implantado de forma crónica en áreas cerebrales de la recompensa. Actualmente, dos laboratorios en el mundo, uno en India y otro en España, están estudiando intensivamente el efecto de este tipo de estimulación cerebral reforzante sobre el aprendizaje y la memoria. Aquí se presentan los principales hallazgos. **Métodos:** Diferentes grupos de ratas sanas y con daño cerebral, jóvenes y viejas, con electrodos implantados en el haz prosencefálico medial recibieron un tratamiento de AEIC después de ser entrenados en diferentes paradigmas de aprendizaje. La memoria se evaluó a corto y largo plazo. **Resultados:** La AEIC mejora la memoria implícita y explícita, especialmente en animales con un bajo rendimiento o con daño cerebral. A nivel estructural y molecular, la AEIC estimula del desarrollo de la arborización dendrítica, promueve la neurogénesis en el hipocampo y regula la expresión de genes relacionados con plasticidad, aprendizaje y memoria. **Conclusiones:** La AEIC en el haz prosencefálico medial, al activar mecanismos de recompensa y de plasticidad neural, constituye un tratamiento prometedor para la mejora de la memoria.

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After its discovery by James Olds and his student Peter Milner in 1954 (Olds & Milner, 1954), intracranial self-stimulation (ICSS) became a new window into the research of the brain. ICSS is a deep brain stimulation technique that activates the neural systems involved in reward and pleasure. Consequently, subjects with an electrode in these areas continuously perform an operant response such as (in rats) pressing a lever, in order to self-administer electrical stimulation. In several species, ICSS response is obtained with electrodes located in several cortical and subcortical regions of the brain. However, the location where ICSS behavior is achieved more easily, is more persistent, and generates higher response rates, is the medial forebrain bundle (MFB) as it passes through the lateral hypothalamus (LH) (Milner, 1991). While ICSS activates the mesolimbic dopaminergic system, similarly to other homeostatic and incentive rewards, evoked dopamine release in the basal forebrain diminishes during ICSS. It is suggested that dopamine could be more related to novelty or reward prediction than to reward itself (Garris et al., 1999), as well as to motivation (Volkow et al., 2017). Moreover, dopamine itself is involved in the molecular and neurophysiological mechanisms underlying hippocampal synaptic plasticity and long-term memory consolidation (Caragea & Manahan-Vaughan, 2022; Jay, 2003).

Shortly after its discovery, in the late 1970s inspired by the positive effect of reinforcement on learning and memory, it was hypothesized that ICSS could - as food does –facilitate the learning process and subsequent memory (Huston et al., 1975). Based on the "law of effect' hypothesized by Thorndike in 1933, early studies showed enhancement of memory consolidation by post-training stimulant treatments (electroconvulsive shock) (Madsen & McGaugh, 1961). Pioneering studies also appeared that demonstrated the benefits of post-training reinforcing electrical stimulation (and ICSS) on a variety of tasks, such as sensory preconditioning, aversive and appetitive classical conditioning, and operant conditioning of appetitive and aversive responses (Coulombe & White, 1980; 1982; Huston et al., 1977; Huston & Mueller, 1978; White & Major, 1978).

According to Huston's former reinforcement theory (Huston et al., 1977), an operant response leaves a trace of immediate memory, and an enhancer applied during the labile period of short-term memory could facilitate long-term memory. Thus, administering an ICSS treatment after training to learn a task could promote the strengthening of the association that had been created. However, the results of subsequent studies suggest that the initial theory based on the relevance of a pairing between the learning process and the rewarding event of ICSS does not explain all the effects that ICSS can have on learning and memory. Thus, it has been observed that neither the contingency between training and the administration of ICSS, nor the reinforcing component of stimulation, seem critical to obtain memory improvement. They have shown, on the one hand, that chronic ICSS administration can predispose to better learning in the future or even facilitate the long-term persistence of a previously created memory (Huguet et al., 2020; Velley & Cardo, 1976; 1982; Yoganarasimha et al., 1998) and, on the other hand, that the stimulation of the MFB is capable of facilitating conditioning even when it is administered at levels below the rewarding threshold (Destrade & Jaffar, 1978). In this regard, one of the characteristics of ICSS in the MFB-LH is the propagation of a generalized arousal state (Nieh et al., 2016; Wright & Craggs, 1977). Considering that a modulation of the arousal states could result in the positive enhancement of memory acquisition and consolidation (Cahill & McGaugh, 1998), it cannot be ruled out that the arousal generated by ICSS would be involved in ICSS's effects on memory. Moreover, the MFB is a major pathway connecting the limbic forebrain, midbrain, and hindbrain (Bielajew & Harris, 1991), so that its stimulation can activate a wide range of brain regions related to learning and memory.

Although the use of brain stimulation in different brain areas to improve memory has been extensively studied in animal models for a long time, the increasing use of Deep Brain Stimulation (DBS) in the clinic to modulate the activity of dysfunctional circuits relevant to specific diseases has increased the interest in laboratory animal studies, which could guide future clinical studies. Initially investigated for Parkinson's disease, DBS has also been studied for treating depression and other psychiatric disorders (Lyons, 2011). Particularly interesting are the studies investigating whether DBS can improve human memory in the context of Alzheimer's disease. To date, most studies of DBS for the treatment of memory deficit, both in clinical trials and in animal models, have targeted brain regions involved in memory (such as the fornix or entorhinal cortex) or in cholinergic activation (such as Basal nucleus of Meynert) (Aldehri et al., 2018). One key question is which brain areas should be best targets of electrical stimulation for the therapeutic application for long-lasting cognitive improvement. Unlike other brain targets of DBS, reinforcing stimulation of the MFB simultaneously activates circuits related to the reinforcement itself and a wide variety of regions involved in several types of memory, such as the septum-hippocampal circuit, the amygdala, certain thalamic nuclei, or the prefrontal and retrosplenial cortices (Aldavert-Vera et al., 2013; Kádár et al., 2016; 2018).

For more than thirty years, our laboratory has been one of only a few exploring the capacity of MFB-ICSS –especially when administered contingently to training- to improve learning and memory in young and old, as well as in healthy and brain-damaged. What follows is a report of the main findings and suggestions.

1. ICSS improves both implicit and explicit learning tasks

ICSS has been shown to improve a variety of implicit learning and memory tasks. In an initial parametric study (Segura-Torres et al., 1991), rats were trained in a two-way active avoidance task (2wAA) and allowed different amounts of ICSS immediately after each of the five conditioning sessions. Stimulated rats showed a greater slope in the learning curve, eventually reaching levels of conditioning much higher than the unstimulated animals. This increase was higher when the number of ICSS trains was also increased from 500 to 2500 in distinct groups of subjects and lasted until 10 and 30 days later. In another experiment, we were able to show a similar capacity of optimal ICSS treatment (2500 trains) to improve acquisition and retention of the same task when it was administered not later, but immediately before, every 2wAA session (Segura-Torres et al., 1988). An implicit visual discrimination task in the Morris water maze was also facilitated by post-training ICSS (García-Brito et al., 2017). In this case the treatment was also administered immediately after each of five conditioning sessions and its effects on retention and reversal were evaluated 72 hours later. It was observed that ICSS subjects committed fewer errors

than non-stimulated subjects and adopted more accurate trajectories in the maze during the task acquisition. The memory improvement was maintained in the retention test, after 72 hours, and stimulated animals also experienced more difficulties than control animals during the reversal of the same learning, reflecting, as expected, that the strengthening of memory consolidation can compromise cognitive flexibility in implicit memories.

Another series of experiments also demonstrated the capacity of post-training MFB-ICSS to improve explicit learning and memory tasks. In the first one (Soriano-Mas et al., 2005), the effect of ICSS administered after every daily session of a delayed spatial alternation task in a T maze, which seems to depend on the integrity of the hippocampus, were tested. In three consecutive learning phases, it was attempted to make the tasks increasingly difficult: 10-s delay, 30-s delay and randomly inverting the starting position of the animals to make their response more dependent on allocentric cues. Every phase finished when the rats achieved a fixed learning criterion. In the last phase, only the rats that received ICSS were able to correctly choose the reinforced arm when the starting arm in the choice-run was opposite (180º) to the one in the sample run. This data suggested the capacity of post-training ICSS treatment to facilitate the flexible expression of the previously spatial learned response. In another experiment, better described below, we were pioneers in demonstrating the capacity of post-training ICSS to facilitate learning and relational or explicit memory in the spatial Morris water maze task (Ruiz-Medina, Morgado-Bernal, et al., 2008).

These results suggest that ICSS appears to have a general ability to facilitate tasks that depend on different brain memory systems.

2. ICSS facilitates memory consolidation and reconsolidation, but it does not affect retrieval

In an early experiment aimed at comparing the effects of MFB-ICSS upon processes of consolidation and retrieval, independent groups of rats were trained in a single acquisition session of 2wAA task and tested 24 hours later in a retention test. One experimental group received the MFB-ICSS treatment immediately after the acquisition session (post-training) and another group received the same treatment immediately before the retention session (pre-retention). Since, as we had observed, the effects of ICSS on memory seem to be dependent on the initial performance level shown by the subjects, the possible influence of initial training on the ICSS effect was also studied in two training conditions, 30 and 50 trials. As expected, post-training ICSS facilitated the 24-hr retention in both groups (30 and 50 trials). In contrast, performance in the retention test was not facilitated by the pre-retention ICSS treatment, suggesting that the ICSS - under these conditions – does not have a direct role in memory retrieval (Redolar-Ripoll et al., 2002). In a subsequent experiment (Soriano-Mas et al., 2007) we tried to facilitate retention by administering the ICSS treatment after memory reactivation instead of administering it pre-retention. Therefore, memory was reactivated 24h after the acquisition session of the same task and the reminder consisted of a 3-s exposure to the conditioned stimulus (a tone) in the same context as the original learning. The ICSS treatment was administered immediately after reactivation and retention was evaluated immediately or 24 hours later in independent groups of rats. Like in the previous experiment, no effect of ICSS was observed in the immediate retention test, whether the animals had been exposed to the reminder or not. However, retention had improved when tested 24 hours after the ICSS treatment alone. In addition, similar enhancement was obtained after the exposure to the reminder alone. However, the greatest memory improvement was observed in the group that received ICSS treatment after exposure to the reminder. Not only do these results indicate that ICSS alone - without being contingent to training - can have positive effects on future retention without the need for memory to be reactivated, but also that ICSS can affect the reconsolidation process.

3. ICSS can improve the extinction of an avoidance response

Because post-training ICSS facilitates the acquisition of ongoing learning, we are trying to find out whether, when administered after the exposure of a conditioned stimulus that has never been preceded by the unconditioned stimulus, it could also be effective in facilitating the extinction of the conditioned response. In an initial experiment, we trained the rats on three 50-trial sessions, one daily, of a 2wAA response in order to get a high conditioning level. Afterward the rats were exposed to two extinction sessions, one daily, of 50 trials each as well, and tested on spontaneous recovery 28 days later in the same context in which they had been trained. Compared to the non-stimulated rats, the rats that received ICSS after each of the extinction sessions showed a higher level of extinction in the second one, which was done 24 hours after the ICSS treatment administration. However, both groups showed similar relapse of the conditioned response in the spontaneous recovery test. These preliminary results suggest that ICSS is also able to exert a positive effect on the extinction process of an avoidance conditioned response but so far, its effect does not seem to be strong enough to be maintained and thus prevent the long-term spontaneous recovery of the conditioned response (Huguet et al., 2017).

4. ICSS equalizes the performance of poor and good learners

To study the duration of the facilitating effect of post-training ICSS on the consolidation of memory, four different retention times (24 hours, 7, 15 or 60 days) were tested in independent groups of rats after a massed (50 trials) 2wAA acquisition session followed by an ICSS treatment session (Aldavert-Vera et al., 1996). In the control subjects, the higher retention performances were observed in the 7- and 15-day tests. However, the ICSS treatment improved the 24-hr retention compared with its control group, allowing the treated subjects to achieve the same level of performance on the 24-hr retention session as the non-stimulated rats in the 7-day retention test —seven days later. No less surprising was the fact that in the 24-hr group the improvement was stronger in the subjects with a low level of conditioning. This result suggests that post-training ICSS could be especially effective when the task turns out to be more difficult or in conditions of less training, circumstances in which the treatment is supposed to have a greater margin for improvement. This possibility was confirmed in a subsequent experiment specifically designed to determine whether ICSS was able to improve memory consolidation in rats exposed to little training (Ruiz-Medina, Redolar-Ripoll, et al., 2008). This time

rats received only a brief acquisition session (5 trials) of 2wAA immediately followed by the ICSS treatment. Forty-eight hours later, in a retention test, we observed a significant improvement when the treated rats were compared with the control ones. This effect lasted for one week.

5. Facilitation of conditioning by post-training ICSS is also possible in old rats

In order to determine if the facilitative effects of ICSS are also possible in old rats, 18-month-old rats were trained in the 2wAA task for five consecutive days following the same distributed conditioning protocol that had been previously used for young rats. The ICSS treatment, which was administered post-training after each conditioning session, led to a significant improvement in acquisition of the task. However, memory enhancement was not maintained long-term as effectively as in young rats (Aldavert-Vera et al., 1997). It is noteworthy that the strongest effect of ICSS in old rats was observed when they had a severe memory deficit, which was fully recovered by ICSS treatment, as described below (Redolar-Ripoll et al., 2003).

6. ICSS is able to reverse learning and memory deficit in brain damaged rats

One of the most impressive capacities of ICSS is the reversal of the deleterious effects caused by injury to brain structures important for learning and memory. We have been able to show and replicate this in several experiments in our laboratory. In an initial work, we tried to ameliorate the conditioning deficit induced by an electrolyticsion of the parafascicular nucleus (PF), in both young-adult and aged rats (three and 18 months respectively) (Redolar-Ripoll et al., 2003). The PF in rats belongs to the posterior intralaminar nuclei of the thalamus, strategically located in the middle of the brain, and related to several functional systems. Like the ascending reticular activating system and the basal ganglia-thalamocortical circuit, the PF is part of the brain arousal systems, and is related to cortical activation and maintenance of states of consciousness underlying attention, learning and memory (Tsai et al., 2016; Varela, 2014). While electrical stimulation of intralaminar thalamus enhances the performance of various kinds of learning tasks in rats (Vale-Martínez et al., 1998), PF lesion impairs it (Guillazo-Blanch et al., 1995; Quiroz-Padilla et al., 2006). This evidence suggests that PF could act on some component shared by different learning or memory systems. In the above-mentioned experiment, after a PF lesion or a sham lesion, rats received a daily session of 2wAA until a fixed learning criterion was achieved. Half of the sham and PF lesioned rats were given an ICSS session after every conditioning session, while the rest of the rats did not receive any stimulation. Surprisingly, the ICSS treatment not only abolished the detrimental effects of PF lesions observed in both young and aged rats, but also further improved conditioning in lesioned rats. Moreover, these effects were even more powerful in aged than in young rats. Subsequently, we questioned whether ICSS would also be able to compensate for the impairment caused by the damage of other brain structures belonging to neuroanatomic systems more critically implicated in the task used, active avoidance. In one study (Segura-Torres et al., 2010), damage was induced to the basolateral nucleus of the amygdala (BLA), which is involved mainly in the instrumental component of active avoidance conditioning (Amorapanth et al., 2000). This time the ICSS treatment was able to completely reverse the disruptive effect of the BLA lesion upon 2wAA and even to improve learning in BLA damaged rats compared to controls. This recovery effect lasted for ten days. Another complementary study of the same experiment allowed us to differentiate the strong recovery effects of the ICSS treatment from the slight effect caused by overtraining the same conditioning response. Finally, in a third series of experiments (Kádár et al., 2014), we observed that bilateral lesions comprising over 40 % of the tissue of the lateral amygdala (LA), which is critically involved in the classical conditioning component of the avoidance task (Amorapanth et al., 2000), completely prevented 2wAA acquisition and retention. However, even in these severe conditions, the functional deficit was fully counteracted by the post-training ICSS treatment, so that even damaged animals treated with ICSS came to present better performance than the controls (which had no lesion). Similar results have also been shown in rats with fornix lesion and with the administration of stimulating treatment in the ventral tegmental area (Yoganarasimha & Meti, 1999).

More recently, the group of Shankaranarayana Rao has also found that chronic ICSS of the LH-MFB can ameliorate learning deficits induced by a clomipramine model of depression, which induces behavioral despair and anhedonia, in rats. Interestingly, this amelioration of learning impairment was associated to reduced volume loss and to the restoration of monoamine metabolism in the prefrontal cortex (Chakraborty et al., 2019). Therefore, as suggested by the authors, chronic brain stimulation rewarding experience could be a potential treatment strategy for the reversal of learning deficits in depression and associated disorders.

7. Neural mechanisms of the facilitative effects of ICSS

Altogether, our results show that MFB-ICSS treatment administered both post-training and non-contingent to training improves the learning of tasks of both the implicit and explicit categories, accelerates memory consolidation and reduces the performance differences between poor and good learner rats. It is also able to restore learning and memory capacities after the damage of certain brain areas, in rats.

These results, and the fact that ICSS gives rise also to arousal and cortical desynchronization, suggest that ICSS could improve memory through non-specific arousal pathways, or the simultaneous activation of various brain structures related to different memory systems. Therefore, to find the mechanisms underlying this positive modulation, various works have been carried out to determine structural and molecular changes induced by MFB-ICSS that could be linked to behavioral improvements.

7.1. Structural changes

Initially, we focused on the effects of ICSS on structural plasticity. Intracellular injections of *Lucifer yellow* were used to assess morphological changes in hippocampal neurons that might be specifically related to the facilitative effect of post-training

MFB-ICSS on the acquisition and retention of a spatial task in the Morris water maze. Stimulated animals showed faster and better performance than the non-stimulated ones, an improvement that was also evident in a probe trial three days after the last training session. The neuromorphological analyses revealed an increment in the size and branching complexity of apical CA1 dendritic arborization in the ICSS-treated subjects as compared to controls. Increased spine density was also observed in the CA1 field in ICSS animals, whereas no effects were observed in DG cells (Chamorro-López et al., 2015). These results show that MFB-ICSS can promote branch-specific formation of dendritic spines after learning and support the hypothesis that ICSS facilitation of the acquisition and retention of a spatial memory task could be related to structural plasticity in hippocampal cells. This idea is consistent with the results obtained by stimulating, for 10 days and not contingent on training, other regions of the reward nervous system, such as the ventral tegmental area, which showed the positive effects of ICSS proactively on structural plasticity and learning (Shankaranarayana Rao et al., 1998; Yoganarasimha et al., 1998).

Furthermore, the ICSS-related plasticity of the hippocampus does not seem to be exclusively related to hippocampal-dependent learning, as we demonstrated in another experiment addressed to explore the effect of ICSS on short-term extinction and long-term spontaneous recovery of an avoidance response. In this study, hippocampal mossy fiber sprouting in the oriens stratum of areas CA3 and CA2 was observed because of ICSS treatment (Huguet et al., 2017). Other studies (Yang et al., 2014) have shown that pyramidal neurons activated during learning of a motor task are reactivated during subsequent non–REM sleep, and that disrupting this neuronal reactivation prevents branch-specific spine formation. Similarly, ICSS could also reactivate specific neurons involved in spatial task or in other kinds of tasks, by strengthening the spines and synapses formed during learning acquisition.

Apart from morphological plasticity, some data are also in favor of an effect of ICSS on neurogenesis, another relevant form of structural change related to learning and memory. In a microarray study of the hippocampus, we showed that an acute ICSS treatment induced the expression of neurogenesis and neuroprotection related genes in 14-week-old rats (Huguet et al., 2009). Similarly, Takahashi (2009) found that the activation of the reward pathway via ICSS at the MFB (1h/day for 3 days) appears to enhance cell proliferation in the hippocampal DG of mice and rats. Therefore, we recently conducted an experiment to determine whether ICSS treatment is also able to promote the proliferation of newborn cells in the hippocampus. We showed that a daily ICSS session for 10 days not only contributed to the improvement of remote memory maintenance, but also increased the number of DCX-positive cells in the DG, indicating a higher amount of new-born cells within the granular layer of 7-month-old rats (Huguet et al., 2020).

7.2. Molecular changes after post-training ICSS alone

In order to identify potential signaling pathways and cellular processes involved in the aforementioned ICSS-mediated learning and memory improvements, we investigated the influence of ICSS on hippocampal gene expression. In the afore mentioned microarray study (Huguet et al., 2009), we used immunohistochemistry to demonstrate a rapid induction of c-Fos expression in hippocampal CA3 and DG areas caused by ICSS. Then, using microarray, we showed that ICSS also modulated the expression of 62 hippocampal genes 70 min after the treatment. Most of the proteins encoded by these genes, such as Pde1a, are part of the signal transduction machinery or are related to antiapoptosis, such as Hspa1a. Importantly, 10 of the regulated genes have been previously associated with learning and memory or neural plasticity, including Cart, Adcyap1, Sgk, Ret, and c-Fos. The fact that the c-Fos gene was differentially expressed in our microarray experiments validated the findings from immunohistochemical studies mentioned above. In addition, using quantitative real-time polymerase chain reaction (PCR), we confirmed the observed expression changes for several of the genes identified by the microarray analyses. Again, in a subsequent microarray data analysis, we showed effects of the ICSS on hippocampal gene expression that lasted for a longer time -4.5 hours- (Kádár et al., 2013). MFB-ICSS resulted in 65 significantly regulated genes. In particular, the expression of CREB-dependent synaptic plasticity related genes (c-Fos, Arc, Bdnf, Ptgs-2 and Crem and Icer) was regulated in a time-dependent manner following treatment administration. Moreover, ICSS induced a significant increase in Arc protein expression in CA1 and DG hippocampal subfields. All this empirical evidence supports the hypothesis that the effect of ICSS on the improvement or restoration of memory functions might be mediated by increased hippocampal expression of activity-dependent synaptic plasticity related genes, including Arc protein expression, similar to the neural mechanisms that have been related to memory consolidation.

As the ICSS has been shown capable of facilitating different tasks dependent on different brain memory systems, similar changes to those found in the hippocampus can be assumed in other memory-related brain regions. In another set of experiments also using PCR, we tested the effects of the MFB-ICSS on the expression of several genes in the amygdala, which is involved in 2wAA conditioning, a task certainly facilitated by post-training ICSS. A bilateral increase in c-Fos protein expression in LA and BLA amygdalar nuclei was showed after the treatment. We also found that c-Fos, BDNF, Arc, ICER, COX-2, Dnajb1, FKpb5 and Ret genes were upregulated in the amygdala 90 min and 4.5 h post (Kadar et al., 2011). These genes are known to be involved in two main functions. On one hand, BDNF, Arc and ICER are functionally associated with the cAMP-responsive element-mediated gene transcription molecular pathway, which plays a pivotal role in memory. On the other hand, Dnajb1 and Ret are associated with protein folding, required for plasticity and neuroprotection.

7.3. Molecular changes after conditioning followed by ICSS

A relevant aspect to be addressed was whether the molecular mechanisms activated by the ICSS, such as the expression induction of some Immediate Early Genes (IEGs), were also related to their functional or cognitive effects. Therefore, we studied the effects of post-training ICSS on both 2wAA retention and on the pattern of c-Fos and Nurr1 expression. The results showed that the 2wAA conditioning alone increased the

expression of the two analyzed IEGs in several hippocampal areas, and 2wAA retention increased Nurr1 expression in the amygdala. Post-training ICSS treatment, as expected, facilitated the 48-h retention of the task and increased the number of c-Fos and Nurr1 positive cells in almost all the brain regions studied when it was measured 70 min, but not 48 h, after the stimulation. The responses of both activity-induced IEGs to ICSS were examined not only as markers of neural activation, but because of their reported role in the neural plasticity occurring during learning and memory formation. It is noteworthy that, in CA3, both 2wAA acquisition and ICSS each separately increased c-Fos expression. However, this increase was greater when both conditioning and stimulation were combined (Aldavert-Vera et al., 2013). Nevertheless, this c-Fos induction was only observed after the acquisition session and not after the retention test at 48 h, when the ICSS improving effect was observed on memory. Therefore, c-Fos expression at the time of the 2wAA retention test in the retrosplenial cortex (RSC), a hippocampus-related brain region more closely involved in long-lasting memory storage, was measured. The most interesting result was that ICSS-treated animals, which showed a higher retention level, also expressed a significantly higher density of c-Fos positive cells in the RSC, specifically in layer V of the RSC granular cortex, than animals that were only stimulated or trained (Kádár et al., 2016). Arc-related synaptic plasticity response induced by ICSS has also been observed not only in the previously mentioned HPC, RSC and amygdala, but also in other learning-related areas such as the dorsolateral thalamus (Kádár et al., 2018). All the previous results suggest that plasticity-related protein activation in brain regions such as the hippocampus, the amygdala or the retrosplenial cortex may be involved in the positive modulatory effects of ICSS on memory consolidation.

8. Discussion

The results obtained by other groups as well as in our laboratory, have shown that ICSS is a type of rewarding deep-brain stimulation able to modulate the activation of many brain regions related to learning and memory. It has been shown that ICSS treatment can facilitate a wide variety of tasks - both implicit and explicit – in healthy rats, in aging rats and in animals with memory deficits associated to brain damage or to some models of psychiatric disorders. Moreover, the results suggest that MFB-ICSS seems to activate plasticity mechanisms that are like the ones involved in the learning process itself, both structurally and molecularly. This is explained by the fact that ICSS stimulation can activate critical genes in several areas related to learning and memory, like the hippocampus and the amygdala. Research must now continue exploring how these genes change the molecules involved in the facilitation of cognitive processes. Currently, more novel and safer non-invasive brain stimulation techniques, like transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS), are available for memory enhancement that also hold promise as effective treatments of neurodegenerative diseases, mental disorders, or simply for cognitive enhancement, in humans. However, experimental ICSS in animal research is still required to determine the most relevant brain targets of stimulation. In addition, to understand the underlying genetic and molecular mechanisms through which ICSS treatment facilitates memory in rats could help to improve the parameters and conditions of application for a more effective administration of other stimulation treatments in the human brain after several conditions, such as neurodegenerative diseases or acquired brain injury.

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