

# Evaluation of Li-TMS as an intervention to enhance cognitive performance in university students

## *Li-TMS Enhances cognitive performance*

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Raúl Sampieri Cabrera participated in the design of the project, design of the stimulation protocol, applied the stimulation sessions, analyzed the results and wrote the article.

Erandi Pérez and Alan Oviedo participated in the design of the project, design of the stimulation protocol, analysis of the results and writing of the article.

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### Abstract

**Background:** Low-intensity transcranial magnetic stimulation (Li-TMS) is a non-invasive neuromodulation technique with reported effects on various pathologies. **Objective:** To evaluate the effect of Li-TMS on university students using the Digit Symbol Substitution Test (DSST). **Methods:** Thirty medical students from UNAM were selected and divided into two groups: experimental and control, participating in a randomised, single-blind controlled trial. The experimental group received Li-TMS at 25 Hz and 50% intensity for 10 days, while the control group received sham stimulation. **Results:** Sham stimulation did not produce significant changes in the control group ( $p > 0.05$ ), whereas the experimental group showed a significant increase in post-intervention scores ( $p < 0.05$ ). Furthermore, inter-group analysis confirmed better cognitive performance in the experimental group after the intervention ( $p < 0.05$ ). **Conclusion:** Li-TMS is an effective tool for improving specific cognitive skills in healthy young individuals. Although these findings are promising, it is suggested to expand the sample size and employ functional neuroimaging to understand underlying mechanisms and explore educational applications.

**Keywords:** Li-TMS; cognitive performance; DSST; neuroscience; cognitive training.

### Resum

**Antecedents:** La estimulació magnètica transcranial de baixa intensitat (Li-TMS) és una tècnica de neuromodulació no invasiva amb efectes reportats en diverses patologies. **Objectiu:** Avaluar l'efecte de la Li-TMS en estudiants universitaris utilitzant la prova de substitució de símbols i dígits (DSST). **Mètodes:** Es van seleccionar 30 estudiants de Medicina de la UNAM, dividits en dos grups: experimental i control, que van participar en un assaig controlat aleatoritzat i cec simple. El grup experimental va rebre Li-TMS amb 25 Hz i 50% d'intensitat durant 10 dies, mentre que el grup control va rebre una estimulació simulada. **Resultats:** L'estimulació simulada no va produir canvis significatius en el grup control ( $p > 0.05$ ), mentre que el grup experimental va evidenciar un augment significatiu en les seves puntuacions postintervenció ( $p < 0.05$ ). A més, l'anàlisi entre grups va confirmar un

millor rendiment cognitiu en el grup experimental després de la intervenció ( $p < 0.05$ ). **Conclusió:** La Li-TMS és una eina efectiva per millorar habilitats cognitives específiques en joves sans. Tot i que aquests resultats són prometedors, es suggereix ampliar les mostres i utilitzar neuroimatges funcionals per comprendre els mecanismes subjacents i explorar aplicacions.

*Paraules clau:* Li-TMS; rendiment cognitiu; DSST; neurociència; entrenament cognitiu.

### Resumen

**Antecedentes:** La estimulación magnética transcraneal de baja intensidad (Li-TMS) es una técnica de neuromodulación no invasiva con efectos reportados en diversas patologías. **Objetivo:** Evaluar el efecto de la Li-TMS en estudiantes universitarios utilizando la prueba de sustitución de símbolos y dígitos (DSST). **Métodos:** Se seleccionaron 30 estudiantes de Medicina de la UNAM, divididos en dos grupos: experimental y control, quienes participaron en un ensayo controlado aleatorizado y ciego simple. El grupo experimental recibió Li-TMS con 25 Hz y 50% de intensidad durante 10 días, mientras que el grupo control recibió una estimulación simulada. **Resultados:** La estimulación simulada no produjo cambios significativos en el grupo control ( $p > 0.05$ ), mientras que el grupo experimental evidenció un aumento significativo en sus puntuaciones post-intervención ( $p < 0.05$ ). Además, el análisis entre grupos confirmó un mejor rendimiento cognitivo en el grupo experimental tras la intervención ( $p < 0.05$ ). **Conclusión:** La Li-TMS es una herramienta efectiva para mejorar habilidades cognitivas específicas en jóvenes sanos. Aunque estos hallazgos son prometedores, se sugiere ampliar las muestras y emplear neuroimágenes funcionales para comprender los mecanismos subyacentes y explorar aplicaciones educativas.

*Palabras clave:* Li-TMS; rendimiento cognitivo; DSST; neurociencia; entrenamiento cognitivo.

## Introduction

Cognitive training is based on the premise that cognitive skills such as memory, attention, and problem-solving can be improved through systematic and structured exercises<sup>1,2</sup>. One of the earliest studies related to cognitive training was conducted by Alfred Binet and Théodore Simon in the early 20th century, who developed the first intelligence tests<sup>3</sup>. Although their work did not focus directly on cognitive training, it laid the groundwork for understanding mental abilities and how they could be assessed and enhanced. In subsequent decades, researchers like Jean Piaget and Lev Vygotsky deepened the understanding of cognitive development, providing theories on how

children learn and develop mental skills through interactions with their environment<sup>4</sup>.

During the 1960s and 1970s, neuroscience began to have a significant impact on learning. Advances in brain imaging techniques allowed scientists to observe changes in the brain in response to learning and experience. Researchers like Merzenich demonstrated brain plasticity and the brain's ability to reorganise and form new neural connections in response to cognitive challenges<sup>5</sup>. The concept of cognitive training as a formal intervention began to emerge in the 1980s and 1990s, with interventions such as Feuerstein's "Instrumental Enrichment Programme" focusing on improving cognitive skills through structured activities designed to strengthen specific men-

tal processes<sup>6</sup>. Simultaneously, the development of educational software and cognitive video games provided new tools for cognitive training, making these interventions more accessible and engaging for a broader audience<sup>7,8</sup>. However, studies on the effectiveness of cognitive training programs have shown mixed results; some have identified improvements in specific skills and brain plasticity, while others have not provided evidence supporting their efficacy<sup>9-12</sup>.

Another technique with the potential to enhance cognitive training is low-intensity transcranial magnetic stimulation (Li-TMS). Li-TMS is a non-invasive technique that is effective in modulating brain activity and improving various cognitive functions. Li-TMS is used to treat several neuropsychiatric conditions, such as treatment-resistant depression and anxiety disorders. This technique involves applying repetitive magnetic pulses to the scalp to stimulate specific areas of the brain and has been proposed as a tool for improving cognitive skills in different populations<sup>13,14</sup>.

The oscillatory effect induced by TMS enhances cognitive functions related to memory, attention, and perception<sup>15</sup>. Moreover, stimulation trains at specific frequencies, such as 5 Hz or individual alpha, improve cognitive tasks according to their interaction with functional oscillations<sup>16,17</sup>. For instance, Romei et al. (2011) demonstrated that theta and beta stimulation in the right parietal cortex produced differential effects on global and local visual processing<sup>17</sup>. TMS also induces synaptic plasticity similar to long-term potentiation (LTP), with effects extending beyond the stimulation period<sup>18</sup>. These results are promising for its application in enhancing motor skills, where pre-training motor task TMS improved performance<sup>19</sup>. Additionally, combining TMS with cortical coactivation during tasks amplifies Hebbian effects on skill learning<sup>20</sup>. The improvement in motor skill development may be associated with the effects of TMS on visual perception and participation in strategic adjustments during visual search<sup>21,22</sup>.

In therapeutic applications, TMS is an effective tool for enhancing neuroplasticity and facilitating rehabilitation after stroke<sup>23,24</sup> and traumatic brain injury<sup>25</sup>. Additionally, it is useful in improving memory and language functions in older adults with cognitive decline<sup>26</sup>. TMS can also optimise human performance in complex work environments<sup>27</sup>. Research by Snyder (2009) has shown how the inhibition of

conceptual processes by TMS can allow more direct access to sensory perception and improve specific skills such as numerosity<sup>28</sup>. This evidence highlights TMS's ability to modulate cognitive skills and accelerate Hebbian learning, paving the way for its application in enhancing human experiences across various domains.

Regardless of the cognitive training technique employed, the challenge remains to evaluate the effect produced by the training. Among the variety of scales used to assess cognitive performance, the Digit Symbol Substitution Test (DSST) is widely used in neuropsychology due to its brevity, reliability, and minimal influence of language, culture, or educational level. However, debate persists about which specific aspects of cognition it evaluates. This cognitive test involves associating symbols with numbers using a key displayed at the top of the page. The participant must reproduce the corresponding symbol in the spaces assigned below a series of numbers. The score is determined by the number of correct associations made within a limited time, usually 90 to 120 seconds<sup>29,30</sup>.

This study focuses on the application of Li-TMS to university students to improve cognitive test scores. The main objective is to evaluate the effect of Li-TMS on the cognitive performance of university students.

The hypotheses to be tested in this study are as follows:

#### Hypothesis 1

Sham stimulation does not produce significant changes in cognitive performance measured by the DSST test before and after the intervention in the control group.

#### Hypothesis 2

Low-intensity transcranial magnetic stimulation (Li-TMS) significantly increases DSST scores after the intervention compared to baseline measurements in the experimental group.

#### Hypothesis 3

Cognitive performance measured by the DSST is significantly higher in the experimental group post-intervention compared to pre-control, post-control, and pre-experimental groups, with no significant differences between these three groups.

## Materials and methods

### Participants

The study included a sample of 30 university students with an average age of  $20.3 \pm 1.5$  years. The sample was evenly divided into 15 women and 15 men. All participants signed an informed consent form before the study began.

### Inclusion criteria

1. Students who voluntarily agreed to participate in the study.
2. Second-year medical students from the School of Medicine, National Autonomous University of Mexico (UNAM).
3. High-performing students with a grade point average of 9.0 or higher.

### Exclusion criteria

1. Participants with a family history of epilepsy.

### Elimination criteria

1. Participants who did not complete the stimulation sessions; no participants were excluded.

### Study design

The study was designed as a randomised, single-blind controlled trial (only the researcher knew the treatment or intervention received by the participant). Participants were randomly assigned to two groups: an experimental group and a control group, each consisting of 15 participants. Randomisation was performed using Excel functions RANDARRAY, SORTBY, and ROWS. The experimental group received daily Li-TMS sessions (Monday to Friday) for 10 days, while the control group received low-intensity sessions following the same schedule. The stimulator used in this study was a Nibbot International device (compliant with regulations to ensure protocol accuracy).

### Variable identification

#### Independent variable

The type of intervention was applied at two levels: low-intensity transcranial magnetic stimulation

(Li-TMS) in the experimental group and a sham intervention in the control group.

#### Dependent variable

Cognitive performance, evaluated through scores on the Digit Symbol Substitution Test (DSST) before and after the intervention.

#### Controlled variables

- Duration and frequency of sessions (10 consecutive days, 45 minutes per session).
- Application area (left dorsolateral prefrontal cortex).
- Low-intensity conditions in the control group (1 Hz, 1% intensity).
- Participant selection based on inclusion and exclusion criteria (e.g., high-performing university students with not a family history of epilepsy).
- Use of the same temporal protocol for both groups.
- Evaluation using the DSST with different number keys to minimise prior learning effects.

#### Intervention

##### Recommendations for participants

Before beginning low-intensity transcranial magnetic stimulation, participants were advised not to consume alcoholic beverages, nicotine, or energy drinks for at least 5 hours before stimulation. They were also encouraged to attend sessions between 10 am and 5 pm.

#### Experimental group

Participants in the experimental group underwent the low-intensity transcranial magnetic stimulation (Li-TMS) protocol for 10 consecutive days. Li-TMS conditions included continuous pulses with a monophasic waveform using a circular coil applied to the left dorsolateral prefrontal cortex (DLPF-LEFT) at 50% intensity, 25 Hz frequency, and 1% pulse width. Each session lasted 45 minutes.

#### Control group

Participants in the control group underwent low-intensity Li-TMS sessions under the same temporal conditions as the experimental group. The intensity used was 1%, with a frequency of 1 Hz and a pulse width of 1%, applied to the DLPF-LEFT area for 45 minutes per session.

### Outcome evaluation

The outcomes were assessed using the Digit Symbol Substitution Test (DSST), a widely used neuropsychological test that assesses cognitive abilities such as motor speed, attention, and visuoperceptual functions. While it does not specify the cognitive domain affected, it is useful for detecting changes in cognitive performance.

The DSST was administered on paper, requiring participants to associate symbols with numbers according to a key and reproduce as many correct symbols as possible in 60 seconds. The DSST score represented the number of correct responses.

The test was administered before (pre-group) and after the 10-day intervention period (post-group) to evaluate changes in participants' cognitive performance. Different numerical codes were used before and after the intervention to minimise prior learning effects.

### Statistical analysis

Data were analysed using GraphPad Prism version 5.0. Normality was initially verified using the Shapiro-Wilk test. As the data did not follow a normal distribution, the Wilcoxon test was used to compare related samples (pre and post) within each group (experimental and control). Statistical significance was set at  $p < 0.05$ .

To evaluate differences between groups (C-pre, C-post, E-pre, E-post), the Friedman Test was used (due to the lack of normal distribution). Post hoc comparisons were performed to identify pairs of groups differed significantly, using the Bonferroni correction for multiple comparisons. Statistical significance was established at  $P < 0.05$ .

## Results

Sham stimulation had no effect on participants' cognitive performance.

In the control group, no significant differences were observed between pre- and post-intervention DSST scores ( $p > 0.05$ , Wilcoxon test). These scores remained relatively constant.

*Low-intensity transcranial magnetic stimulation (Li-TMS) improved cognitive performance in the experimental group.*

In the experimental group, a significant increase was observed in post-intervention scores compared

to pre-intervention measurements ( $p < 0.05$ , Wilcoxon test).

*Low-intensity transcranial magnetic stimulation (Li-TMS) improved cognitive performance in the experimental group compared with the control group.*

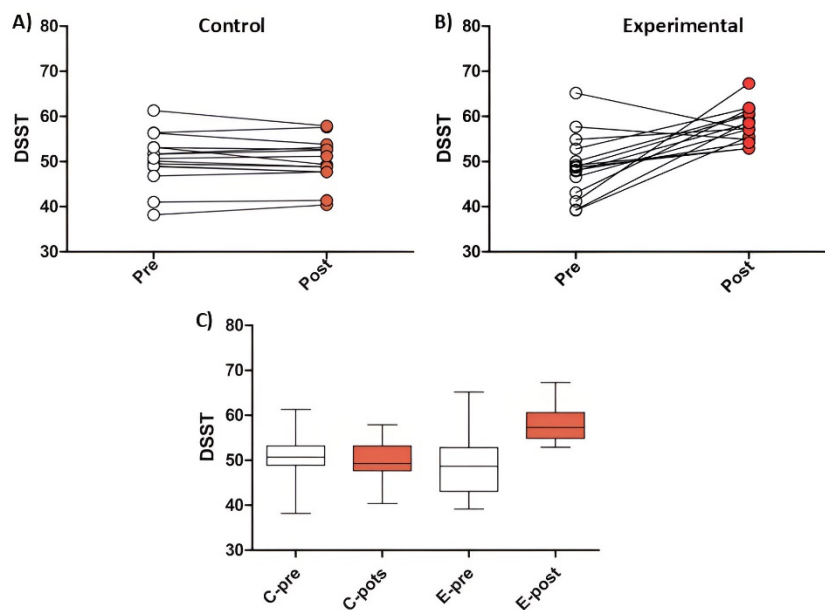
The grouped scores of both groups (control and experimental) revealed that post-intervention cognitive performance in the experimental group was significantly higher compared to the other groups: control pre, control post, and experimental pre ( $p < 0.05$ , Friedman test with Bonferroni post hoc correction). No significant differences were found between these three latter groups ( $p > 0.05$ ) (see **figure 1**).

## Discussion

The results of this study demonstrate that low-intensity transcranial magnetic stimulation (Li-TMS) is effective in improving cognitive performance in university students, specifically in tasks assessed by the DSST test. This improvement, which was only observed in the experimental group after the intervention, reinforces the notion that Li-TMS can act as an effective modulator of neural networks associated with attention, processing speed, and executive functions. In contrast, the control group showed no significant differences, highlighting the specificity of the stimulation effects compared to potential changes due to external factors or prior learning.

There is evidence that cognitive interventions, such as specific video games, can induce improvements in cognitive and non-cognitive skills<sup>32</sup>. However, these strategies have faced criticism due to inconsistent results and challenges in the far transfer of acquired skills<sup>33,34</sup>. In contrast, TMS has demonstrated the ability to induce synaptic plasticity and modulate cortical dynamics in a focal manner, allowing for a more robust and direct impact on cognitive functions<sup>35,40,41</sup>.

Our findings align with research documenting the beneficial effects of Li-TMS in populations with cognitive impairment, such as patients with traumatic brain injury, Alzheimer's disease, and mild cognitive impairment<sup>36-39</sup>. While these studies have predominantly explored clinical applications, our findings extend these applications by demonstrating that Li-TMS can also be effective in healthy individuals, paving the way for its use as a preventive or cognitive optimisation tool in educational settings.



**Figure 1.** Effect of low-intensity transcranial magnetic stimulation (Li-TMS) on cognitive performance measured by the DSST test. A) Pre- and post-scores in the control group ( $p > 0.05$ , Wilcoxon test). B) Pre- and post-scores in the experimental group ( $p < 0.05$ , Wilcoxon test). C) Comparison of scores between the control groups (C-pre, C-post) and experimental groups (E-pre, E-post), with a significant difference in the experimental post-intervention group compared to all other groups ( $p < 0.05$ , Friedman test with Bonferroni post hoc correction).

A distinctive feature of this study is the improvement observed in the experimental group post-intervention, which was significantly superior not only compared to the control group but also to their own pre-intervention assessment. This suggests that the stimulation frequency (25 Hz) and location (left dorsolateral prefrontal cortex) may have facilitated the activation of neural networks associated with executive function<sup>31</sup>. The choice of the DSST as the assessment measure proved suitable for capturing changes in visuospatial skills and processing speed, given its low cultural and educational bias.

However, although the results are encouraging, future studies should expand the sample to include more diverse populations and adopt multidimensional cognitive batteries to explore far transfer effects and the sustainability of improvements. Additionally, this study did not include functional or molecular assessments to propose a mechanism of action for Li-TMS, underscoring the need to incorporate functional neuroimaging tools to identify correlations between observed changes and brain activity induced by Li-TMS.

## Conclusions

This study highlights the potential of Li-TMS as an innovative tool to enhance specific cognitive skills beyond clinical settings. Li-TMS offers opportunities to optimise cognitive performance in young and healthy populations, which could have a positive impact on learning processes.

## Limitations

1. The sample size of this study was relatively small.
2. Only the DSST was used to measure cognitive performance.
3. The study population was made up of students with grades above 9.0 (considered high academic performance), so it is necessary to include students with different academic backgrounds to evaluate whether the effect is consistent and generalizable.
4. Li-TMS is an expensive technique.

### Ethical statement

This project was approved by the Ethics Committees of the School of Medicine of the National Autonomous University of Mexico (registration number FMED/CIE/AECR/150/2024).

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