NeuroTech

evidence book

NeuroTech's Effiectiveness and Safety

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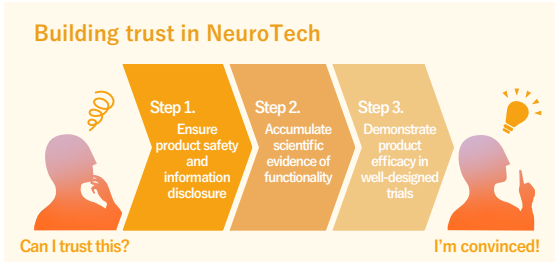
CONTENTS

Preface

This evidence book is written for those interested in scientific evidence on the efficacy and safety of NeuroTech. "Neurotechnology," commonly referred to as "NeuroTech," has gained considerable attention in recent years. NeuroTech aims at estimating and regulating the state of the human brain. Brochures for such products make enticing claims such as "improved athletic performance," "improved memory," or "visualized emotions." However, is there any scientific basis for these claims? Are such products potentially risky to general consumers?

The efficacy and safety of NeuroTech products available to the general public remain unclear. Most NeuroTech products lack robust scientific evidence and rely on limited published literature to support their claims [1]. However, citing several studies does not guarantee the reliability of claims of effectiveness or safety, particularly if the referenced trials are poorly designed and provide low-quality evidence. Furthermore, it can be challenging for general consumers to assess the certainty of these claims and evaluate their efficacy.

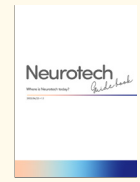
To address these concerns, we have compiled



Consumer NeuroTech products represent emerging technologies with varying levels of reliability. In this book, we investigated the scientific basis for NeuroTech functional claims, which corresponds to Step 2 in the above chart.

this evidence book to provide the public with an accurate overview of the efficacy and safety of NeuroTech. The content is based on the results of systematic reviews that explored the existing scientific evidence supporting the effects of NeuroTech products and their safety. This evidence book discusses 12 key questions about commonly claimed effects of NeuroTech products, such as "Can neurofeedback training improve motor performance?" These questions are explained based on the findings of relevant systematic reviews. The first edition addressed four questions; the second edition includes six additional questions, with the remaining two to be published after the systematic reviews are completed.

This book was developed by an Evidence Evaluation Committee, comprising 12 researchers specializing in neuroscience. Systematic reviews were conducted by a team of more than 20 researchers and graduate students under the supervision of the Evidence Evaluation Committee. To improve the book's impartiality and comprehensibility, an External Review Board consisting of various experts reviewed the systematic review process, correctness of the contents, and transparency of the disclosure of conflicts of interest. For basic information on NeuroTech, please refer to the previously published NeuroTech Guidebook [2].



<Guidebook>
- For individuals interested in NeuroTech products.
- Developed by experienced researchers, physicians, and professionals with expertise in neuroscience.
- Provides insights and current perspectives and information on how to approach NeuroTech.

<Evidence Book>
- For NeuroTech users and providers of products and services.
- Created by Evidence evaluation committee, comprising researchers specializing in neuroscience.
- Summarizes the effectiveness and safety of NeuroTech based on the results of systematic reviews.

This book provides clear and concise explanations, particularly in the headline section of each question, for better comprehension for the general consumers. The Appendix summarizes the foundational knowledge necessary for understanding the content. This book also offers in-depth specialized information for those with scientific and technical expertise, such as professionals involved in the sales or development of NeuroTech products and services, researchers, and medical personnel. Although certain sections may be complex for the general consumers, we believe that the scientific perspective acquired through this book will help mitigate the potential drawbacks and health risks associated with NeuroTech products. We hope that this book fosters enhanced scientific understanding of NeuroTech and supports its development as a reliable

November 2025
By Evidence Evaluation Committee

Preface

Disclaimer

The authors of this book have meticulously checked that the contents and analyses described are accurate. Furthermore, the contents have been verified by an external review board comprising professionals in medicine, neuroscience, and law, and experts in medical publishing and neuroethics. However, the accuracy of the content cannot be completely guaranteed because of several uncertain factors, including future technological developments, the unique complexity of brain research, changes in social circumstances, differing individual perspectives, variations in the physical characteristics and usage conditions of consumers, and revisions to the legal framework. Although we strive for accuracy and aim to provide reliable information, we assume no responsibility for any unforeseen health hazards, legal issues, or misinterpretations of the information presented in this book. Please note that this book should not be considered a definitive guide as it does not provide scientific evidence for specific products with functional claims. Similarly, the absence of evidence supporting functionality based on the literature review in this book does not imply that products lack a scientific foundation. We request readers to refrain from referring to this book regarding NeuroTech intended for minors or medical purposes, including the diagnosis or treatment of illnesses, as these are not within the scope of this book.

This evidence book was developed as part of the "Liberation from Biological Limitations via Physical, Cognitive and Perceptual Augmentation (Project Manager Ryota Kanai)" project for Goal 1 of the Cabinet Office Moonshot Research and Development Program, "Overcoming limitations of body, brain, space, and time" by 2050. The funders, the Japan Science and Technology Agency, and the Cabinet Office, had no involvement in the development or content of this book.

RQ1

Can neurofeedback training improve motor performance?

Answer

The use of neurofeedback for ≥ 7 days possibly improves motor performance. However, given the limited research, the extent and specific areas of improvement in motor performance remain unclear.

Neurofeedback training for ≥ 7 days may improve motor performance in healthy adults* immediately after training. However, owing to the limited number of studies, the evidence is currently insufficient to draw definite conclusions on the specific areas of motor performance (e.g., balance and endurance) and to what extent it is effective. Additionally, the optimal frequency and duration of daily training necessary to achieve an effect are yet to be fully elu-

*In this RQ, healthy adults were defined as those aged 18–64 years who had not been diagnosed with any physical, mental, or neurological disorders or diseases at the time of participation in the experiment.

Background and Purpose

Neurofeedback training (NFT) has gained considerable attention as a potential alternative to general motor training or a method to enhance the effectiveness of mental imagery. NFT has demonstrated positive effects in improving golf putting and fine motor skills [3,4], whereas a meta-analysis revealed no significant impact of NFT on motor performance among athletes [5]. This raises a potential concern about the safety and reliability of NFT in improving motor performance in healthy adults.

Results - Safety

Given the limited number of studies focusing on potential adverse events, the safety of NFT could not be determined. To date, no adverse events have been reported. Of the 33 studies that utilized NFT to enhance motor performance in healthy adults, only 5 studies (including 129 participants) assessed adverse events. Therefore, it was not possible to draw definitive conclusions on the safety of NFT. Notably, none of the five studies focusing on adverse events reported adverse effects.

Results - Effectiveness

- NFT for ≥ 7 days may improve motor performance (Fig. 1A). However, the scientific evidence supporting this claim is insufficient, given the risk of bias in the results and the limited number of participants in the studies conducted.
- The effectiveness of NFT on specific motor performance parameters, such as movement accuracy, reaction time[#1], hand dexterity, whole-body balance, and endurance, could not be adequately evaluated owing to an insufficient number of studies (Fig. 1B).
- The effects of NFT on motor performance may be comparable to those of non-NFT motor training methods such as mental practice (Fig. 1C). However, considering the total number of participants in the available studies and the inconsistency of the results, the scientific evidence remains inconclusive.
- Four studies repeatedly assessed motor performance after NFT. Further research is needed to confirm the duration of training effects. In addition, the training intervals required to maintain or enhance performance need to be determined.

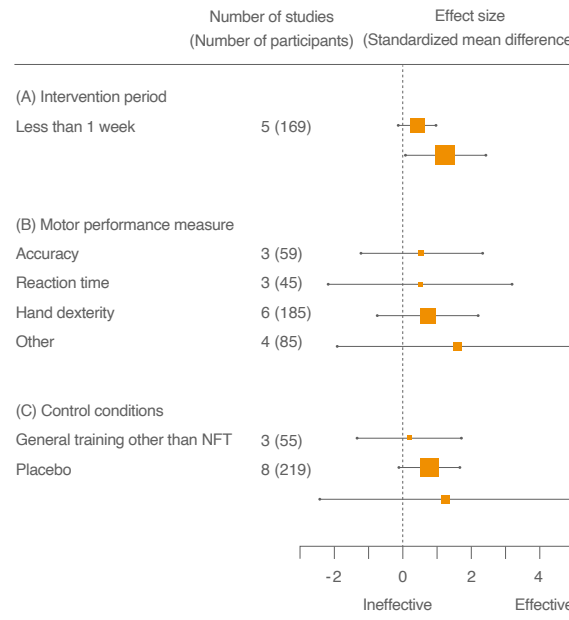


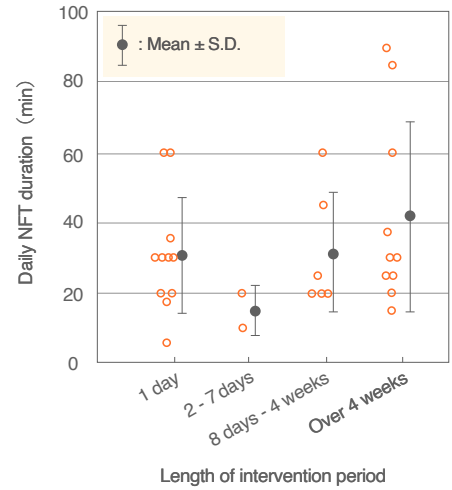
Figure 1. Results of the effectiveness assessment. (A) Effects of intervention period. (B) Differences in effects by the targeted motor performance. (C)

Can neurofeedback training improve motor performance?

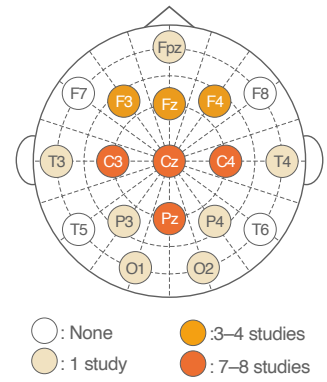
Study characteristics

- Intervention period (Fig. 2A): Ranging from single-day sessions in 13 studies , 2-7 days in 4 studies, 8 days to 4 weeks in 5 studies, and more than 4 weeks in 11 studies. The longest training duration per day was 90 min and the shortest was 6 min. No apparent trend was observed linking shorter daily training duration with longer training periods.
- Intervention frequency: Daily if the training period is < 4 days and every 2-7 days for longer training periods.
- Methods to measure brain activity for NFT: EEG (26 studies), fMRI (3 studies), MEG (2 studies), and fNIRS (2 studies).
- Channels recorded for EEG-based NFT (Fig. 2B): Of the 26 studies, 16 recorded EEG signals from the central region (Cz, C3, and C4). The most common measurement was from the parietal region (Pz: 7 studies).
- Frequency band(s) targeted by the EEG-based NFT study (Fig. 2C): The most common frequency bands used for NFT were alpha and theta (13 studies each), followed by beta (12 studies). Fifteen studies used a combination of theta, alpha, and/or beta. In addition, eight studies used a component called the sensorimotor rhythm (SMR)[#2], and five studies used the power ratio between theta and beta oscillations.
- The control conditions were as follows: placebo (18 studies), no intervention (10 studies), and general motor training other than NFT (8 studies). Placebos use methods such as feedback from previously recorded brain activity of others or random information similar to brain activity.
- Targeted motor performance: movement accuracy, such as shooting and golf putting (8 studies), hand dexterity (8 studies), reaction time (8 studies), whole-body balance (2 studies), and endurance (2 studies).

(A) Daily NFT duration grouped by the length of the intervention period



(B) EEG recording channels utilized in NFT studies



(C) EEG components targeted by NFT studies

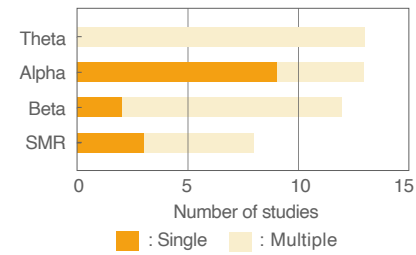


Figure 2. Study characteristics.

RQ1

Can neurofeedback training improve motor performance?

Systematic review processes

- A comprehensive search was conducted across five databases to identify studies focusing on NFT to improve motor performance in healthy adults aged 18-64 years [6].
- A total of 2,325 articles were identified from database search and other sources, which were screened according to the predetermined inclusion criteria. Finally, 33 articles were selected to summarize the characteristics of the published studies and assess the safety of NFT.
- Of the 33 studies, 13 were randomized controlled trials that calculated effect sizes related to motor performance and had a low to moderate risk of bias. These studies were used for statistical analyses to evaluate the effectiveness of NFT.

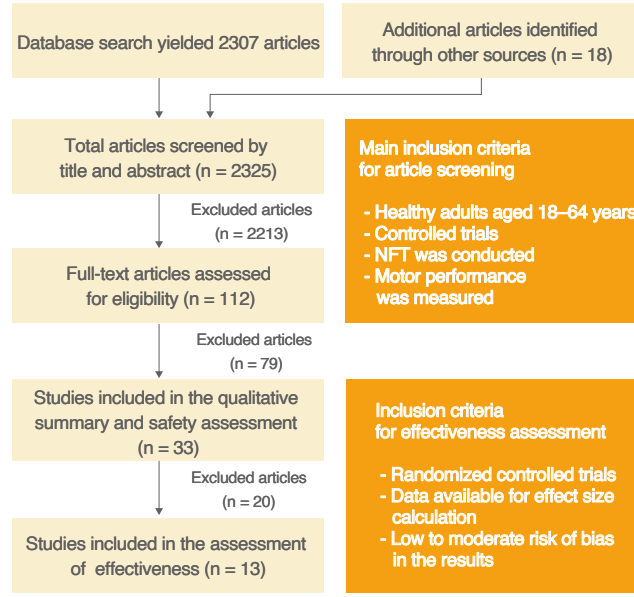


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Reaction time: Reaction time is the time interval required to respond to an event. In the context of starting to run in response to a cue, like "on your mark, get set, go!" refers to the time from the start of the signal to the movement (go!) to the actual start of movement (beginning to run). The reaction time serves as a metric for evaluating various functions. For instance, memory function measures the time taken to recall and respond to learned information. Reaction time in movement is also referred to as “simple reaction time” and is the shortest among different types of reaction times. Reaction time increases when more complex cognitive processes, such as memory tasks, are involved.

#2. Sensorimotor rhythm (SMR): SMR refers to the EEG signal in the 12-15 Hz range, typically measured from the central region of the brain. Previous studies considered the primary motor cortex, which sends the muscle the command "Move," and the primary somatosensory cortex, which is adjacent to the primary motor cortex and receives muscle and skin sensory information, as the SMR signal sources [7].

RQ2

Can neurofeedback training improve sleep quality?

Answer

Given the limited available research, evidence to support the claim that neurofeedback improves sleep quality in healthy adults is currently lacking.

Currently available scientific evidence is insufficient to determine whether neurofeedback training can improve sleep quality in healthy adults*. Studies focusing on this topic are scarce, and investigations on the effectiveness and safety of neurofeedback in enhancing sleep quality are underway. Further research is required to better understand the specific aspects of sleep that can potentially benefit from neurofeedback. Meanwhile, if the reader wants to improve sleep quality, we recommend following the sleep guidelines for health promotion provided by sleep science experts and the Ministry of Health, Labour, and Welfare [8].

* Healthy adults were defined as those aged ≥ 18 years who had not been diagnosed with any physical, mental, or

Background and Purpose

Various methods are available to maintain good sleep and improve sleep quality, such as moderate exercise during the day, avoiding bright lights at night, maintaining a regular sleep schedule, and going to bed when sleepy [8]. NFT has recently emerged as a potential method for improving sleep quality [9]. However, the safety and reliability of NFT in improving sleep quality in healthy adults without sleep disturbances needs to be validated.

Results - Safety

Owing to the lack of studies reporting potential adverse events, assessing the safety of NFT remains challenging. Although four studies have investigated the impact of NFT on sleep quality in healthy adults, none

Results - Effectiveness

- Studies on the effectiveness of NFT have reported inconsistent results. Currently, no scientific evidence supports the claim that NFT improves sleep quality in healthy adults (Fig. 1A). This uncertainty could be attributed to the inconsistent methods#1 used to assess sleep quality.
- The impact of NFT on daytime nap and nighttime sleep (Fig. 1B) and the differences in the effects of different EEG components used in NFT (Fig. 1C) could not be determined because of the limited available research.
- Additionally, the optimal training period and hours per day required for NFT to affect sleep remain unknown.

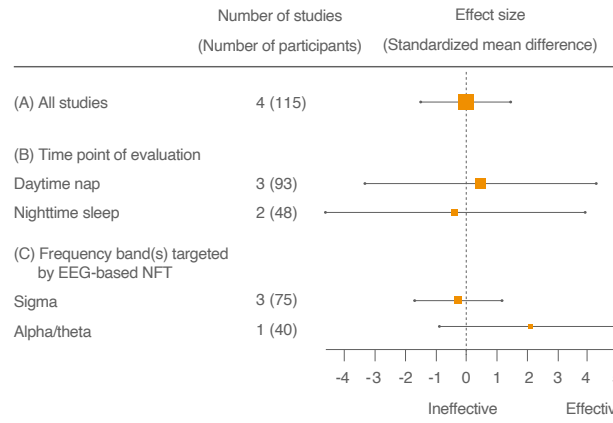


Figure 1. Results of the effectiveness assessment. (A) Overall effect. (B) Comparison between daytime nap and nighttime sleep. (C) Comparison in frequency band(s) targeted by EEG-based NFT.

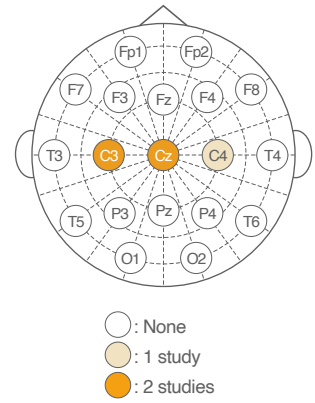
RQ2

Can neurofeedback training improve sleep quality?

Study characteristics

- Intervention period: Ranged from 1 day to ≥ 10 days
- Intervention duration: 24-90 min per day
- Channels recorded for EEG-based NFT (Fig. 2A): All studies measured EEG signals from the central area (Cz, C3, and C4).
- Frequency band(s) targeted by the EEG-based NFT study (Fig. 2B): Power in the sigma frequency band and a combination of power in the alpha and theta frequency bands were used.
- Types of control conditions: All four studies used placebos, with feedback based on non-EEG data such as heartbeat, EEG components not utilized in NFT, and EEG data from others.
- Timing of sleep quality assessment: Three studies assessed sleep quality during daytime naps, and two evaluated during nighttime sleep.

(A) EEG recording channels utilized in NFT studies



(B) EEG components targeted by NFT

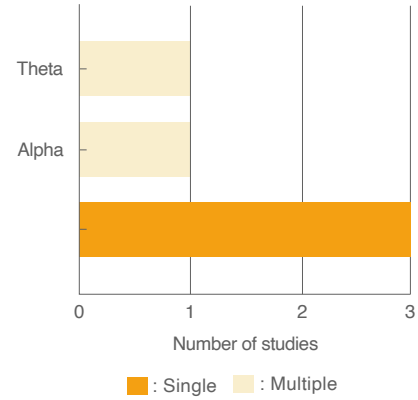


Figure 2. Study characteristcs.

RQ2

Can neurofeedback training improve sleep quality?

Systematic review processes

- A comprehensive literature search was conducted across four databases to identify studies that focused on NFT for improving sleep quality in healthy adults aged ≥18 years[10].
- Our search yielded 827 articles, which were screened according to the predetermined inclusion criteria. Finally, four selected articles were used to summarize the main characteristics of the published studies and investigate the safety of NFT.
- These studies were also used for statistical analyses to evaluate the effectiveness of NFT.
- To assess these studies, we employed widely accepted sleep quality indices, including the proportion and duration of N3 sleep stages[#2], amplitude of sleep EEG[#3] (such as sigma and delta waves), sleep efficiency[#4], sleep latency[#5], and wake time after sleep onset[#6].

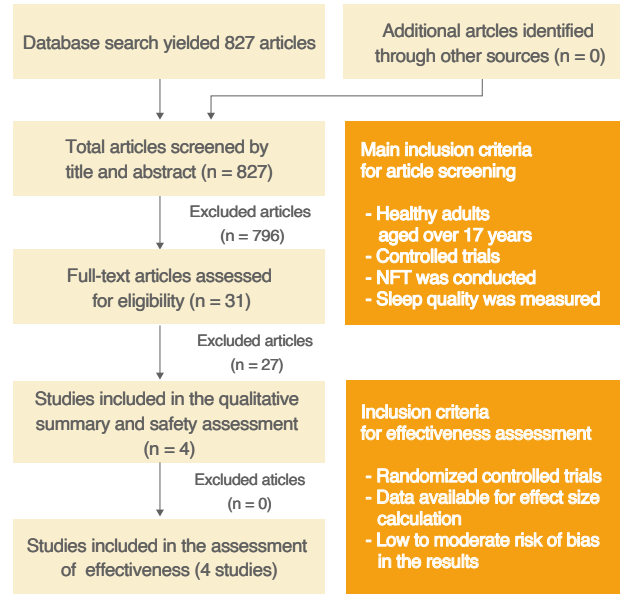


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Sleep quality is currently evaluated using various indices [11]. Using polysomnography and actigraphy, evaluations can be conducted based on objective indicators such as sleep EEG and sleep latency. Additionally, sleep satisfaction and overall subjective sleep quality are evaluated through questionnaires or interviews. However, consensus among experts on a standardized approach for evaluating sleep quality is lacking.

#2. Sleep Stages: Sleep is categorized into two main stages: non-REM and REM sleep. Non-REM sleep is further subdivided into three stages: N1, N2, and N3. N1 denotes the dozing-off state, and N3 represents the deep-sleep state. During N3, the external sounds were less likely to cause individuals to wake up.

#3. Sleep EEG: Theta oscillations are commonly observed during the initial stage of non-REM sleep (N1). During progression to N2, sleep spindles were present, indicating a deeper sleep stage. Sleep spindles are reliable indicators of sleep stability. The deepest non-REM stage, N3, was characterized by slow waves with a frequency of 0.5-4 Hz.

#4. Sleep efficiency refers to the proportion of time spent in any of the sleep stages, including non-REM (N1, N2, and N3) and REM sleep, of the total time spent in bed.

#5. Sleep latency refers to the time between turning the lights off and the first onset of any sleep stage.

#6. Wake time after sleep onset refers to the time between falling asleep and getting up that is considered awake.

RQ3

Can neurofeedback training enhance attentional functions?

Answer

Neurofeedback training (NFT) enhances attentional performance; however, whether its effects are greater than those of other general training methods remains unclear.

Attentional functions are categorized into three key elements: "executive control" (also called the central executive), which involves focusing on what needs to be done in the present moment and staying focused on the task at hand; "spatial orientation," which directs attention toward the intended target; and "arousal," which creates and maintains an appropriate state of readiness [12]. NFT may result in immediate improvements in executive control and spatial orientation in healthy adults*. Although these observed effects are greater than those of doing nothing, it remains unclear whether NFT outperformed placebos and general training methods, such as meditation or tasks mimicking playing video games (e.g., Tetris® or Concentration). The effects of neurofeedback on attention-deficit hyperactivity disorder (ADHD) have been previously described [13] and are beyond the scope of this review.

*In this RQ, healthy adults were defined as those aged 18-65 years who had not been diagnosed with any physical,

Background and Purpose

NFT as a training method to enhance attentional functions has garnered considerable attention. The effectiveness of NFT in improving attentional function using specific EEG components, such as sensorimotor rhythm (SMR) or beta, has been reported [14,15]. However, other studies have suggested that NFT only alters brain activity and does not affect behavioral aspects, such as correct response rate or reaction time [16]. This raises the question: what types of attentional functions can NFT reliably enhance in healthy adults, and to what extent?

Results - Safety

Given the limited number of studies focusing on adverse events, the safety of NFT could not be determined. To date, no adverse events have been reported. Of the 41 studies that utilized NFT to improve attentional function in healthy adults, only 2 studies involving a total of 124 participants assessed adverse events. These studies did not report any serious adverse events that required medical intervention or other unfavorable outcomes.

Can neurofeedback training enhance attentional functions?

Results - Effectiveness

- NFT may enhance attentional functions (Fig. 1A).
- Among attentional functions, NFT demonstrated positive effects on executive control, such as decreased reaction time when alternating between two types of judgments [17] (Fig. 1B).
- Effects on spatial orientation were also observed. However, scientific evidence supporting this claim is insufficient because of the risk of bias in the results and the total number of participants in the included studies (Fig. 1B).
- No effect of NFT on arousal was observed (Fig. 1B).
- Few studies compared the effects of NFT to other general attentional training methods, such as meditation or tasks mimicking Tetris® or Concentration, making it difficult to determine whether NFT has potential advantages (Fig. 1C).
- The difference in the enhancement of attentional functions between the NFT and placebo groups remains unknown (Fig. 1C).
- Only two studies have evaluated the effects of NFT on attentional function over time, making the duration of the training effect uncertain. Additionally, the optimal training intervals required to maintain or improve the performance could not be determined.

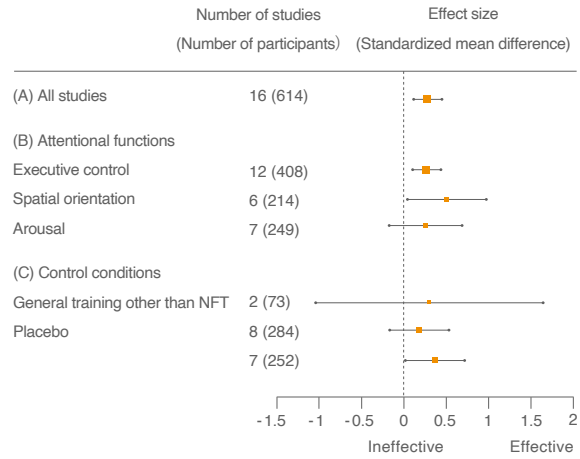


Figure 1. Results of the effectiveness assessment. (A) Overall effect. (B) Differences in effects by attentional functions. (C) Superiority of NFT by control conditions.

Can neurofeedback training enhance attentional functions?

Study characteristics

- Intervention period: Ranging from single-day sessions in 3 studies, 2-7 days in 4 studies, 8 days to 4 weeks in 15 studies, and 13 studies lasted longer than 4 weeks, with the longest training duration of 13.5 weeks. The duration of training per day was approximately 5 min in 1 study, 10-20 min in 8 studies, approximately 20-60 min in 20 studies, and further prolonged in 5 studies, the longest being 136 min.
- Intervention frequency: In our analysis of studies with NFT intervention for ≥ 3 days, intervention frequency varied between once daily in 7 studies, 4-5 days/week in 4 studies, 2-3 days/week in 12 studies, and less than 2 days/week in 7 studies.
- The targeted attentional functions (Fig. 2A) included executive control (26 studies), spatial orientation (12 studies), and arousal (19 studies), with some studies targeting multiple attentional functions.
- Types of control conditions: placebos (26 studies), no intervention (12 studies), and general training methods other than NFT (4 studies). The feedback for the placebo group included brain activity from nontarget regions, EEG components of other individuals, or random information unrelated to brain activity.
- The methods used to measure brain activity included EEG (33 studies), fMRI (4 studies), NIRS (3 studies), and MEG (1 study).
- Channels recorded for the EEG-based NFT (Fig. 2B): central region (Cz, C3, and C4) in 24 studies, frontal region (Fz, F3, and F4) in 12 studies, parietal region (Pz, P3, and P4) in 11 studies, occipital region (Oz, O1, and O2) in 7 studies, and frontal pole (Fpz, Fp1, Fp2) in 5 studies.
- Frequency band(s) targeted by the EEG-based NFT study (Fig. 2C): The theta and beta frequencies were the most commonly utilized (13 studies) and were often combined. Alpha waves were used individually in 6 out of 11 studies. SMR was used in 10 studies, and only 2 studies incorporated event-related potentials, including P300.

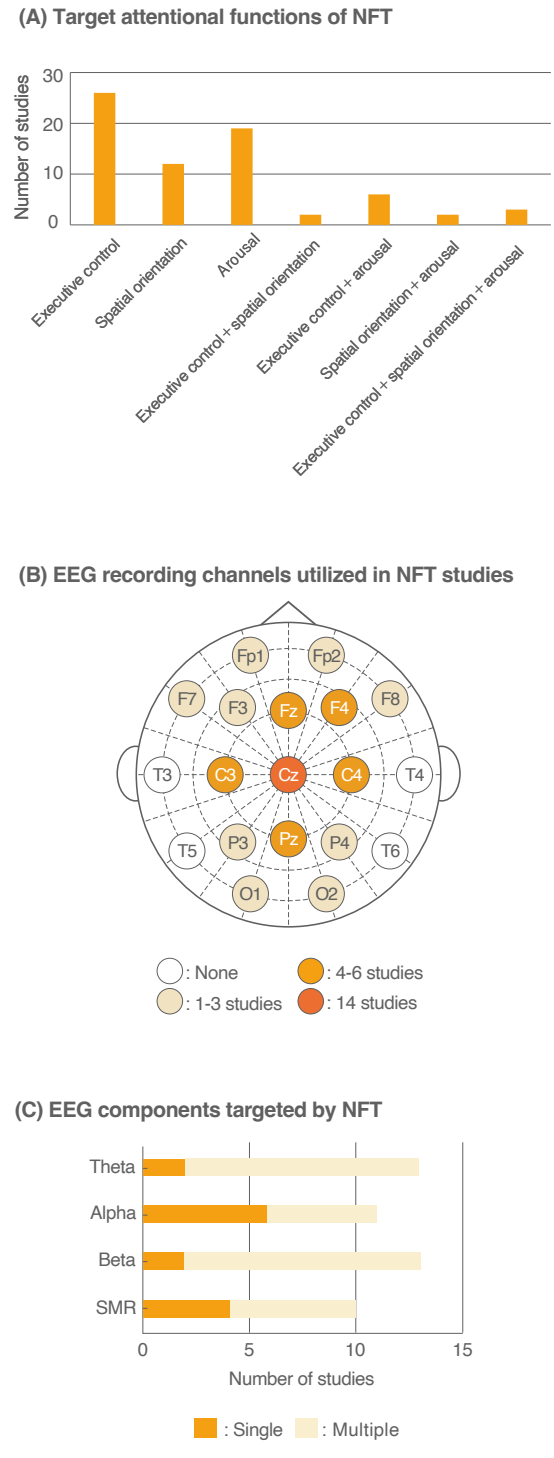


Figure 2. Study characteristics.

Can neurofeedback training enhance attentional functions?

Systematic review processes

- A comprehensive literature search was conducted across six databases to identify studies that used NFT to enhance attentional function in healthy adults aged 18-65 years [18].
- Our search yielded 3,337 articles, which were screened according to the predetermined inclusion criteria. Among them, 41 selected articles were used to summarize the main characteristics of the studies to date and investigate the safety of NFT.
- Of the 41 studies, 15 were randomized controlled trials that calculated effect sizes related to attentional function with a low risk of bias. These studies were used for the statistical analyses to evaluate the effectiveness of NFT.

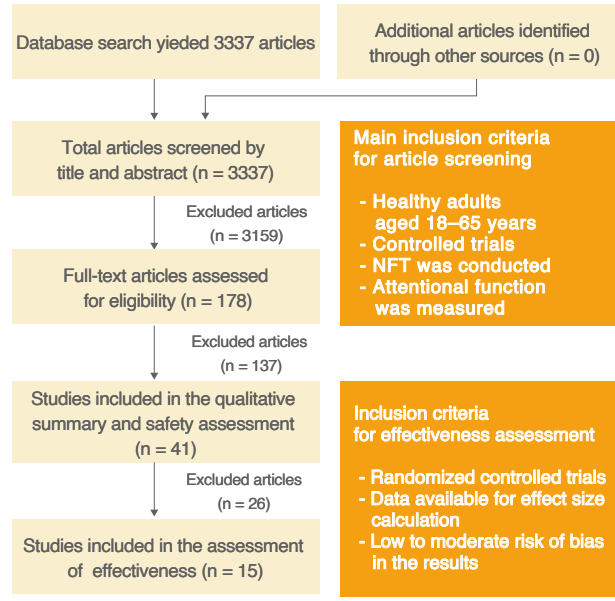


Figure 3. Flowchart of the systematic review process.

RQ4 Can neurofeedback training enhance memory functions?

Answer

Neurofeedback training (NFT) improves short-term memory and declarative memory on the day of training and the following day in healthy adults aged 18-59 years.

Based on retention duration[#2], memory[#1] is classified into sensory memory, short-term memory, and long-term memory. "Sensory memory" lasts only for the moment something is perceived, "short-term memory" is retained for a brief period, typically a few seconds, and "long-term memory" lasts for extended periods, ranging from several minutes to hours or even longer. Additionally, memory can be categorized by the type of information, such as "declarative memory," which stores auditory or verbal information, and "visuospatial memory," which stores visual or spatial information not related to language[#3]. This review revealed that NFT using EEG may improve short-term and declarative memory in healthy adults* aged 18-59 years on the day of training and the following day. However, the most appropriate NFT method may vary depending on the type of memory being targeted. Furthermore, NFT may not be effective in individuals aged ≥ 60 years.

*In this RQ, healthy adults were defined as those aged ≥ 18 years who had not been diagnosed with any physical,

Background and Purpose

NFT has garnered attention as a method to enhance memory function. Several studies have demonstrated that NFT using EEG, specifically alpha oscillations, are effective in improving short-term memory [19-21]. This raises several questions: How reliably can NFT enhance memory functions in healthy adults aged ≥ 18 years? What specific types of memory can it improve? Additionally, what types of brain activities are involved in NFT that contribute to improvements in memory?

Results - Safety

Available data to support conclusions regarding adverse events are scarce. However, no adverse events have been reported to date. Of the 44 studies, only 4 reported the presence or absence of adverse events associated with NFT. No adverse events, including serious ones requiring medical intervention, were reported.

Can neurofeedback training enhance memory functions?

Results - Effectiveness

- NFT improves memory functions in healthy adults aged 18-59 years; however, it may not be effective in healthy individuals aged ≥ 60 years (Fig. 1A).
- Owing to the limited number of studies, no definitive conclusions can be drawn. However, the effects of NFT may be comparable to those of other memory training methods, such as tasks similar to brain training games (Fig. 1B).
- In memory functions[#4], NFT demonstrated improved effects on short-term memory and declarative memory (Fig. 1C). However, this approach may not be effective for long-term or visuospatial memory.
- NFT using signals measured from the parietal region is effective in enhancing memory functions (Fig. 1D). In contrast, NFT that used signals measured from the central and occipital regions demonstrated no substantial effect.
- NFT, aimed at increasing the power of alpha oscillations in the EEG, is effective in improving memory function (Fig. 1E). However, the effects of NFT using theta or beta oscillations remain inconclusive owing to variability and potential bias in the results.
- The effects of the NFT may be evident on the day of training and the following day. However, memory tests conducted 2 days after training revealed no effects.
- NFT sessions lasting for > 33 min per day may enhance memory. However, the appropriate NFT method and training duration may vary, depending on the type of targeted memory.

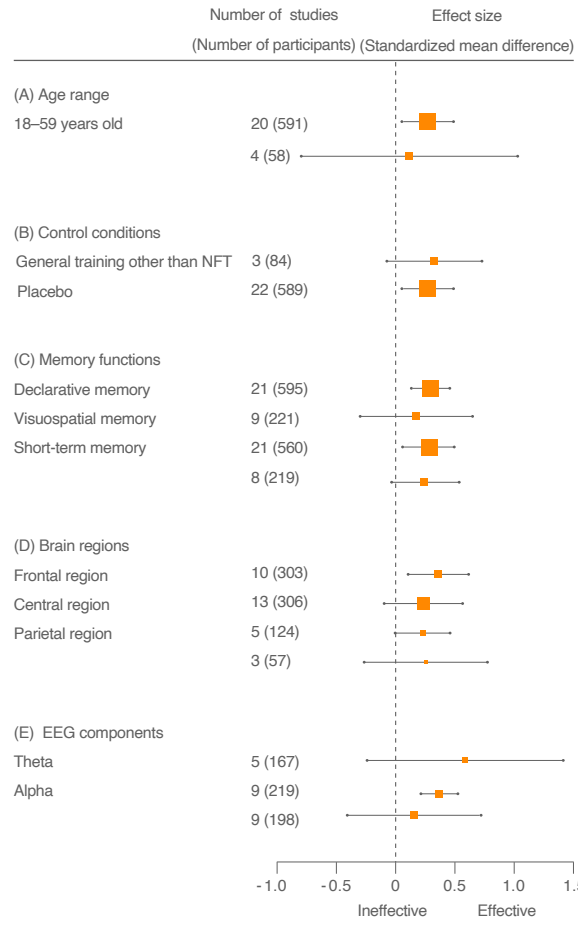
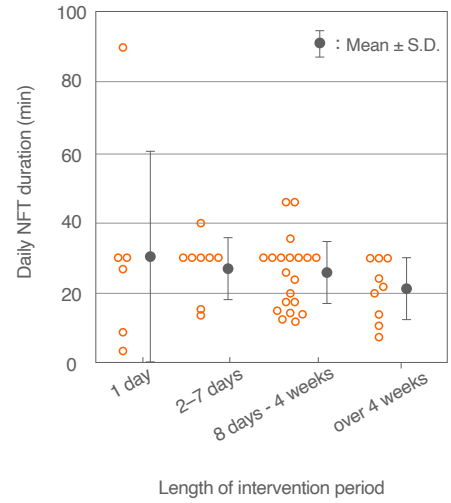


Figure 1. Results of the effectiveness assessment. (A) Effects of age. (B) Superiority of NFT by control conditions. (C) Difference in effects by the targeted memory functions. (D) Channels recorded for EEG-based NFT. (E) EEG components targeted by NFT.

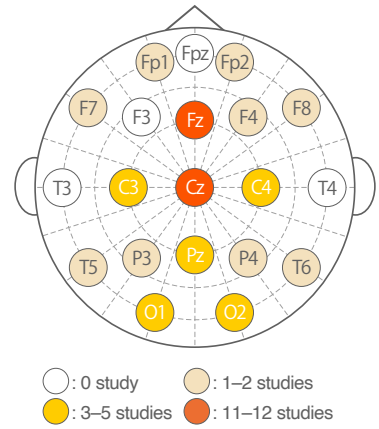
Study characteristics

- Intervention period (Fig. 2A): Ranging from single-day sessions in 6 studies, 2-7 days in 8 studies, 8 days to 4 weeks in 21 studies, and more than 4 weeks in 9 studies, with the longest training duration of approximately 18 weeks. The longest training time per day was 90 min, and the shortest was 3 min.
- Intervention frequency: In our survey of studies conducting NFT intervention for ≥ 3 days, intervention frequency varied between once daily in 6 studies, 4-6 days/week in 12 studies, 2-3 days/week in 14 studies, and less than 2 days/week in 3 studies.
- Targeted memory functions: Based on the duration of memory retention, sensory memory (2 studies), short-term memory (40 studies), and long-term memory (17 studies) were evaluated. Declarative memory (34 studies) and visuospatial memory (23 studies) were evaluated based on the memory content.
- The control conditions were placebos (34 studies) and general training methods other than the NFT (6 studies). The feedback for the placebo group included brain activity different from that of the intervention group (17 studies) or EEG components of other individuals (4 studies).
- Methods to measure brain activity included EEG (37 studies) and fNIRS (7 studies).
- Channels recorded for EEG-based NFT (Fig. 2B): central region (Cz, C3, C4), 20 studies; frontal region (Fz), 12 studies; parietal region (Pz, P3, P4), 5 studies; occipital region (O1, O2), 6 studies; and temporal region (T5, T6) in 3 studies.
- Frequency band(s) targeted by the EEG-based NFT (Fig. 2C): The most common frequency band used for NFT was alpha (17 studies), followed by beta (15 studies), theta (14 studies), and gamma (2 studies). Eight studies used a combination of these two components. No studies incorporated event-related potentials.

(A) Daily NFT duration grouped by the length of the intervention period



(B) EEG recording channels utilized in NFT studies



(C) EEG components targeted by NFT studies

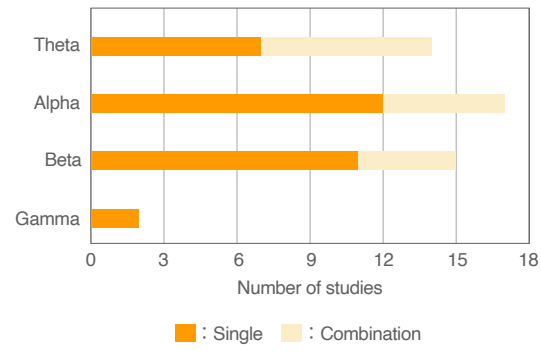


Figure 2. Study characteristics.

Can neurofeedback training enhance memory functions?

Systematic review processes

- Studies that utilized NFT using EEG or fNIRS to enhance memory functions in healthy adults aged ≥ 18 years were searched across four databases [22].
- A total of 3,927 articles were identified through our search and manual additions from other sources, which were screened according to the predetermined inclusion criteria. Finally, 44 selected articles were used to summarize the characteristics of the published studies and investigate the safety of NFT.
- Of the 44 studies, 24 were randomized controlled trials that calculated effect sizes related to memory functions with a low to moderate risk of bias. These studies were used for the statistical analyses to evaluate the effectiveness of NFT.

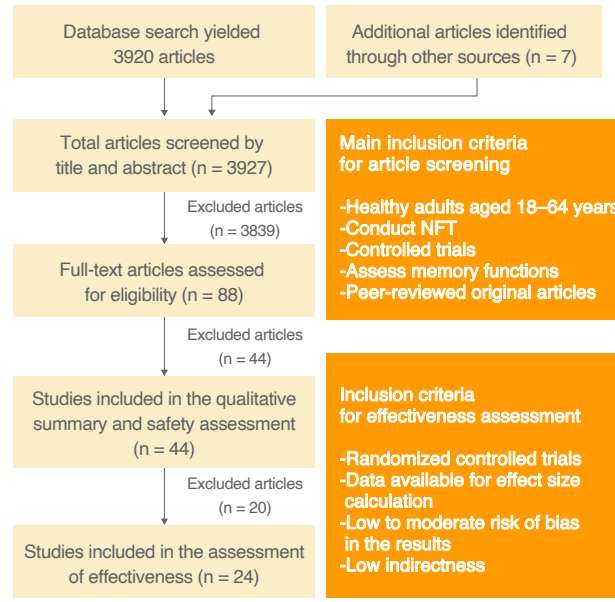


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Memory can be categorized not only by retention time but also by content and function.

#2. Classification by retention time: (1) "Sensory memory," which holds sensory information (such as sight, sound, and touch) for a brief period of approximately 0.1-1 s; (2) "Short-term memory," which retains information for a short period (≥ 1 s); (3) "Long-term memory," which stores information for an extended period (several minutes to several hours or longer). Working memory, which is related to attention, was classified as short-term memory in this context [23, 24].

#3. Classification by content: This includes "declarative memory," which can be expressed in words, like letters, numbers, or events, and "procedural memory," which is related to skills, such as riding a bicycle.

#4. Memory has functions such as encoding (the ability to remember), retention (the ability to maintain information while focusing attention on it), and recall (the ability to retrieve previously stored information) [24]. In this study, we did not conduct a stage-by-stage analysis of these three processes.

RQ5

Can non-invasive brain stimulation*1,*2 improve motor performance?

Answer

Anodal transcranial direct current stimulation (tDCS) may improve motor performance; however, the current scientific evidence remains inconclusive.

Anodal transcranial direct current stimulation (tDCS) may improve motor task performance in healthy adults*3. However, the wide variability in outcomes across studies raises concerns regarding the reliability of these findings. The effects of anodal tDCS depend on the targeted brain regions (e.g., primary motor cortex and cerebellum) and targeted motor performance (e.g., speed and accuracy) remains unclear. No severe adverse events have been reported to date.

*1 Non-invasive brain stimulation is not recommended for individuals without specialized knowledge. For further details, refer to Neurotech Guidebook Vol. 1 GQ3, "What is neuromodulation?"
*2 In this RQ, we assumed that anodal tDCS effectively enhances the excitability of the neural activity located beneath the electrodes. Our goal was to determine whether this increase in neural activity contributed to improvements in motor performance.
*3 In this RQ, healthy adults were defined as those aged 18-64 years who had not been diagnosed with any physical, mental, or neurological disorder or disease at the time of participation.

Background and Purpose

Non-invasive brain stimulation (NIBS) regulates neural activity by applying various types of stimulation to the brain from the scalp. The tDCS is a NIBS that alters neural activity by passing a weak direct current between electrodes placed on the scalp[25]. In particular, it facilitates neural activity under the anode and is gaining attention for its potential application in the efficient training of motor performance. The effects of anodal tDCS on rehabilitation after brain injury and its impact on sports performance, including endurance in activities such as cycling and running, have been documented[26, 27]. Therefore, investigating the effects of anodal tDCS in improving their motor performance in healthy adults, what specific motor performance can be improved, and to what extent can these improvements be reliably and safely achieved is essential.

Results - Safety

Given the limited number of studies focusing on adverse events, the safety of NIBS could not be determined. Some studies have reported that adverse events were generally mild, such as itching from electrode use or a tingling sensation on the skin. No severe adverse events were reported to date.
Of the 25 studies that used tDCS to enhance motor performance in healthy adults, 15 (involving 373 participants) reported adverse events. Among them, six studies quantitatively assessed the degree of adverse events, itching or tingling on the skin, which was comparable to that experienced under placebo conditions.

Can non-invasive brain stimulation improve motor performance?

Results - Effectiveness

- Anodal tDCS may improve motor performance. However, considering the potential bias in the results, the scientific reliability remains insufficient (Fig. 1A).
- Motor performance may improve when brain stimulation is applied before starting a motor task. However, brain stimulation during a task does not improve motor performance (Fig. 1B).
- Notably, improvements in motor performance were observed 24 h after stimulation (Fig. 1C).
- The effectiveness of NIBS on specific motor performance could not be adequately evaluated because of potential bias in the results and variability in outcomes across studies (Fig. 1D).
- Stimulation around the primary motor cortex may enhance motor performance at the stimulation site (electrode placement); however, the scientific reliability of this finding remains unclear (Fig. 1E).
- The intensity or duration of stimulation was not associated with the effectiveness of improving the motor performance.

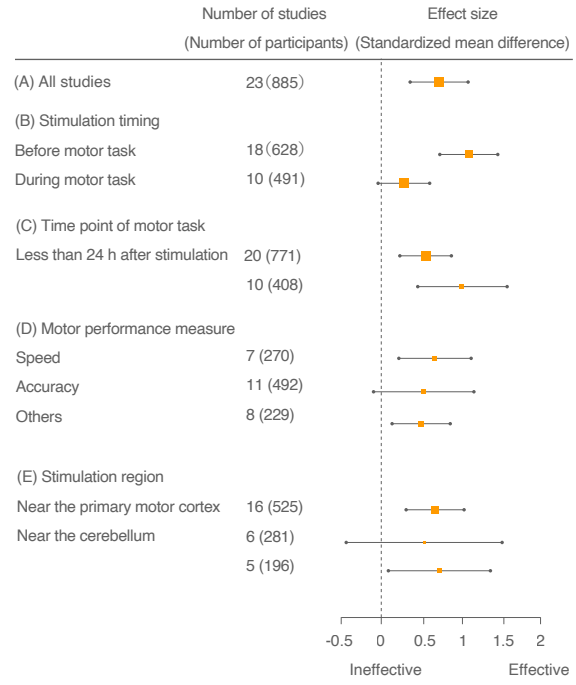


Figure 1. Results of the effectiveness assessment. (A) Overall effects. (B) Stimulation timing. (C) Time points of motor tasks. (D) Types of motor performance. (E) Stimulation regions.

Can non-invasive brain stimulation improve motor performance?

Study characteristics

- Stimulation electrode locations (Fig. 2A): The central region (Cz, C3, C4) was stimulated in 19 studies, the cerebellum in 7 studies, and other regions in 9 studies. In 14 studies that focused on motor tasks with only one hand, stimulation was applied to the contralateral primary motor cortex (11 studies) or the ipsilateral cerebellum, both of which are considered important for hand movements.

- Number of electrodes (Fig. 2B): In 20 studies, two electrodes (anode and cathode) were used, whereas in 5 studies, stimulation patterns were generated using multiple electrodes.

- Stimulation intensity (Fig. 2C): Almost all studies (24 of 25) used a stimulation intensity between 1 and 2 mA, with a maximum intensity of 2 mA. The remaining studies used an intensity of 0.6 mA.

- Intervention period and duration (Fig. 2D): The duration of NIBS interventions varied across studies, ranging from single-day sessions in 17 studies, 2-5 days in 6 studies, and 7-20 days in 2 studies. The duration of stimulation per day ranged from a minimum of 10 min to a maximum of 40 min. For studies involving multiple days of stimulation, the frequency was once every 1-3 days.

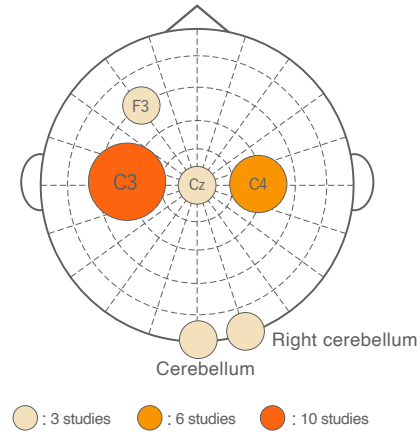
- Targeted motor performance: Movement accuracy, such as tasks requiring reaching toward a target (13 studies); movement speed, such as reaction time[#1] or task completion time (9 studies); and other motor performance (e.g., force production or endurance task: 8 studies) were evaluated.

- Types of motor tasks: The most common studies focused on upper limb movements, such as rapid and precise reaching toward a target or performing sequential finger movements (18 studies). One study involved lower-limb strength training, whereas six studies examined whole-body movements, including activities such as dancing or walking.

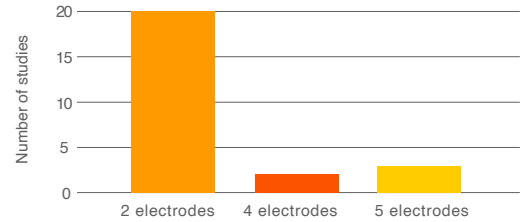
- Brain stimulation during motor tasks: Nineteen studies applied brain stimulation during motor tasks, whereas four studies administered stimulation prior to the onset of motor tasks.

- Types of control conditions: All studies used sham stimulation as a control, in which the same brain region was stimulated for only a short period of several tens of seconds.

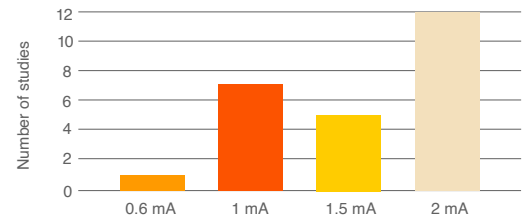
(A) Stimulation electrode locations



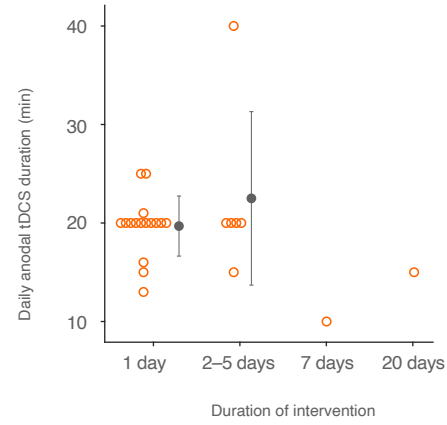
(B) Number of stimulation electrodes



(C) Stimulation intensity



(D) Daily anodal tDCS duration grouped by the length of the intervention period



RQ5

Can non-invasive brain stimulation improve motor performance?

Systematic review processes

- A literature search of studies focusing on anodal tDCS to enhance motor task performance in healthy adults aged 18-64 years was conducted across five databases [28].
- Our search yielded 3,796 articles, which were screened according to the predetermined inclusion criteria. Finally, 25 randomized controlled trials were selected to summarize the main characteristics of the studies to date and investigate the safety of NIBS.
- Of the included studies, 23 calculated the effect sizes related to motor performance with a low risk of bias. These studies were used for the statistical analyses to evaluate the effectiveness of NIBS.

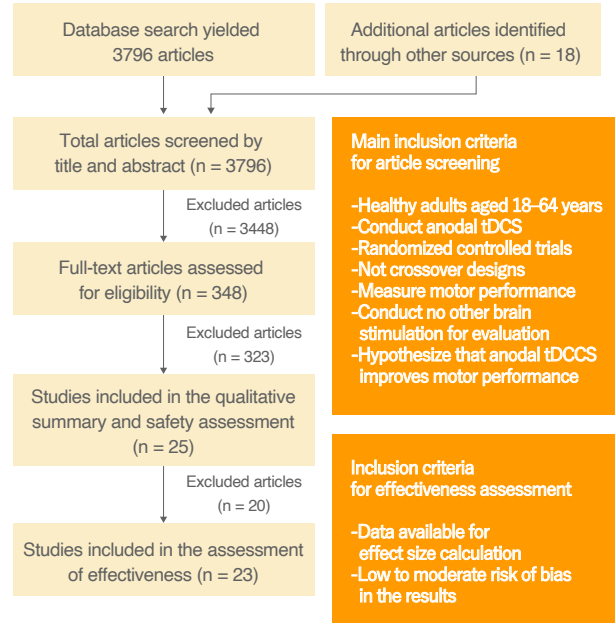


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Reaction time: For further details, refer to the keywords in RQ1: "Can neurofeedback training improve motor performance?"

RQ6

Can non-invasive brain stimulation*1*2 improve sleep quality?

Answer

Transcranial alternating current stimulation (tACS) may extend sleep duration, whereas non-invasive brain stimulation (NIBS) before sleep may prolong the time it takes to fall asleep. However, owing to the limited number of studies, these findings cannot be considered conclusive.

Transcranial alternating current stimulation (tACS) may extend sleep duration in healthy adults*3. Conversely, non-invasive brain stimulation (NIBS) while awake before sleep may prolong the time required to fall asleep. No serious adverse events have been reported to date.

*1 Non-invasive brain stimulation is not recommended for individuals without specialized knowledge. For further details, refer to Neurotech Guidebook Vol. 1 GQ3, "What is neuromodulation?"
*2 In this RQ, we focused on NIBS and excluded transcranial magnetic stimulation and transcranial ultrasound stimulation.
*3 In this RQ, healthy adults were defined as those aged ≥ 18 years who had not been diagnosed with any physical, mental, or neurological disorder or disease at the time of participation.

Background and Purpose

Good sleep is essential for maintaining and promoting physical and mental health. However, in today's society, which is often referred to as "24-hour society," sleep-related issues are becoming more prevalent. Common sleep hygiene behaviors#1, such as maximizing exposure to daylight, engaging in regular moderate exercise, avoiding caffeine in the evening or later, and minimizing bright light before bedtime, are widely recommended for improving sleep quality[8]. Recently, NIBS has been suggested as a potential alternative approach for enhancing sleep quality. The reliability and safety of NIBS in improving sleep quality in healthy adults without sleep disturbances need to be validated.

Results - Safety

The safety of NIBS could not be determined because of the limited number of studies focusing on adverse events. However, no adverse events have been reported to date.
Among the 39 studies investigating sleep quality in healthy adults undergoing NIBS, the incidence of adverse events has been reported in 9 studies, involving 227 participants with stimulation durations of up to 60 min per night. Only one study (19 participants) conducted a systematic assessment of adverse events and reported sensations such as stinging (17 participants), tingling (4 participants), and itching (9 participants) at the electrode application site, with frequencies comparable to those observed in the sham (placebo) conditions. Additionally, five participants reported headaches, which occurred at approximately twice the rate than that observed in the sham group. Isolated reports of nausea, burning sensation, and minor burns caused by unintended electrode contact have been documented in separate studies (in one participant each).

Can non-invasive brain stimulation improve sleep quality?

Results - Effectiveness

- A collective analysis of all studies suggests that tACS may improve sleep quality. However, scientific evidence remains insufficient, largely owing to potential biases in the reported outcomes and limited sample sizes across the available studies.
- Conversely, the findings also indicate that tDCS does not significantly improve sleep quality. Moreover, slow oscillatory tDCS[#2] (so-tDCS) had no effect on sleep quality (Fig. 1A).
- Regarding the stimulation timing, the overall effect of NIBS application before sleep did not influence sleep quality. Similarly, the effect of NIBS administration during sleep on sleep quality remains inconclusive (Fig. 1B).
- Analysis of specific sleep indices[#3] revealed that NIBS prolongs the time required to fall asleep (sleep latency); however, no measurable effect on the power of the delta waves was observed. The presence or absence of effects on other sleep indices could not be definitively established (Fig. 1C).
- tACS may extend sleep duration, although its effect on improving sleep efficiency remains unclear (Fig. 1D).
- In relation to sleep latency, NIBS applied before sleep was associated with a prolongation of sleep latency (Fig. 1E).
- Notably, these findings were predominantly obtained from laboratory studies conducted under controlled conditions using sleep measurement devices. Consequently, it remains unclear whether these analogous effects are manifested in typical daily sleep environments.

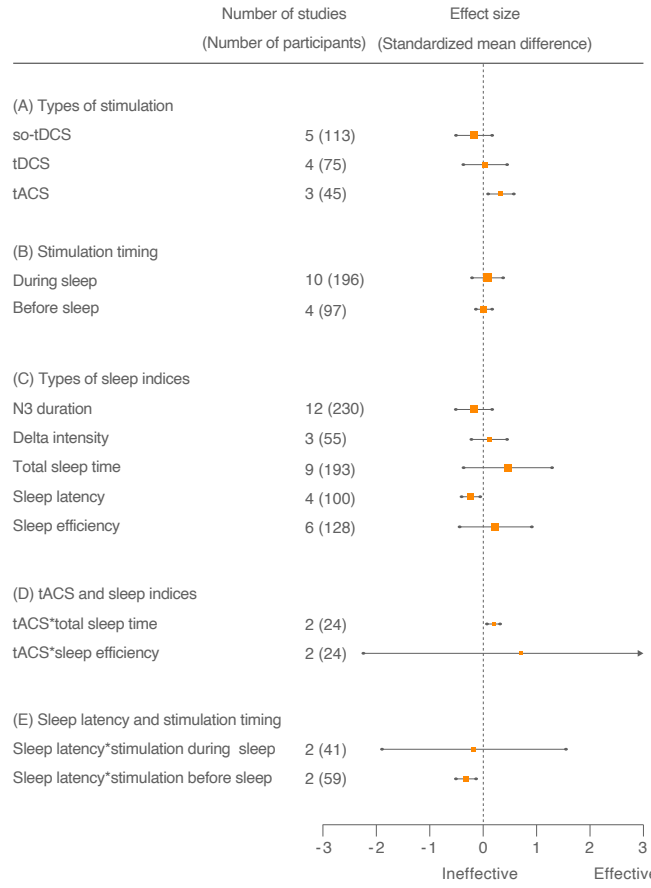


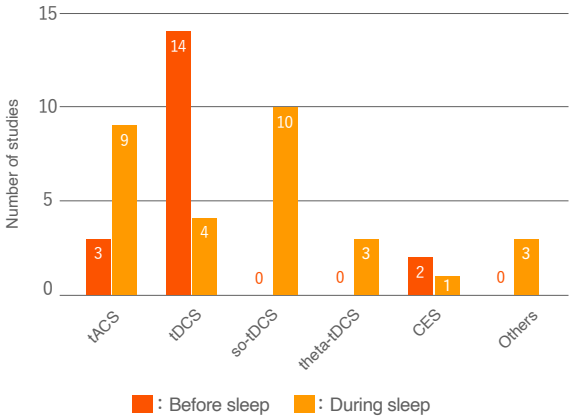
Figure 1. Results of the effectiveness assessment. (A) Effects by stimulation method. (B) Effects by stimulation timing. (C) Effects on sleep indices. (D) Effects of tACS on each sleep index. (E) Effects of stimulation timing on sleep latency.

Can non-invasive brain stimulation improve sleep quality?

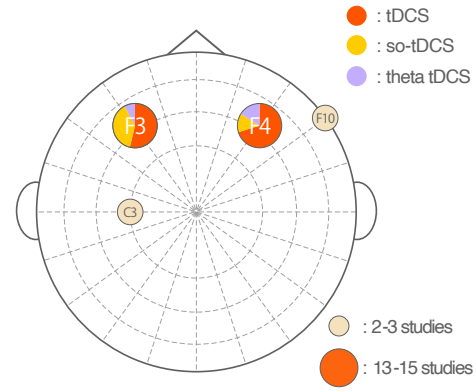
Study characteristics

- Participants: A total of 33 studies involving participants aged ≤ 64 years and 6 studies included participants aged ≥ 65 years.
- The types of NIBS (Fig. 2A) included tDCS (18 studies), tACS (12 studies), so-tDCS (10 studies), theta tDCS[#4] (3 studies), cranial electrotherapy stimulation (CES; 3 studies), and other stimulation methods (3 studies).
- Stimulation electrode locations (Fig. 2B, C): The frontal region was most commonly stimulated (F3, F4: 25 studies; F7, F8: 3 studies; and F10: 3 studies).
- Stimulation frequency: 0.5 Hz (4 studies), 0.75 Hz (17 studies), 0.84 Hz (1 study), 5 Hz (5 studies), 12 Hz (1 study), 40 Hz (1 study), and 140 Hz (1 study).
- Stimulation timing: Thirty studies administered stimulation during sleep, whereas 17 administered stimulation before sleep.
- Methods of sleep assessment included polysomnography (34 studies), actigraphy (2 studies), sleep quality questionnaires (16 studies), and psychomotor vigilance test[#5] (1 study).
- Evaluated sleep indices (Fig. 2D) Primary sleep indices evaluated using polysomnography included N3 (41 studies), wakefulness (20 studies), N1 (19 studies), total sleep time (13 studies), sleep efficiency (13 studies), and sleep latency (10 studies).

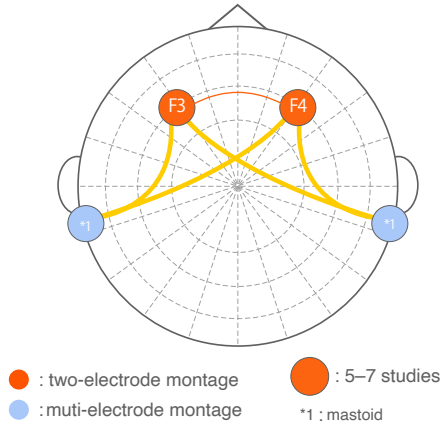
(A) Types of stimulation and timing



(B) Stimulation electrode locations of tDCS



(C) Stimulation electrode locations of tACS



(D) Main indices of sleep quality assessment

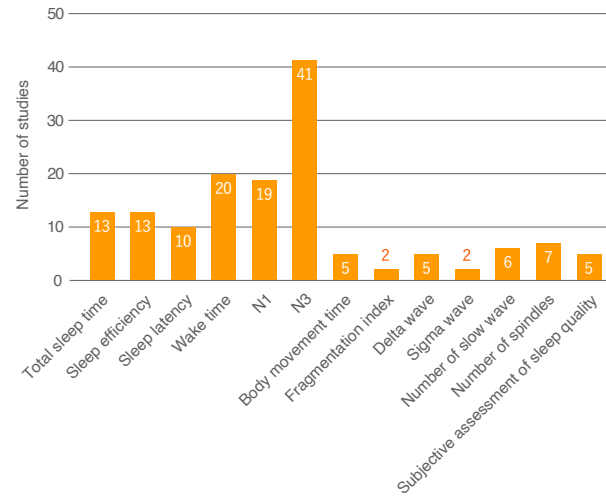


Figure 2. Study characteristics. (B) and (C) show the placement examples of two or more studies. For (C), the line thickness represents the number of cases and the color indicates the type of montage.

Can non-invasive brain stimulation improve sleep quality?

Systematic review processes

- Studies focusing on NIBS to improve sleep quality in healthy adults ≥ 18 years were searched across five databases[29].
- A total of 1,182 articles were identified through our search and other sources, which were screened according to the pre-determined inclusion criteria. The 39 selected articles were used to summarize the characteristics of the available studies conducted and investigate the safety of NIBS.
- Of the 39 studies, 14 were randomized controlled trials that calculated effect sizes related to sleep quality with a low to moderate risk of bias. These studies were used for statistical analyses to evaluate the effectiveness of NIBS.

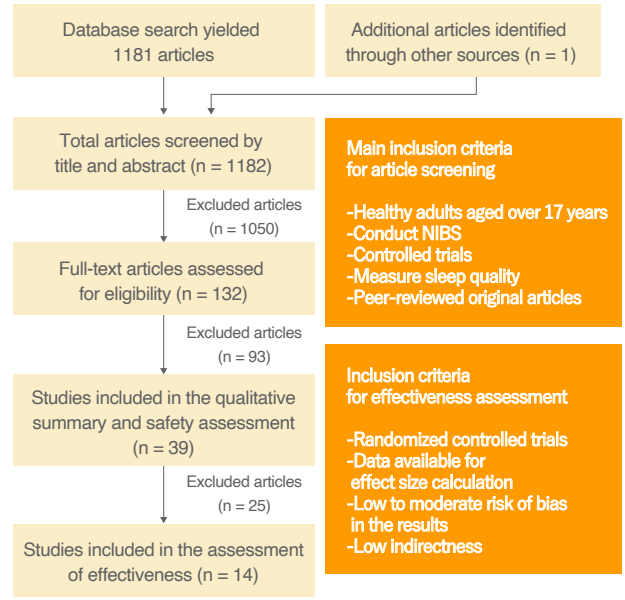


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Sleep hygiene behaviors refer to appropriate practices that contribute to the improvement in sleep quality. To improve sleep quality, we recommend referring to the guidebook for maintaining and improving sleep quality developed by sleep science experts in collaboration with the Ministry of Health, Labour and Welfare[8].

#2. Slow oscillatory tDCS involves a current intensity that changes at a consistent rhythm. For further information, refer to Appendix 2, “Non-invasive brain stimulation.”

#3. Sleep indices: In line with RQ2, we employed commonly used sleep indices, including the percentage and emergence time of N3 among the sleep stages, sleep EEG power (sigma and delta waves), sleep efficiency, sleep latency, and wake time after sleep onset. Additionally, subjective assessments of refreshing sleep, overall sleep quality, and sleepiness levels were used as indicators of sleep quality. For more detailed information on sleep quality assessment methods and specific sleep indices (such as sleep stages, sleep EEG, sleep efficiency, sleep latency, and wake time after sleep onset), refer to the keywords in RQ2, “Can neurofeedback training improve sleep quality?"

#4. Theta tDCS: Similar to slow oscillatory tDCS, this method features rhythmic changes in current intensity that align with the theta oscillation frequency of the EEG (4-8 Hz).

#5. Psychomotor vigilance test: This is a simple response task that requires sustained attention and is widely used for the objective assessment of sleepiness.

RQ7

Can non-invasive brain stimulation*1*2 enhance attentional functions?

Answer

Non-invasive brain stimulation (NIBS) may enhance attentional functions. However, owing to the low reliability of the available evidence, it remains unclear which aspects of attentional functions are affected and to what extent they are affected.

In healthy adults*3, NIBS may lead to slight improvements in attentional functions, particularly after stimulation. However, it remains unclear which specific attentional functions, such as spatial orientation, arousal, or executive control, are improved by NIBS. To date, no serious adverse events have been reported.

*1 NIBS is not recommended for individuals without specialized knowledge. For further details, refer to the NeuroTech Guidebook Vol. 1, GQ3 "What is neuromodulation?"
*2 This RQ focused on types of NIBS that could potentially become accessible to the general public in the future, excluding transcranial magnetic stimulation and transcranial ultrasound stimulation.
*3 In this RQ, "healthy adults" were defined as those aged 18–65 years who were not diagnosed with any physical, mental, or neurological disease at the time of participation in the experiment.

Background and Purpose

NIBS is a group of methods that modulate brain function by applying external stimulation through the scalp. Among these methods, transcranial direct current stimulation (tDCS) delivers a weak direct current via electrodes placed on the scalp, whereas transcranial alternating current stimulation (tACS) applies alternating currents to the scalp. A growing number of studies have explored whether NIBS enhances attentional functions. However, the evidence remains inconclusive, and the effectiveness of NIBS has not been established. Attentional function consists of three main components: spatial orientation, which directs attention toward the intended target; arousal, which refers to generating and maintaining an appropriate state of readiness; and executive control, which involves inhibiting irrelevant information and resolving conflicts [30]. This review examined whether NIBS can reliably and safely modulate these attentional components in healthy adults and the extent to which such modulation occurs.

Results - Safety

As most studies did not quantitatively report adverse events, it was not possible to accurately assess safety. However, no serious adverse events have been reported to date in the literature. Among the 58 studies that applied NIBS to healthy adults and evaluated attentional function, 40 mentioned adverse events. The reported adverse events included tingling or itching sensations on the scalp where the electrodes were attached, headaches, dizziness, nausea, fatigue, and decreased concentration. Some studies quantitatively compared the occurrence of these adverse events between participants who received actual NIBS and those who underwent sham stimulation#1, in which only a brief, weak stimulation was applied to the same brain region to mimic the sensation of NIBS without producing lasting effects. Eight studies (314 participants in the NIBS group and 187 in the sham group) reported data on the frequency of adverse events, and 17 studies (424 participants in the NIBS group and 405 in the sham group) reported data on their severity. Across these studies, no significant differences were observed between the NIBS and sham conditions in terms of the frequency or severity of adverse events.

Can non-invasive brain stimulation enhance attentional functions?

Results - Effectiveness

- An analysis of all studies suggested that NIBS may slightly improve attentional functions (Fig. 1A).
- However, the available evidence was insufficient to determine whether NIBS can reliably improve any specific aspect of attentional function, including spatial orientation, arousal, and executive control (Fig. 1B).
- Compared with control conditions, NIBS showed greater improvements in attentional function than sham stimulation, which was briefly applied to the same brain region (sham #1) or stimulation, which was continuously applied to other brain regions (sham #2). In contrast, no clear difference in effectiveness was observed when NIBS was compared with stimulation using the opposite polarity (anodal vs. cathodal) or no stimulation (Fig. 1C).
- Regarding evaluation timing, significant effects of NIBS on attentional functions were not observed during stimulation but were observed immediately after stimulation (Fig. 1D).
- Among the various types of NIBS, anodal tDCS may enhance attentional functions, whereas other stimulation methods did not demonstrate significant effects (Fig. 1E).

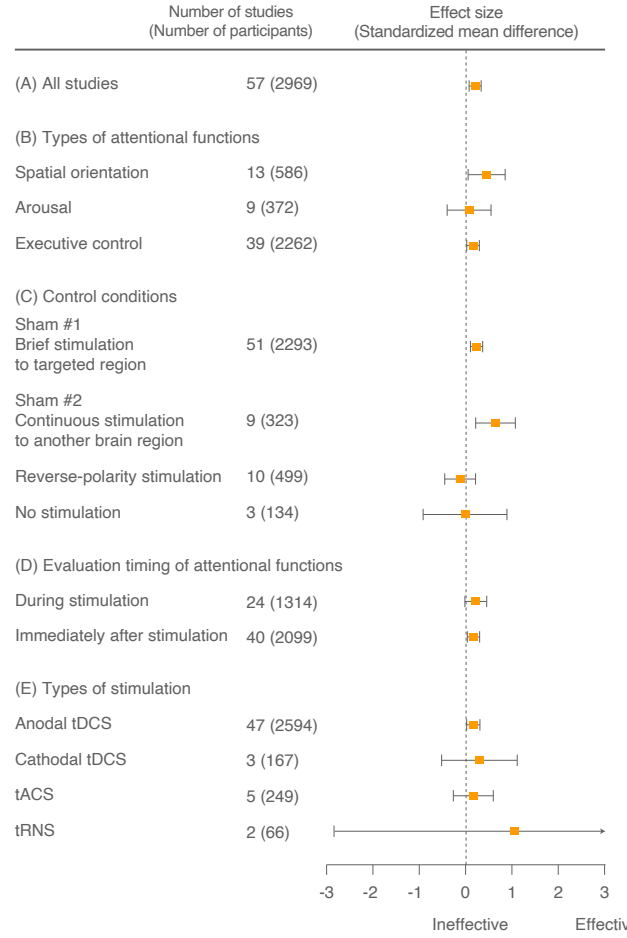


Figure 1. Results of the effectiveness assessment. (A) Overall effects. (B) Effects of NIBS on different attentional functions. (C) Superiority of NIBS under control conditions. (D) Effects of evaluation timing. (E) Effects of stimulation methods.

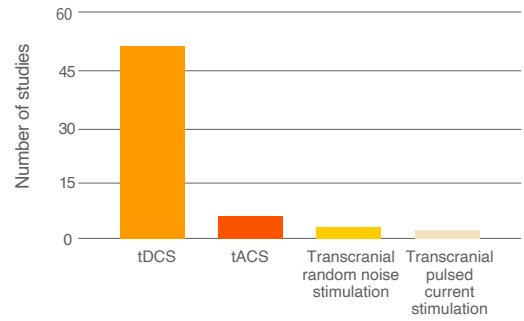
RQ7

Can non-invasive brain stimulation enhance attentional functions?

Study characteristics

- Types of NIBS (Fig. 2A) included tDCS (anodal : 48 studies; cathodal : 3 studies), tACS (5 studies), transcranial random noise stimulation (2 studies), and transcranial pulsed current stimulation (1 study).
- The stimulation electrode locations (Fig. 2B) : The frontal region was the most commonly stimulated (F3 : 26 studies; F4 : 14 studies), with some studies focusing on the parietal, frontopolar, and central regions.
- Stimulation intensity : Almost all studies (53 studies) used a stimulation intensity between 1 and 2 mA, with a maximum of 2 mA. The remaining four studies used an intensity of 0.5 mA, and one study did not report the intensity used.
- Intervention period and duration : The duration of NIBS interventions varied across studies, ranging from single-day sessions in 47 studies to multiple days in 11 studies. The duration of stimulation per day ranged from a minimum of 5 to a maximum of 60 min.
- Targeted attentional functions : Spatial orientation (13 studies), arousal (9 studies), and executive control (39 studies).
- Brain stimulation during attentional tasks : 24 studies applied brain stimulation during tasks, whereas 40 studies administered stimulation prior to the onset of tasks.
- Types of control conditions : 51 studies used the sham #1 condition, nine used the sham #2 condition, ten used stimulation with the opposite polarity, and three used no stimulation.

(A) Types of stimulation



(B) Anodal electrode locations of tDCS

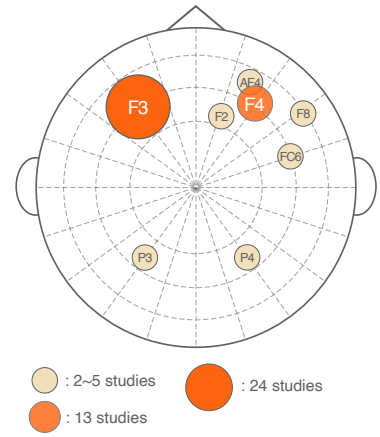


Figure 2. Study characteristics. (B) shows examples of electrode locations from two or more studies.

Can non-invasive brain stimulation enhance attentional functions?

Systematic review processes

- Studies focusing on NIBS to improve attentional functions in healthy adults aged 18–65 years were searched in four databases [31].
- A total of 2,634 articles identified through our search were screened according to the predetermined inclusion criteria. Among these, 58 randomized controlled trials were selected to summarize the main characteristics of the studies to date.
- Of the 58 studies, 55 were judged to have a low-to-moderate risk of bias. These studies were used for statistical analyses to evaluate the efficacy and safety of NIBS.

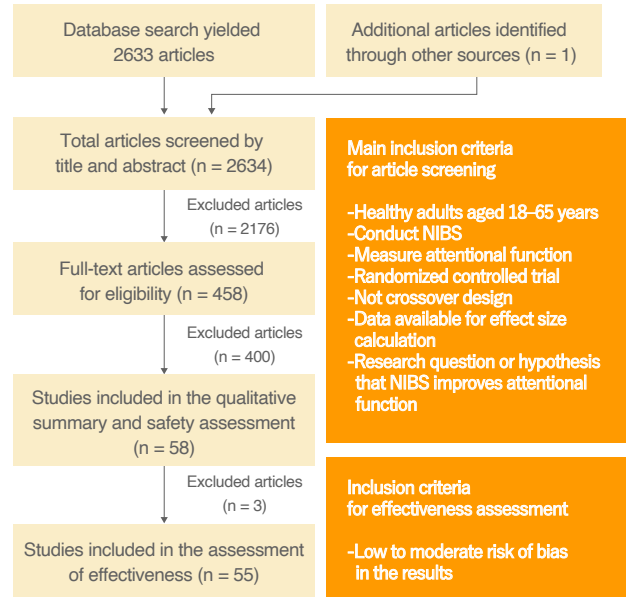


Figure 3. Flowchart of the systematic review process.

Keywords

#1. For details regarding the explanation of sham stimulation, refer to Appendix 3.

RQ8

Can non-invasive brain stimulation*1*2 enhance memory functions?

Answer

Anodal transcranial direct current stimulation (tDCS) of the frontal region may improve memory.

Anodal tDCS applied to the frontal region may yield a modest enhancement in memory#1 in healthy adults*3. This effect is anticipated to last for several hours following stimulation, although it is unlikely to extend beyond 1 week. In contrast, cathodal tDCS and transcranial alternating current stimulation (tACS) had no effect on memory. No serious adverse events were reported to date.

*1 Non-invasive brain stimulation is not recommended for individuals without specialized knowledge. For further details, refer to Neurotech Guidebook Vol. 1 GQ3, "What is neuromodulation?"
*2 In this RQ, we focused on NIBS and excluded transcranial magnetic stimulation and transcranial ultrasound stimulation.
*3 In this RQ, healthy adults were defined as those aged ≥ 18 years who had not been diagnosed with any physical, mental, or neurological disorder or disease at the time of participation in the experiment.

Background and Purpose

Non-invasive brain stimulation (NIBS) refers to techniques that stimulate the brain through electrodes placed on the scalp to modulate brain function. The tDCS is a NIBS method that employs a weak direct current to modulate neuronal activity. In contrast, tACS uses alternating currents for stimulation. Memory enhancement is a topic of substantial interest across various age groups, prompting extensive research on the potential of NIBS for memory improvement. However, there is no consensus on its efficacy. Although some studies reported improvement in recall of memorized letters and figures following NIBS, others demonstrated no significant difference compared with placebo conditions [32,33]. Therefore, the reliability and safety of NIBS in enhancing memory in healthy adults need to be explored.

Results - Safety

The safety of NIBS could not be determined because of the limited number of studies discussing adverse events. However, no adverse events have been reported to date.
Among the 51 studies investigating memory function in healthy adults undergoing NIBS, 11 provided data on the incidence of adverse events involving 484 participants with stimulation durations of up to 30 min/-day. In these 11 studies, 20-50% of participants experienced sensations such as tingling or itching on the scalp, likely attributed to the application of electrodes or the electrical stimulation itself. Furthermore, the participants reported more intense sensations of pain and burning with NIBS than with the sham (placebo) condition. Nevertheless, all reported adverse events were classified as mild.

RQ8

Can non-invasive brain stimulation enhance memory functions?

Results - Effectiveness

- A collective analysis of all studies suggests that anodal tDCS may improve memory. However, scientific evidence remains insufficient, largely because of potential biases in the reported outcomes. Conversely, the findings also indicate that cathodal tDCS and tACS do not significantly improve memory (Fig. 1A).
- Regarding memory contents, anodal tDCS has demonstrated the potential to improve working memory; however, overall scientific evidence validating these findings is scarce. Therefore, the impact of anodal tDCS on declarative memory remains inconclusive (Fig. 1B).
- Regarding the duration of its effects, anodal tDCS may enhance memory within a few hours of stimulation. However, no memory improvements were observed during stimulation or within a day to a week following stimulation, and no lasting effects were detected beyond 1 week (Fig. 1C).
- Regarding electrode placement, anodal tDCS applied to the frontal region may improve memory. However, the effect of stimulation targeting other areas such as the frontal pole or parietal region remains unclear (Fig. 1D).
- Notably, these findings were obtained under controlled experimental conditions. Given the minimal memory changes observed, it is uncertain whether such effects would result in meaningful functional enhancements in daily life.

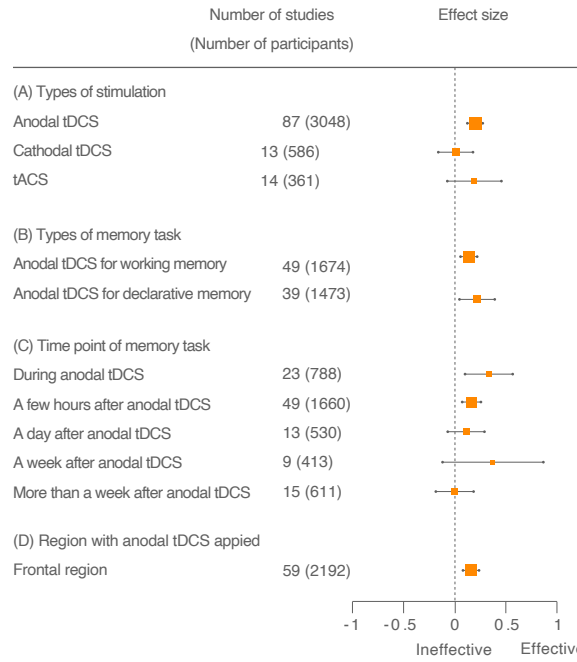


Figure 1. Results of the efficacy assessment. (A) Effects by stimulation method. (B) Effects of anodal tDCS by memory task. (C) Effects of anodal tDCS by time point of memory task. (D) Effects of anodal tDCS by stimulation region.

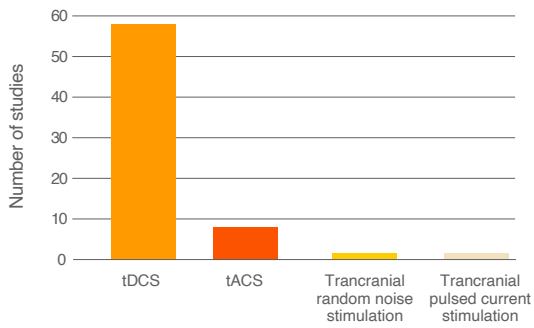
1

Can non-invasive brain stimulation enhance memory functions?

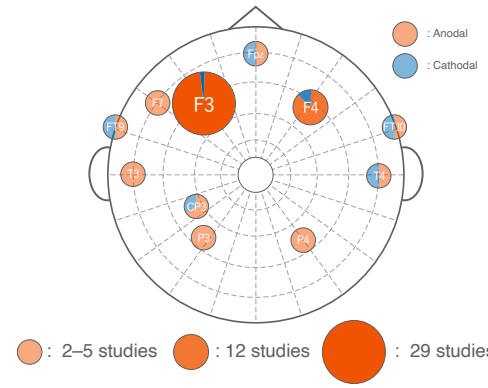
Study characteristics

- Participants: A total of 56 studies included participants aged ≤ 64 years, and 14 studies included participants aged ≥ 65 years.
- Types of NIBS (Fig. 2A) included tDCS (58 studies), tACS (8 studies), transcranial random noise stimulation (1 study), and transcranial pulsed current stimulation (1 study).
- Stimulation polarity of tDCS (Fig. 2B): Anodal stimulation, aimed at activating targeted brain regions, was employed in 57 studies, and cathodal stimulation, designed to inhibit brain activity, was used in 9 studies.
- Stimulation electrode locations (Fig. 2B): The frontal region was the most commonly stimulated (F3: 29 studies; F4: 12 studies), with some studies focusing on the parietal and central regions.
- Targeted memory functions: Working memory (38 studies), declarative memory (31 studies), and others (9 studies).
- Memory content (Fig. 2C, D): In working memory testing, various types of stimuli were used, including letters (17 studies), figures (14 studies), word/sentence combinations (4 studies), numbers (13 studies), and figure/word combinations (3 study).
- For declarative memory, the tasks included word/sentence combinations (20 studies), figures (7 studies), visual language (3 studies), and numbers (4 studies).
- Assessment Methods: Memory performance was evaluated using the percentage of correct responses (61 studies), reaction time[#3] (17 studies), and other measures (6 studies).
- Timing of the Memory Task: Seventeen studies conducted memory tasks during NIBS, whereas 42 studies tested participants within hours of stimulation. Furthermore, follow-up assessments were performed 1 day after NIBS (9 studies), 7 days after (6 studies), and 8 days or later (11studies).

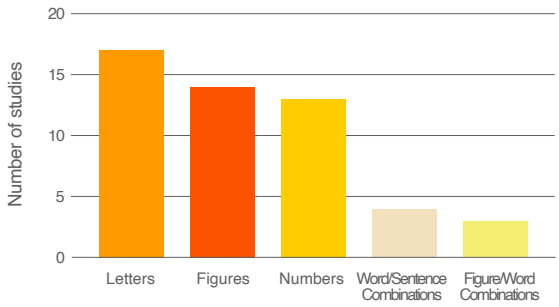
(A) Types of stimulation



(B) Stimulation electrode locations of tDCS



(C) Memory contents of working memory



(D) Memory contents of declarative memory

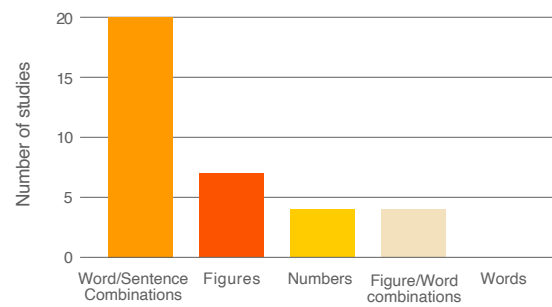


Figure 2. Study characteristics.

RQ8 Can non-invasive brain stimulation enhance memory functions?

Systematic review processes

- Studies focusing on NIBS to improve memory in healthy adults aged ≥ 18 years were searched across six databases [34].
- A total of 11,385 articles identified through our search were screened according to the predetermined inclusion criteria. Among these, 67 randomized controlled trials were selected to summarize the main characteristics of the studies to date and investigate the safety of NIBS.
- Of the 67 studies, 65 calculated effect sizes related to memory function with a low to moderate risk of bias. These studies were used for statistical analyses to evaluate the efficacy of NIBS.

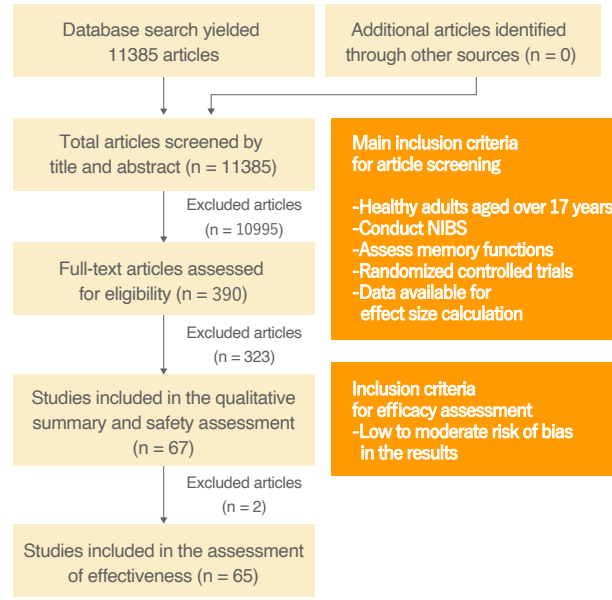


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Memory: There are several categories of memory. For further details, refer to the keywords in RQ4: "Can neurofeedback training enhance memory functions?" This RQ focused on declarative memory and working memory; procedural memory was not included in the analysis.

#2. Working memory is the capacity to temporarily retain information for a brief period, typically ranging from a few seconds to several tens of seconds, enabling the execution of various cognitive functions. Working memory is often assessed using an n-back task in which sequences of letters, numbers, or other stimuli are presented and participants must respond to items that were presented n positions earlier.

#3. Reaction time: For further details, refer to the keywords in RQ1: "Can neurofeedback training improve motor performance?"

RQ9

Is EEG a biomarker of relaxation?

Answer

The amplitude of alpha oscillations in EEG possibly indicates the level of relaxation, depending on the measurement site. However, these results should be interpreted with caution.

In healthy adults*, the amplitude of alpha oscillations in the central, occpital, and frontal regions may serve as an indicator of relaxation. Specifically, alpha oscillations in the central region were primarily associated with physiological relaxation reflected by autonomic nervous system activity obtained from electrocardiograms (ECG), whereas those in the occipital region were related to subjective feelings of relaxation. However, the alpha oscillations measured in other areas or other EEG components (such as delta, theta, beta, gamma, and other indices) did not show a consistent relationship with the relaxation. These results suggest that although the common belief that alpha oscillations provide some insights into relaxation levels is not entirely incorrect, the relationship between alpha oscillations and relaxation varies depending on the recording region and type of relaxation index[#1]. Therefore, their use as reliable biomarkers of relaxation requires careful consideration. In actuality, the amplitude of alpha oscillations is influenced by the level of relaxation and multiple factors, including sleepiness, fatigue, and attention [35-39]. Additionally, no universally accepted gold standard for the relaxation index has been established.

*In this RQ, healthy adults were defined as those aged 18-65 years who had not been diagnosed with any physical, mental, or neurological disorders or disease at the time of participation.

Background and Purpose

Among the general public, alpha oscillations in EEG are often associated with a relaxed state, as reflected in the marketing of products like "alpha oscillation-producing music CDs" to induce relaxation. Some researchers believe that alpha oscillations strengthen during relaxation. However, there is no consensus on the relationship between relaxation indices and various EEG components, including alpha oscillations. This is primarily because the definition of relaxation varies among studies and includes subjective and objective measures, such as autonomic nervous system[#2] measures obtained from electrocardiograms (ECGs). Therefore, it is essential to explore to what extent EEG measurements and relaxation are actually related.

Is EEG a biomarker of relaxation?

Results - Safety

Given that EEG measurements are generally considered safe, they are used to evaluate relaxation. EEG measures weak electrical signals using electrodes placed on the scalp. Skin rashes may occasionally develop from the tape used to attach the electrodes. However, the risk is comparable to that of using adhesive bandages on the skin. Although the reviewed studies did not include safety statements, no inherent adverse events are generally associated with EEG measurements.

Results - Validity

- Weak positive correlations were observed between the alpha oscillations and relaxation indices, including correlations between the alpha power in the central regions and ECG-related relaxation indices (r = 0.24), between the alpha power in the occipital region and questionnaire-based relaxation indices (r = 0.31), and between the alpha power in the frontal region and overall relaxation indices (r = 0.17) (Fig. 1A).
- No significant correlation was observed between the relaxation indices and the amplitude of alpha oscillations in the parietal and frontopolar regions (Fig. 1A).
- No significant correlations were observed between the relaxation indices and delta, theta, beta, or gamma oscillations or other EEG indices (Fig. 1B).

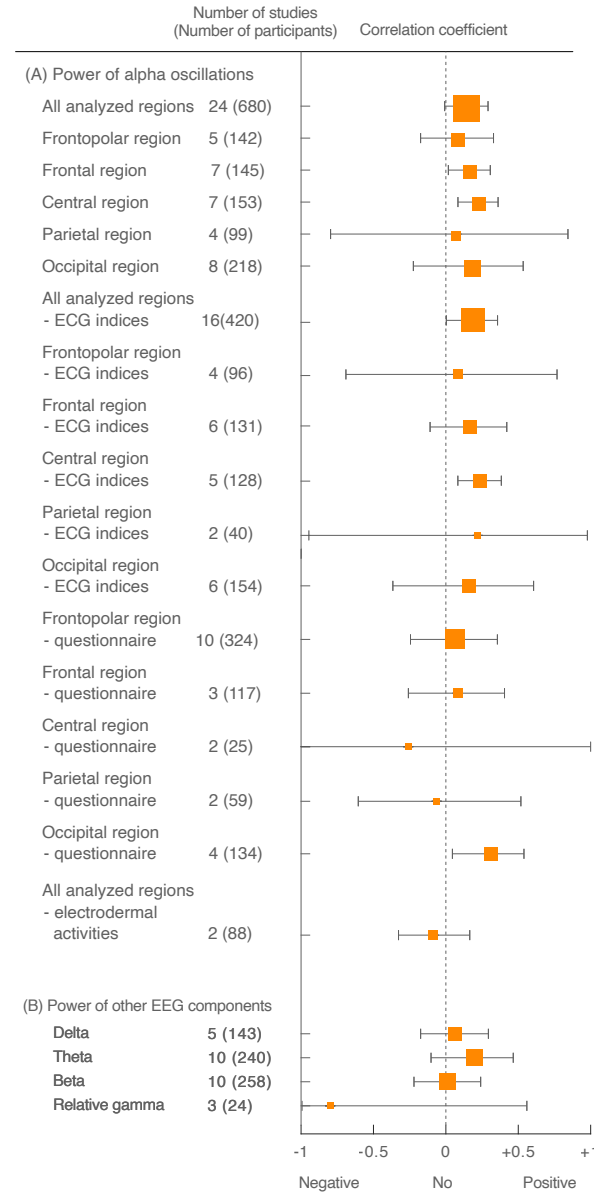
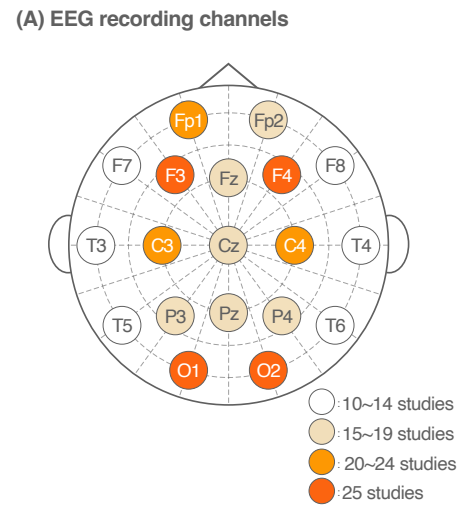


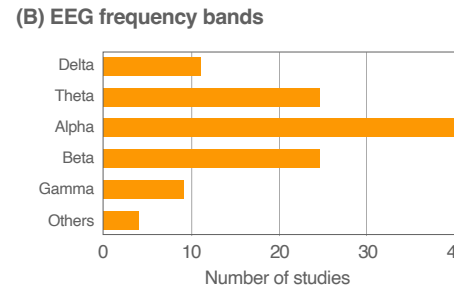
Figure 1. Results of the validity assessment. (A) Alpha oscillation recording sites and correlations with relaxation indices. (B) Correlation between the power of other EEG components and relaxation index.

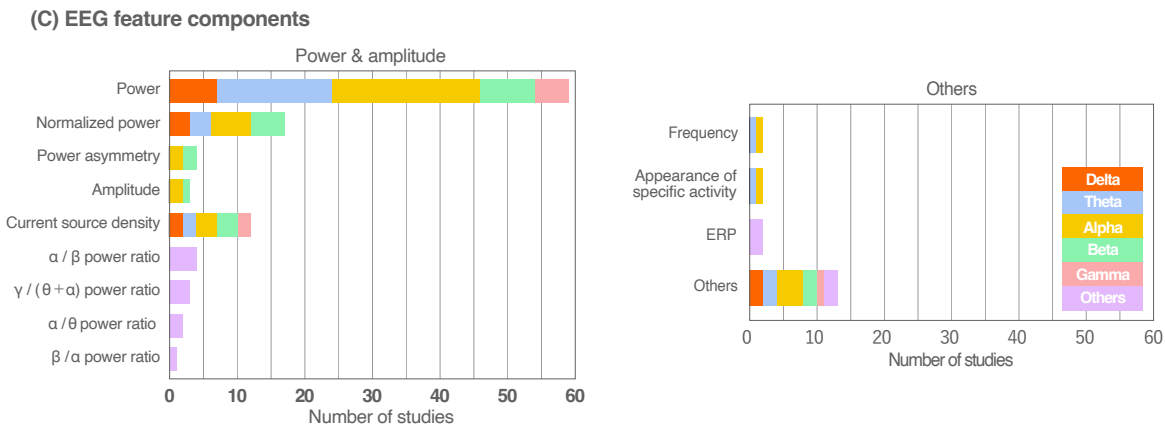
Is EEG a biomarker of relaxation?

Study characteristics

- EEG recording channels (Fig. 2A): Measurements from the frontal region (F3: 29; F4: 28 studies) and occipital (O1: 27; O2: 28 studies) regions were the most common, followed by the central (C3: 21; C4: 22 studies) regions. In addition, 18–20 studies recorded EEG signals from the frontopolar (Fp1 and Fp2) and parietal (P3 and P4) regions.
- EEG frequency bands (Fig. 2B): Alpha oscillations were the most commonly used EEG index (40 studies), followed by theta and beta oscillations (24 studies each), and approximately 10 studies used delta and gamma oscillations.
- EEG feature components (Fig. 2C): Most studies have used power or normalized power for each frequency band. Few studies have used power ratios between multiple frequency bands or asymmetries in oscillatory power between the left and right hemispheres.
- Types of relaxation indices (Fig. 2D): ECG-related indices were the most frequently used, including heart rate, low frequency (LF, typically 0.05-0.15 Hz) power, high frequency (HF, typically 0.15-0.4 Hz) power, and LF/HF ratio. Several subjective measures of the level of relaxation have also been used, such as the Profile of Mood State (POMS) tests. Some studies have used physiological indices derived from electrodermal activity or salivary indices, such as the cortisol test.







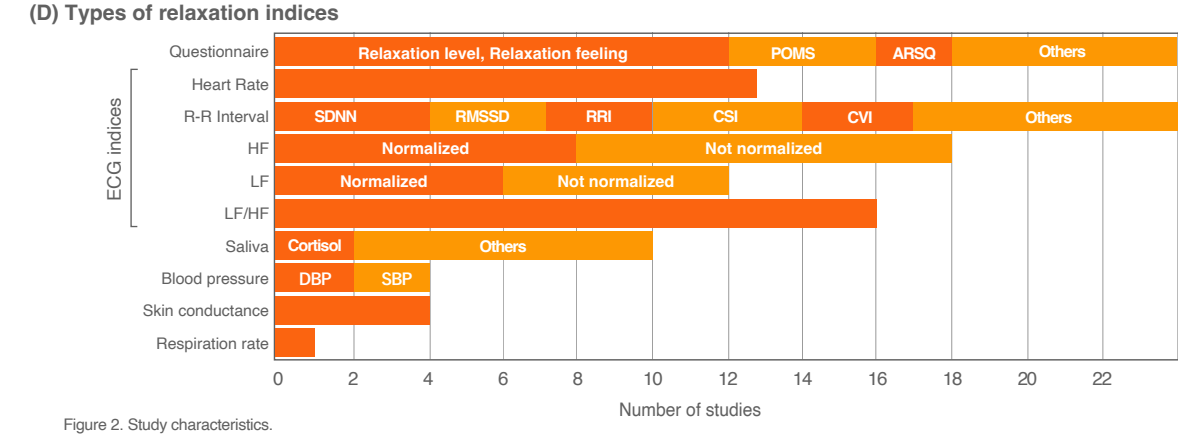


Figure 2. Study characteristics.

Is EEG a biomarker of relaxation?

Systematic review processes

- A comprehensive literature search of studies that measured EEG and relaxation indices (e.g., ECG-related indices associated with parasympathetic nervous system activity and subjective relaxation indices) in healthy adults aged 18-65 years was conducted across five databases [40].
- Our search yielded 4,194 articles screened according to the predetermined inclusion criteria. Finally, 54 articles were selected to summarize the main characteristics of the available studies and investigate their safety profiles.
- Of the 54 included articles, 31 provided correlation values between EEG and relaxation indices with a low to moderate risk of bias in the results. These studies were used for statistical analyses to evaluate the validity of EEG indices.
- Two primary types of relaxation indices are commonly used: subjective indices obtained through questionnaires and ECG-related indices. Because some indices increase with deeper relaxation, whereas others decrease, adjustments were made to standardize the interpretation, ensuring that higher values consistently represent greater relaxation. For instance, the signs of subjective indices, such as nervousness and heart rate, were reversed, as smaller values indicated a more relaxed state.

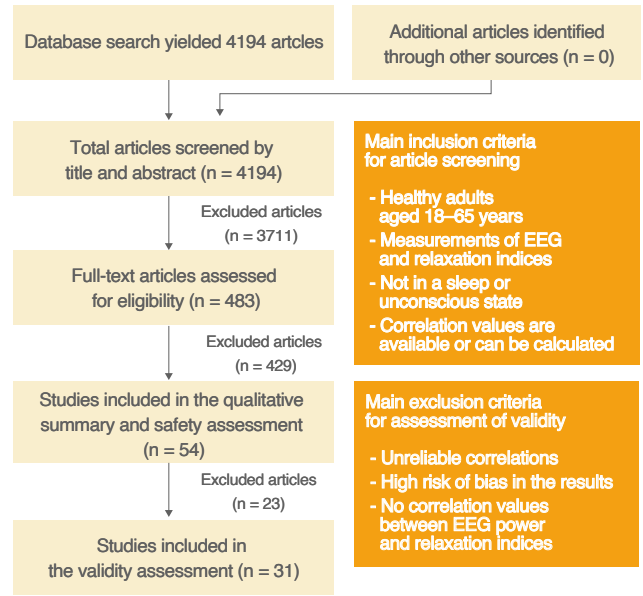


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Relaxation index: Relaxation is generally defined as a state of parasympathetic dominance. Quantitative measures of relaxation include subjective measures (questionnaires), electrodermal activities, and ECG- and saliva-related measures, with different studies using different measures.

#2. Autonomic nervous system: Controls involuntary functions such as breathing, sweating, temperature regulation, and metabolism. It maintains balance in the body by coordinating the sympathetic nervous system that drives the "fight or flight" response in stressful situations and the parasympathetic nervous system, which predominates in quiet "rest and digest" conditions.

RQ10 Is EEG a biomarker of stress level?

Answer *Systematic review is in progress. Please wait for the answer.*

RQ11 Is EEG a biomarker of attention level?

Answer *Systematic review is in progress. Please wait for the answer.*

RQ12 Is EEG a biomarker of certain emotion categories?

Answer **Some EEG indices may signal that an emotional response has been elicited. However, commonly used EEG indices are not sufficient to reliably distinguish between the types of emotions experienced.**

When images or words inducing pleasant or unpleasant emotions were presented to healthy adults*, the amplitude of late positive potential (LPP)#1, recorded from the central/parietal regions, increased compared to that observed in neutral emotional states. However, no significant difference in LPP amplitude was observed between pleasant and unpleasant emotions. This suggests that, although LPP can serve as an indicator of the presence of emotional responses, it does not function as a marker for distinguishing specific emotions. Notably, studies on the accuracy of emotion estimation using EEG fall outside the scope of this RQ, and the findings here do not invalidate such techniques.

*In this RQ, healthy adults were defined as those aged 18-64 years who had not been diagnosed with any mental or neurological disorder or disease at the time of participation. Additionally, individuals with self-reported characteristics that could influence emotions, such as depressive or dependent tendencies, were excluded.

Background and Purpose

Traditionally, the assessment of emotions elicited by viewing photographs or listening to music has relied primarily on subjective evaluations through questionnaires or interviews. However, technologies have been developed to objectively evaluate emotions using biological signals such as EEG and autonomic nervous system indicators (e.g., heartbeat and sweating). This technology has potential applications in marketing and healthcare . A previous study investigating whether autonomic nervous system indicators reflect specific categories of basic emotions#2 reported that certain indicators modulate in response to emotional induction; however, they cannot distinguish between different types of emotions. [41]. This raises the question of whether EEG signals can modulate emotional induction and whether it is possible to distinguish emotions based on specific EEG indicators.

Results - Safety

Although the reviewed studies we reviewed did not specifically address safety concerns, EEG measurements are generally considered safe, and the use of EEG for emotion assessment has a high level of safety. For more detailed information on the potential risks of EEG measurement, please refer to the “Results (Safety)” section in RQ9.

RQ12 Is EEG a biomarker of certain emotion categories?

Results - Effectiveness

- Research focusing on emotional valence[#3] (Fig. 1A): The amplitude of LPP was larger when pleasant and unpleasant emotions were induced than with neutral emotions. Additionally, the P300[#1] amplitude increased when unpleasant emotions were induced.
- Research focusing on basic emotions (Fig. 1B) revealed that the LPP amplitude increases when disgust is elicited more than with neutral emotions.
- However, no significant differences in LPP amplitude were observed between pleasant, unpleasant, or disgust emotions. Additionally, P300 amplitude between pleasant and unpleasant emotions showed no differences when compared with neutral emotions (Fig. 1A, B).
- The amplitudes of early posterior negativity (EPN)[#1], components of visual evoked potentials (P1, N1, P2)[#1], and N400[#1] did not show obvious differences between pleasant and neutral emotions or between unpleasant and neutral emotions. (Fig. 1A, B).
- Few studies have investigated the relationship between alpha power and emotion; therefore, whether alpha power can serve as a reliable index of emotion remains unclear (Fig. 1A, B).

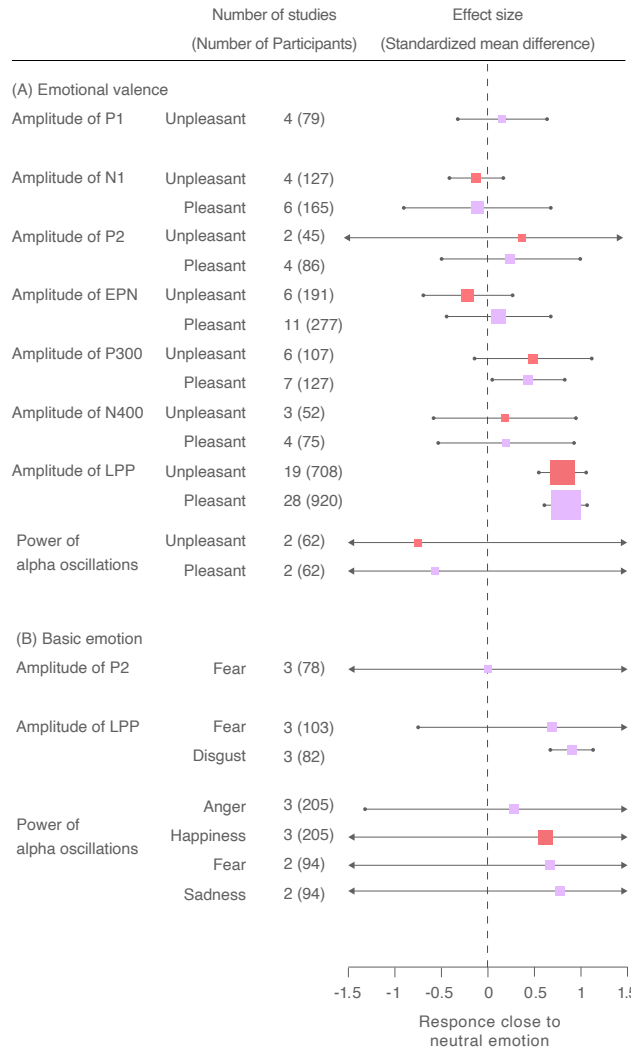


Figure 1. Results of the validity assessment. (A) Studies focusing on emotional valence. (B) Studies focusing on basic emotion.

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RQ12 Is EEG a biomarker of certain emotion categories?

Study characteristics

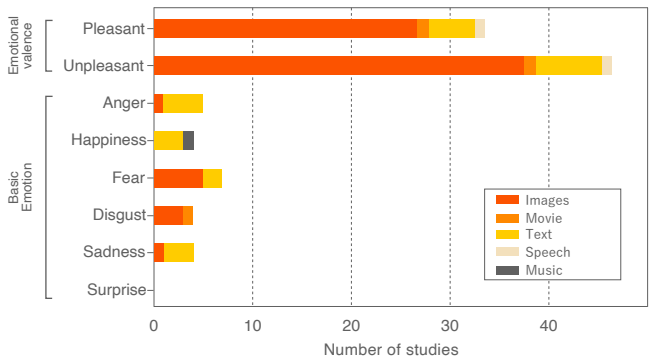
- Targeted emotion (Fig. 2A): Most studies focused on emotional valence, with 46 studies examining unpleasant emotions and 33 studies examining pleasant emotions. Studies targeting basic emotions were as follows: fear (n = 7), anger (n = 5), disgust (n = 4), happiness (n = 4), and sadness (n = 4). However, none of these studies specifically focused on surprise.

- Stimuli-inducing emotions (Fig. 2A): Images were the most commonly used stimuli in 46 studies, mostly utilizing images from the International Affective Picture System (IAPS)[#4]. Other types of stimuli included words (9 studies) and videos (5 studies).

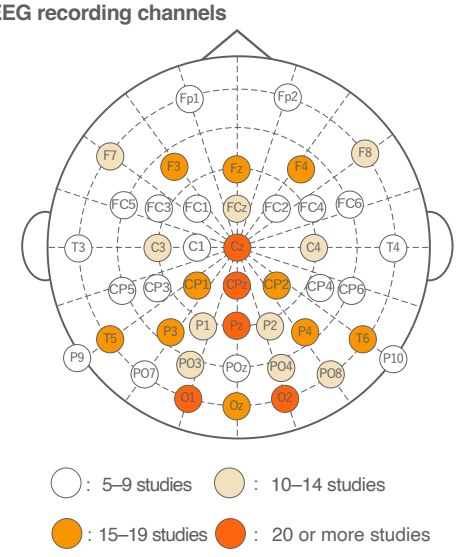
- EEG recording channels (Fig. 2B): Many studies have recorded EEG signals from the central/parietal areas (Cz, CPz, CP1, CP2, Pz, P3, and P4), parietal/occipital areas (Oz, O1, O2, P7, and P8), and frontal areas (Fz, F3, and F4). Some studies have also measured EEG signals from the temporal areas (CP5, CP6, T7, and T8).

- EEG features (Fig. 2C): In studies focusing on emotional valence, the most commonly used EEG feature was the LPP amplitude (pleasant, 19 studies; unpleasant, 28 studies). This was followed by EPN (pleasant: 6 studies, unpleasant: 11 studies), P300 (pleasant: 6 studies, unpleasant: 7 studies), N1 (pleasant: 4 studies, unpleasant: 6 studies), N400 (pleasant: 3 studies, unpleasant: 4 studies), P2 (pleasant: 2 studies, unpleasant: 4 studies), P1 (unpleasant: 4 studies), and alpha power (pleasant: 2 studies, unpleasant: 2 studies). Studies focusing on basic emotions included alpha power (anger: 3 studies, happiness: 3 studies, fear: 2 studies, sadness: 2 studies), LPP (fear: 3 studies, disgust: 3 studies), and P2 (fear: 3 studies). Additionally, some studies have used features not commonly shared in the literature, such as event-related potential (ERP) component latencies or the power of non-alpha oscillations.

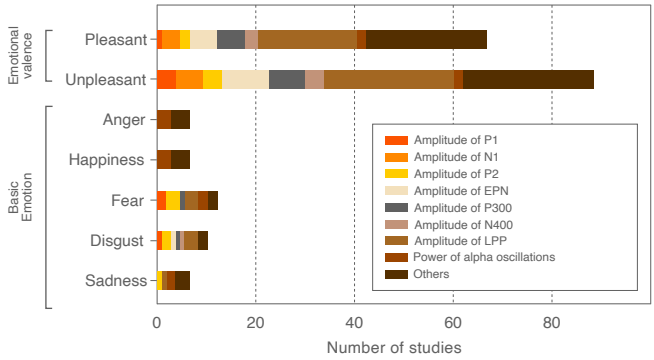
(A) Number of studies by emotions and breakdown of stimuli inducing emotion



(B) EEG recording channels



(C) EEG features



*A single study does include multiple features

Is EEG a biomarker of certain emotion categories?

Systematic review processes

- A comprehensive literature search was conducted across four databases to identify studies that measured EEG in healthy adults aged 18-64 years when exposed to emotionally inducing stimuli such as images, videos, or words [42].
- Our search yielded 3,268 articles, which were screened based on predetermined inclusion criteria. Subsequently, 116 articles were selected to summarize the main characteristics of the studies conducted to date and investigate their safety. Studies that induced emotions through recollection or imagination of emotional episodes were excluded.
- Of the 116 articles, 61 provided numerical data on the differences in EEG indices between pleasant, unpleasant, and neutral emotions, with a low to moderate risk of bias. These studies were used to summarize the current state of research and conduct statistical analyses to evaluate the validity of the EEG indices.

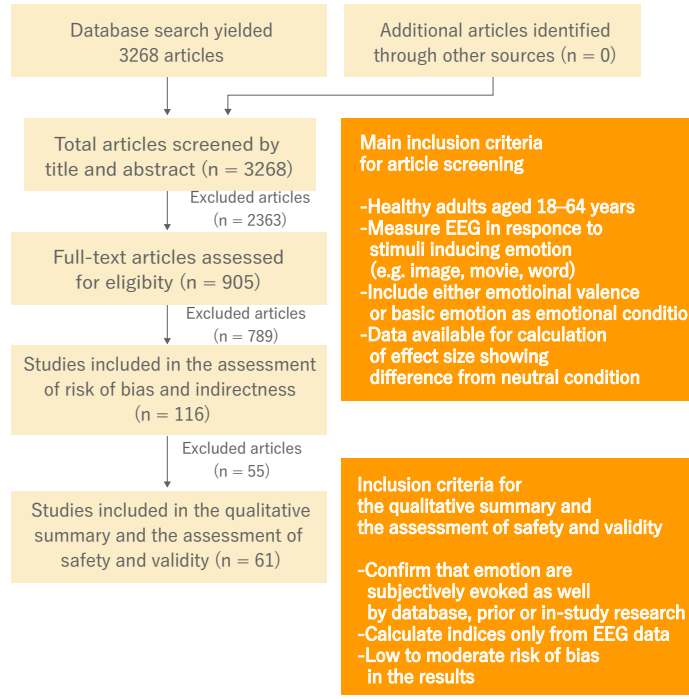


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Refer to Appendix 1 for the components of ERPs.

#2. Basic emotions: Innate and universal emotions are shared by all humans. Although researchers differ in their classification of basic emotions, a common and widely used classification is the six emotions proposed by Paul Ekman: anger, happiness, fear, disgust, sadness, and surprise [43].

#3. Emotional valence: James A. Russell proposed a circumplex model of emotion [44] that expresses emotions in two dimensions: valence (pleasant-unpleasant) and arousal (activation-deactivation).

#4. International Affective Picture System (IAPS): A database of emotionally evocative images developed at the University of Florida. Each image was assigned standardized scores for emotional valence and arousal, and the dataset is widely used in emotion research.

Appendix 1

Basic knowledge of EEG

Types and frequencies of EEG

Electroencephalograms (EEGs) are waveform signals that reflect the electrical activity in the brain. EEG recording is done using an electroencephalograph. The recorded EEG contains multiple oscillations with constantly changing waveforms (Fig. 1). These oscillations are classified based on their frequency, indicating their rhythm's speed. Frequency refers to the number of times a wave repeats in 1 s; for instance, if it repeats 10 times per second, its frequency is 10 Hz. The types of oscillations in the EEG were classified from the lowest (fewer waves) to the highest frequency as delta, theta, alpha, beta, and gamma (Table 1). Delta and theta oscillations, which have lower frequencies, are classified as slow waves, whereas beta and gamma oscillations, which have higher frequencies, are classified as fast waves, with alpha oscillations serving as intermediate waves. The amplitudes of the alpha and slow waves were greater than those of the fast waves (Fig. 1).

Because the physiological significance of EEG rhythms differs depending on their frequency, the state of brain activity can be roughly determined by examining changes in the signal amplitude at each frequency range (Table 1). However, achieving a one-to-one correspondence between the EEG frequencies and the functions they reflect remain challenging. Moreover, the criteria for the frequencies that delimit wave types are inconsistent. For instance, an 8 Hz wave can be classified as either alpha or theta, given that it reflects the functions and states associated with both. The relationship between EEG rhythm and function varies slightly with age, sex, and exercise habits [45-47].

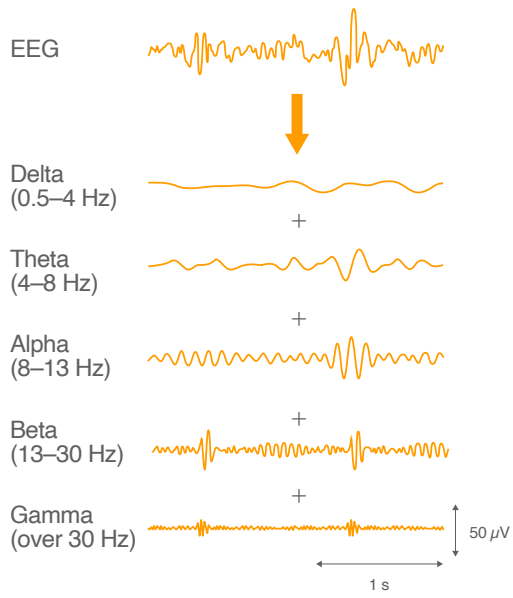


Figure 1. EEG and the multiple waves that make up an EEG. An EEG is a superimposed figure of multiple waves oscillating at various rhythms.

Table 1. Types of waveforms in EEG and their functions and states*

Types	Frequencies	Functions and states
Delta	0.5–4 Hz	Observed during deep sleep.
Theta	4–8 Hz	Associated with cognitive function and concentration.
Alpha	8–13 Hz	Related to relaxation and visual function.
Beta	13–30 Hz	Associated with motor function.
Gamma	Over 30Hz	Associated with various functions, including higher cognitive functions and meditation.

*The functions and states that each wave is believed to reflect are only generalizations. Please refer to the corresponding RQ to explain whether the theta oscillations actually indicate concentration or the alpha oscillations indicate a level of relaxation.

Event-related potential (ERP)

ERPs are time-locked variations in EEG potentials that occur in response to specific events, such as the presentation of stimuli (e.g., images or sounds) or task-related actions [48]. Because these potentials are typically small, they are often masked by spontaneous EEG activity (the brain's ongoing electrical signals are not associated with specific stimuli or tasks) during a single event. To detect ERPs, it is common to repeat the same event several times, sometimes dozens or more, and average the EEG recordings over several hundred milliseconds to a few seconds after the event (Fig. 2). ERP waveforms are composed of multiple waves, each of which consists of several overlapping ERP components occurring simultaneously in time and space [49]. Methods for examining the characteristics of ERP components include the direct measurement of the amplitude and peak latency (the time from event occurrence to the maximum potential fluctuation) of a waveform, assuming that it is composed of a single component. Another approach involves isolating and extracting specific components from overlapping ERP signals by analyzing the differences in ERP waveforms across conditions or between the left and right electrodes, followed by measurement of amplitude and latency.

Previous studies have linked ERP components to various cognitive functions, including perception, attention, memory, and prediction (Table 2). ERP components are generally named based on a combination of polarity (negative: N; positive: P) and latency (e.g., P300), order of peaks (e.g., N1), or the cognitive processes that they reflect (e.g., mismatch negativity). The timing of these components is determined relative to the stimulus onset, but their latencies can vary depending on the type of stimulus and difficulty of the task. Therefore, measuring the amplitude and latency of the ERP components and analyzing the differences across various conditions and groups may provide valuable insight into brain function.

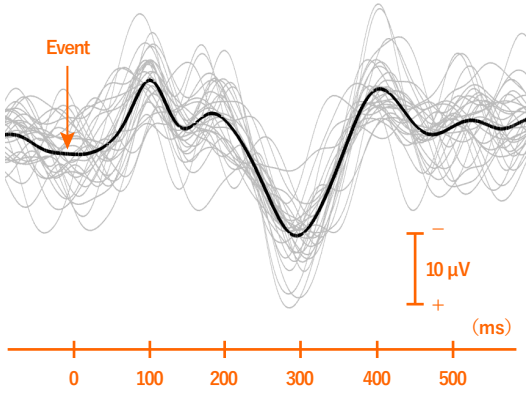


Figure 2. Examples of event-related potentials for auditory stimuli. Multiple peaks occur in response to a single auditory event. The thin gray lines represent individual waveforms for each event, and the thick black line shows the average waveform derived from 30 events. Through this process of averaging, the key components of ERPs are highlighted, and the influence of spontaneous EEG fluctuations and noise is reduced, enabling precise detection of ERP components.

Table 2. Characteristics of each component of ERPs in this book and the brain processes they reflect.

Component	Latency (ms)	①Main electrode position ②Brain process
N1 (Visual evoked potential)	150	① Broad area centered on the occipital region ② Early visual processing and identification of visual features
P2 (Visual evoked potential)	200	① Broad area centered on the central region ② Higher-order visual processing and selective attention
Early Posterior Negativitiy	200-300	① Parietal and occipital regions ② Perception of emotional stimuli and selective attention
P300	250-300	① *Central, parietal and frontal regions ② Attention allocation and detection of novel stimuli
N400	300-500	① Central and parietal regions ② Semantic processing (accessing semanti memory and contextual processing)
Late Positive Potential	300-1500	① Central and parietal regions ② Emotional processing and sustained attention to emotional stimuli

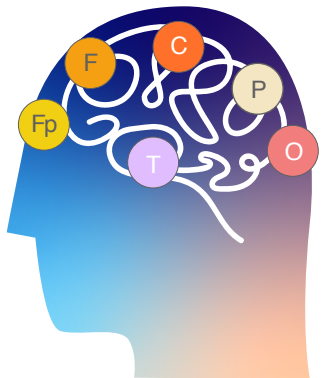
*The P300 primarily occurs at two electrode positions, as it consists of multiple subcomponents whose prominence varies depending on the experimental conditions

EEG electrode position: International 10-20 system

The International 10-20 system is a universal standard for electrode placement, which outlines the positions and names of electrodes. This ensures that EEG recording electrodes are placed equidistantly on the scalp (Fig. 2). This system enables EEG measurements from approximately the same brain region, regardless of head size, and ensures that recording electrodes are consistently placed when measuring EEG from the same person. However, EEG recordings from the scalp do not exclusively reflect the activity from the brain region directly under the recording electrode. Because brain activity is measured through multiple tissues and substances (including the skull, dura mater, and cerebrospinal fluid), the resulting EEG contains diverse activities from various brain regions.

The International 10-20 system uses alphabets to denote the location of recording electrodes on the head. For instance, "Fp" represents the frontal pole, the most anterior part of the head, while "F" refers to the group of electrodes located in the frontal region. Among the electrodes located on the line connecting the front of the left and right ears (preauricular points), "C" located in the central region mainly corresponds to the area around the motor cortex, and "T" located in the temporal region corresponds to the area around the auditory cortex. The "P" in the parietal region corresponds to the posterior parietal cortex, and the "O" in the occipital region corresponds to the visual cortex and other areas. Notably, the measurement position and number of electrodes may differ depending on the electroencephalogram used.

(A) Head position of each electrode symbol in the sagittal plane (head viewed from the side)



(B) Head position of each electrode symbol in the horizontal plane (head viewed from above)

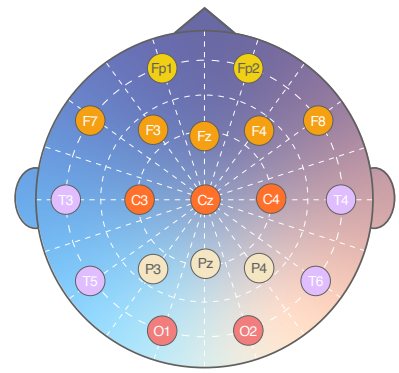


Figure 2. Electrode positions based on the International 10-20 system.

Appendix 2

Non-invasive brain stimulation

What is non-invasive brain stimulation?

Non-invasive brain stimulation is a technique used to modulate brain function by externally applying stimulation without requiring surgery or invasive procedures [50]. Stimulation methods include electrical, magnetic, and ultrasonic techniques, each capable of temporarily influencing a specific brain region (though not limited to the area directly under the stimulation site) based on different mechanisms.

Electrical stimulation involves delivering a weak current, typically 1-2 mA, to the brain through electrodes placed on the scalp[50] . Most commercially available brain-stimulation devices on online shopping platforms use this technique. Magnetic stimulation techniques include transcranial magnetic stimulation (TMS) [50], which generates strong magnetic fields that induce currents within the brain and transcranial static magnetic stimulation (tSMS) [51], which applies a constant magnetic field using a magnet. In contrast, ultrasound stimulation uses high-frequency sound waves to target specific brain regions, including deep brain areas [50].

Non-invasive electrical brain stimulation: Direct and alternating current stimulation

Two primary methods of non-invasive electrical brain stimulation are transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) [50]. Direct current is a type of electrical current that flows continuously in one direction for a fixed period, whereas alternating current periodically changes both magnitude and direction. These methods have different effects on brain activity, making the choice of stimulation dependent on the desired outcome.

The tDCS modulates neural activity via direct current (Fig. 1A) and can be classified into anodal and cathodal tDCS. In anodal tDCS, a positive electrode (anode) is placed over the targeted brain region and a direct current is applied to increase neuronal excitability. This method is commonly used to enhance motor and cognitive functions, improve learning and memory, and reduce the symptoms of certain psychiatric disorders. Cathodal tDCS involves placing a negative electrode (cathode) over the target region to decrease neuronal excitability and is often used in contexts where excessive brain activity needs to be suppressed.

In contrast, tACS uses an alternating current to modulate the brain activity (Fig. 1B). Each frequency of brain activity corresponds to a different function, even within the same brain region. The tACS applies an alternating current that matches the spontaneous frequency of the brain activity related to the targeted function. Specific brain functions can be selectively modulated by enhancing or inhibiting the brain activity at this frequency.

In addition to tDCS and tACS, other stimulation techniques include transcranial random noise stimulation (tRNS), which applies a random white noise-like current that is neither purely direct nor alternating, and transcranial pulsed current stimulation (tPCS), which delivers current in brief, pulse-like bursts. Moreover, specialized methods, such as slow oscillatory tDCS (so-tDCS), have been developed using currents that mimic the brain's natural slow oscillations during sleep [52] (Fig. 1C).

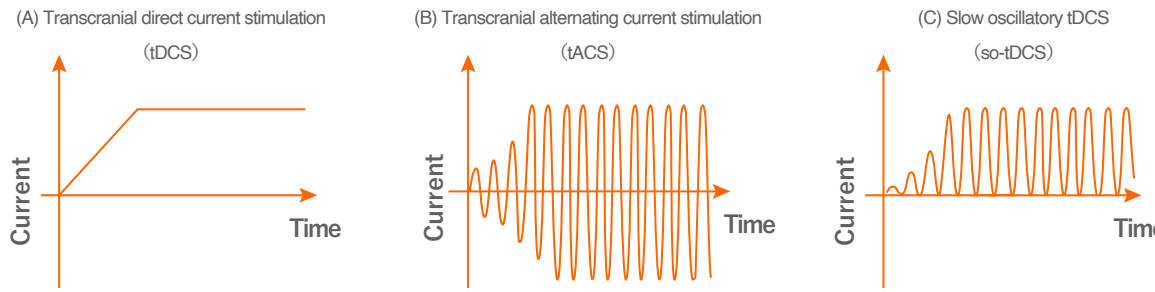


Figure 1. Schematic diagram of non-invasive brain stimulation with electrical current.

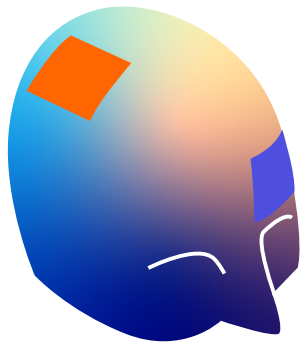
Factors influencing the effectiveness of tDCS and tACS

The effectiveness of tDCS and tACS varies depending on the electrode placement method [50]. The most commonly used configuration is the bipolar montage, in which one large electrode (25-35 cm^2) is placed over the area targeted for stimulation and the other is positioned on the forehead (Fig 2A). For instance, in a bipolar montage, the anode can be positioned near the motor cortex to enhance motor function. Although this configuration is relatively simple to implement, a major limitation is that the stimulation current may spread beyond the intended target area, potentially affecting the brain regions where the second electrode is placed.

To address this issue, high-density montage has gained popularity in recent years, as it allows for more localized stimulation. In this setup, a small electrode (approximately 1 cm in diameter) was placed directly over the targeted brain area and was surrounded by multiple smaller electrodes to create a more focused effect (Fig. 2B).

Additionally, factors such as sex, age, medical history, and smoking habits may influence the effects of tDCS and tACS [50,53]. However, these factors have not yet been thoroughly investigated, and the degree to which they affect outcomes remains unclear.

(A) Bipolar montage



(B) High-density montage

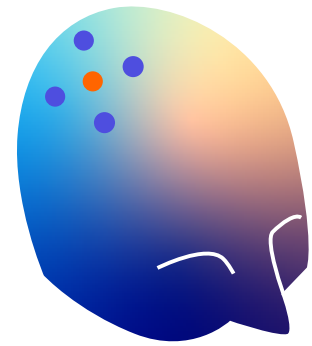


Figure 2. Schematic diagram of electrode positions in non-invasive brain stimulation with electrical current.

Appendix 3

Design and role of placebos in NeuroTech

In clinical trials designed to evaluate the effectiveness of a drug, the participants are allocated into two groups. One group receives the actual medication, while the other group receives a placebo that mimicked the actual drug in appearance and taste but does not contain the active therapeutic ingredient. The primary objective is to compare changes in symptoms between the two groups. However, why is it important to administer a placebo under such circumstances? One may argue that it is sufficient to compare the group that receives the drug with the group that does not.

If a comparison is made without a placebo, it is impossible to rule out the possibility that the psychological comfort of taking the drug may have a therapeutic effect. Therefore, when placebo-controlled trials are conducted, participants are unaware of whether they will receive a veritable drug or placebo. Even physicians administering the drug/placebo and evaluators assessing the drug's efficacy can have unconscious assumptions that may affect the accuracy of the drug's assessment. Therefore, clinical trials are conducted in a double-blind manner; that is, a trial with physicians, evaluators, and participants are not aware whether the participant is given a medication containing an active ingredient or a placebo. This approach reduces the risk of unconscious assumptions by those involved in the trial, which would influence the results and make the evaluation of drug efficacy more reliable.

When testing the efficacy of NeuroTech products, it is recommended to compare it to placebo conditions, as in drug efficacy studies. In non-invasive brain stimulation, electrodes placed on the scalp are often used to stimulate the brain. Sham stimulation was used as the placebo condition to mimic the tested stimulus (Fig. 1A). The typical placebo stimulus lasted from a few to a few dozen seconds, after which no stimulus was applied (Fig. 1B). This method provides the participant with a sensation similar to that of actual stimulation, even though the stimulation intensity is insufficient to produce any physiological effect. If veritable stimulation is more effective than placebo stimulation, it indicates that sustained stimulation is necessary to induce changes in motor performance or memory, and stimulated sensation alone cannot induce such changes.

Other placebos involve stimulating brain regions unrelated to the specific functions or performance under investigation (Fig. 1C). If actual stimulation is more effective than the placebo, stimulation of a particular brain region is essential for inducing changes in function and performance.

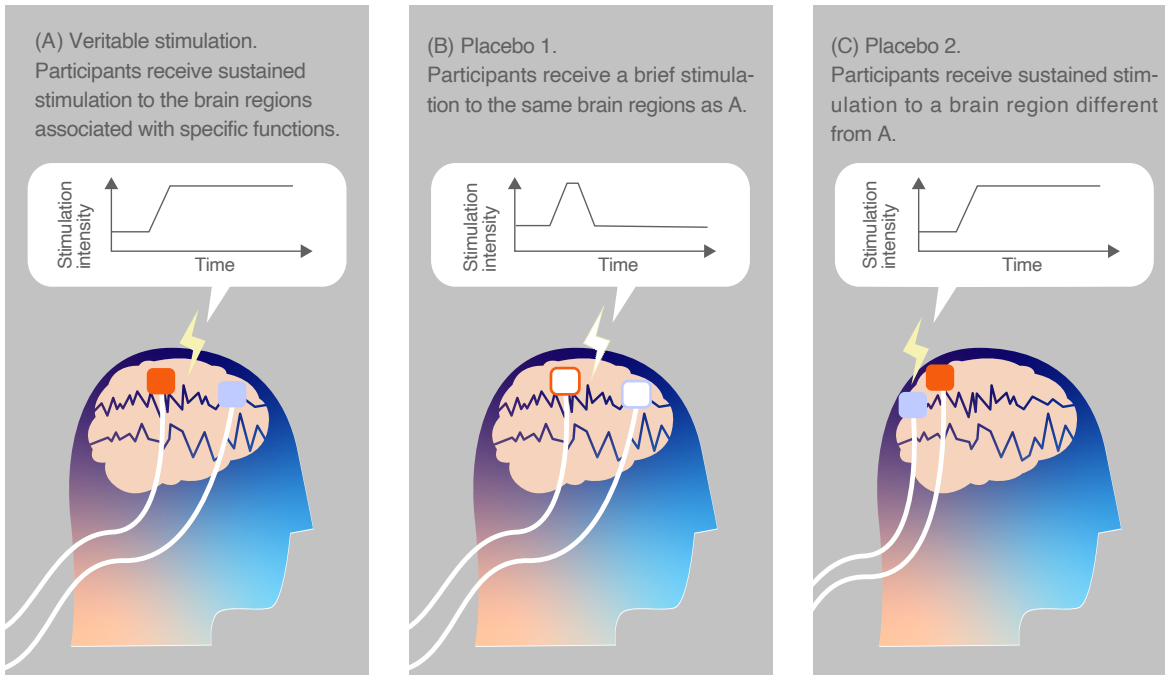


Figure 1. Schematic diagram of non-invasive brain stimulation and its placebo condition

Design and role of placebos in NeuroTech

Placebos in Neurofeedback Training (NFT) modify the feedback information in various ways, as shown in Fig. 2B-E. The first placebo (Fig. 2B) provided participants with random information that resembled brain activity. The second placebo (Fig. 2C) presented participants with biometric information other than brain activity, such as heart rate. If veritable neurofeedback is more effective than placebos, this indicates that the feedback of brain activity information, such as EEG, is crucial for inducing changes in function and performance.

The third placebo (Fig. 2D) provided participants with brain activity indices derived from non-target brain regions and other components. If veritable neurofeedback is more effective than the placebo, it confirms that feedback of the targeted brain activity is essential for inducing changes in function and performance. Although this method measures brain activity in the same manner as the first and second placebos, it differs by focusing on the feedback of the brain activity index, more precisely validating the importance of providing feedback from specific brain regions and at particular EEG activity frequencies [54].

The fourth placebo (Fig. 2E) involves assessing brain activity indices identical to those used in veritable neurofeedback but derived from previously recorded brain activity of others, such as EEG, and presenting them to the participants. If veritable neurofeedback is more effective than this placebo, it suggests that regulating brain activity through neurofeedback is crucial for inducing changes in function and performance.

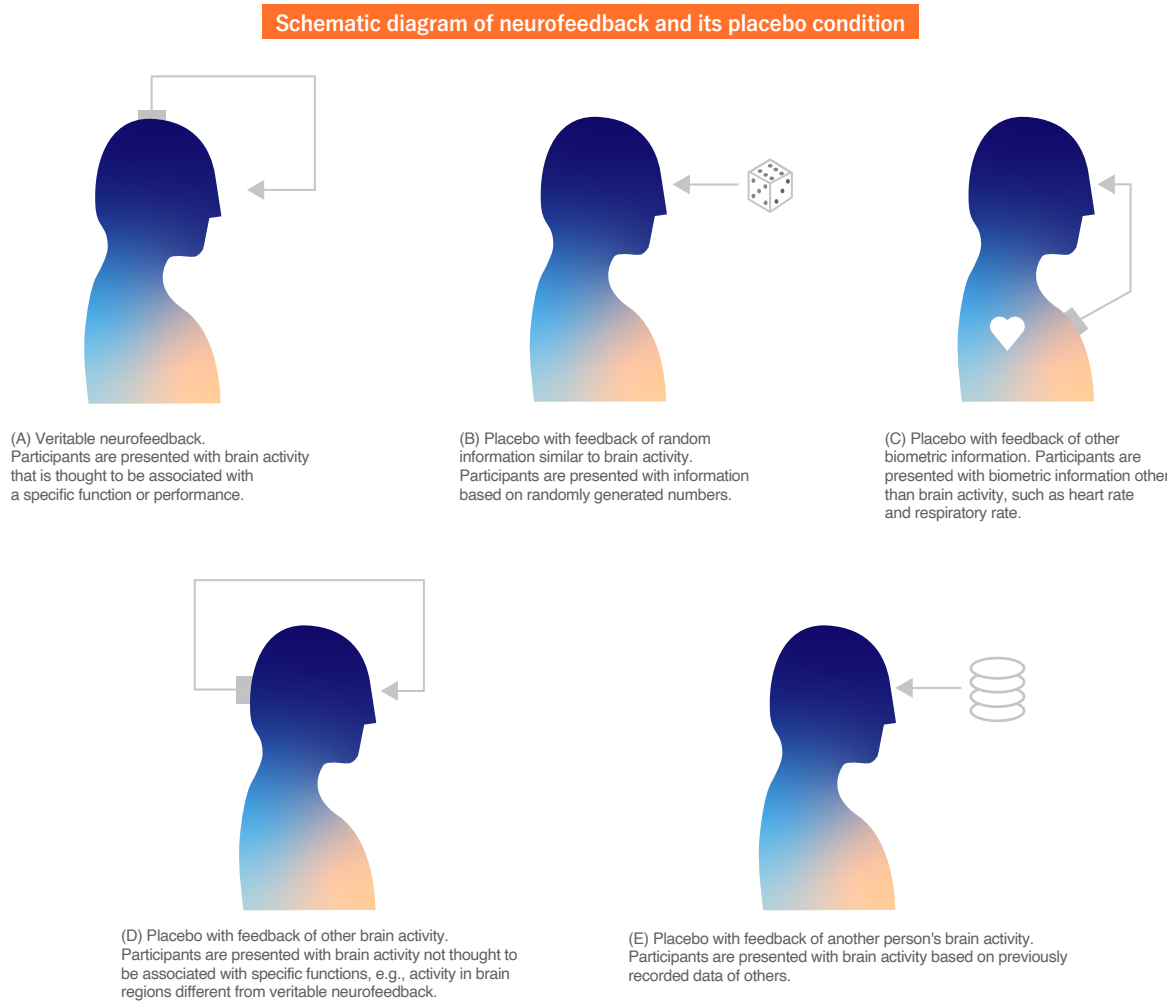


Figure 2. Schematic diagram of neurofeedback and its placebo condition.

Appendix 4

Reported adverse events following NeuroTech use

An adverse event is an undesired medical event, other than the intended effect, that occurs during or after using NeuroTech products [55]. Consider an antihypertensive drug as an example; the intended effect of antihypertensive medications is to lower blood pressure to an appropriate level. To this end, some antihypertensive drugs dilate the blood vessels or suppress the sympathetic nervous system. However, dilating blood vessels may cause the body to feel hot, and excessive suppression of the sympathetic nervous system may cause bradycardia. In addition, some individuals may experience dizziness following excessive reduction of blood pressure or may experience allergic reactions.

Occurrences other than the targeted effects are called adverse events. We also defined occurrences as adverse events, even if they are not assumed to be directly related to the use of the NeuroTech products but occurred during the study to determine the effectiveness of a NeuroTech product (e.g., when a participant catches a cold and is hospitalized during the study period).

Accumulating research data revealed insights on specific NeuroTech products or participant characteristics associated with adverse events. Table 1 shows the adverse events reported in reviewed studies during the development of this evidence book. Studies using non-invasive brain stimulation are conducted in accordance with the guidelines established by relevant academic societies [56,57] and are planned with consideration of the safety of the participants. Deviation from these guidelines when using non-invasive brain stimulation may increase the risk of adverse events.
Serious adverse events are adverse events that fall under the following categories (1) to (6) [55]

(1) Death.
(2) Those potentially leading to death.
(3) Requiring hospitalization or prolonged hospitalization for treatment.
(4) Permanent or significant disabilities or dysfunctions.
(5) Transmission to the next generation of children or grandchildren with congenital diseases or abnormalities.
(6) Patients judged to be medically significant, in addition to the above.

Possible non-serious adverse events associated with the use of NeuroTech products investigated in this book include: (1) temporary fatigue, (2) sick feeling, (3) pain or burning sensation at the site of stimulation, (4) headache, (5) dizziness or nausea, and (6) drowsiness [56]. Adverse events may vary among individuals and may also be influenced by the physical condition of the given day and the patient's mental state, such as tension level, and do not always occur.
A term similar to an adverse event is side effect. These refer to harmful effects on the user that may have occurred directly due to the usage of NeuroTech products [55].

Appendix 4

Reported adverse events following NeuroTech use

Table 1. Adverse events reported in studies selected for each RQ

	Intervention methods	Number of studies mentioning the presence or absence of adverse events	Serious adverse events	Non-serious adverse events
RQ1	Neurofeedback	5 / 33	No occurrence	No occurrence
RQ2	Neurofeedback	0 / 4	Unclear	Unclear
RQ3	Neurofeedback	2 / 41	No occurrence	No evaluation
RQ4	EEG- or fNIRS-based neurofeedback	4 / 44	No occurrence	No occurrence
RQ5	Non-invasive brain stimulation (anodal tDCS)	15 / 25	No occurrence	Tingling and itching on the scalp
RQ6	Non-invasive brain stimulation (excluding transcranial magnetic stimulation and ultrasound stimulation)	9 / 39	No occurrence	Tingling, itching on the scalp, headache, nausea, and burns from unintended electrode contact
RQ7	Non-invasive brain stimulation	40 / 58	No occurrence	Tingling and itching on the scalp
RQ8	Non-invasive brain stimulation (excluding transcranial magnetic stimulation and ultrasound stimulation)	11 / 51		Tingling and itching on the scalp
RQ9	EEG measurement	1 / 54	No evaluation	No occurrence
RQ10	EEG measurement	Under investigation		
RQ11	EEG measurement	Under investigation		
RQ12	EEG measurement	0 / 61	No evaluation	No evaluation

Supplementary Information

Evidence Book Creation

The "Liberation from Biological Limitations via Physical, Cognitive, and Perceptual Augmentation" (Project Manager: Ryota Kanai, Representative Organization: Advanced Telecommunications Research Institute International, hereinafter referred to as "Moonshot Kanai Project"), an R&D project under Moonshot Goal 1 of the Moonshot Research & Development Program, established the "BMI Usage Guideline Development Committee" (now, the Guidebook Development Committee) in July 2021 and started an initiative to develop the "BMI Usage Guideline" [2]. The development committee first conducted a preliminary survey on the sales status of NeuroTech products for general consumers in Japan and abroad and whether they are accompanied by scientific evidence. The survey revealed that despite the increasing number of products, the efficacy and safety of most products have not been validated. Consequently, we believed that the development of the BMI usage guidelines was not appropriate at this time because of the lack of reliable sources.
From the perspective of preventing health hazards, the committee members considered that conducting a comprehensive survey of the efficacy and safety of NeuroTech products and sharing the current results with the general public may be beneficial. In addition, to promote the sound development of the NeuroTech market, the same information should be shared with businesses that develop and provide such products and those that consider entering the NeuroTech market. Therefore, the Guidebook Development Committee has decided to develop two books: a "Guidebook" aimed at informing the general public about the current status of NeuroTech and an "Evidence Book" summarizing the scientific evidence on the effectiveness and safety of NeuroTech. To ensure the integrity of the evidence search results, more than 60% of the members of the Evidence Evaluation Committee, who are responsible for the creation of the Evidence Book, and all the external review board members, who conduct the content audit of the deliverables, were selected from among those with no conflicts of interest in the Moonshot Kanai Project.
To create the evidence book, the NTT Data Institute of Management Consulting, Inc., commissioned by the development committee, first conducted a market survey on the effectiveness widely advocated for NeuroTech products. Based on these results, the Evidence Evaluation Committee established 12 review questions (RQs) that should be scrutinized for their effectiveness, safety, and reliability. Each RQ was assessed by a systematic review (SR) and meta-analysis by two Evidence Evaluation Committee members and at least two SR members. Upon completion of the SR, an external review was conducted by the SR external review board using an SR evaluation tool called AMSTAR2 [59]. If any issues were raised during this external review, the SR processes were revised until the external review board approved that all steps had been conducted appropriately. After completing an external review of the SR process, two members of the Evidence Evaluation Committee were responsible for compiling the answers to the RQ. Additionally, volunteer SR members wrote appendices that provided complementary information to help them comprehend the evidence book.
Upon completion of the initial draft of the evidence book, it was reviewed externally by medical science experts. For this review, a modified version of AGREE2 [60], originally developed to evaluate the quality of clinical practice guidelines, was used. Based on these results, the text was revised and reviewed from a legal perspective by jurists and attorneys. The revised text was further polished after a second external review by all external review board members of the evidence book. The external review results and responses from the Evidence Evaluation Committee members can be found on the Moonshot Internet of Brains website[2].

Future Revision Plans

This evidence book has been published in three separate editions. In the first edition, we published responses to 4 of the 12 RQs and invited public comments to help guide the development of subsequent editions by incorporating public insights. Feedback was used to revise the second edition, which is now publicly available. This edition included six additional responses, resulting in a total of 10 RQs. The third edition, which contains responses to all 12 RQs, is scheduled for publication in March 2026.

We plan to update the evidence book every 3-5 years. By regularly updating systematic reviews, we aim to provide information on the efficacy, safety, and reliability of NeuroTech, incorporating the latest research developments. We plan to maintain ongoing discussions with relevant academic societies and organizations to establish a system that will allow us to update this document and incorporate addenda based on the actual progress of social implementation, even after the completion of the MS Kanai Project research period.

In addition, in July 2024, MS Kanai PJ has recently released the NeuroTech Guidebook Vol. 2 (Guide to Responsible Product Development). This guidebook is primarily intended for individuals considering the development, sales, or business use of NeuroTech products. The guidebook outlines the key guidelines and requirements for ensuring responsible practices in the development, marketing, and utilization of NeuroTech products. For instance, it highlights the importance of distinguishing between device safety (electrical and mechanical) and biological safety (effects on the body and psychological state) and underscores the need for adequate and thorough monitoring of side effects such as headaches, dizziness, and anxiety. Additionally, it outlines the importance of conducting bias-free trials to ensure efficacy, along with methodologies for designing trials that minimize bias.

Through the publication of this evidence book and guidebook, we will continue to promote NeuroTech as a safe and reliable technology. We appreciate your continued support in these efforts.

Management of COI

Conflict of interest (COI) is a common issue in both academic and scientific publications. COIs have the potential to influence several aspects of research, including study design, data collection, processing, and publication, and individuals involved in the study.

COI is categorized into economic COI, which pertains to financial relationships and research funding from specific companies/organizations, and non-economic COI, such as academic COI, which involves research activities and expertise. In addition to personal COI, financial and academic COI with educational institutions such as universities and other academic organizations, such as academic societies to which committee members belong, may also affect evidence book development [61]. Therefore, the Guidebook Development Committee formulated a method for managing COI before developing the evidence book under the Minds Manual for Guideline Development, 2020 ver. 3.0 [61] and published guidelines regarding COI [2]. Specifically, members of the Evidence Evaluation Committee, Systematic Review Team, Secretariat, and External Review Boards are obliged to report their financial COI for 3 years prior to their appointment. Moreover, they were requested to declare academic COI for 3 years prior to the start of the systematic review. If any COI exceeds predefined standards, members must also report both financial and academic COIs during the previous year. If any errors are identified in previously self-reported information, the concerned individuals must notify the Secretariat and promptly submit a revised report.

Based on the COI declarations submitted by members, we assessed potential conflicts of interest and determined whether a management plan was necessary. The declaration criteria for economic and academic COI are published on the website (avalable only in Japanese). In addition, the declarations' contents will be made publicly available alongside the publication of the evidence book. Through these efforts, we aim to ensure that the content of the evidence book is neutral and appropriate, fostering society's trust in the use of NeuroTech.

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(Blue indicates systematic review papers written by the members of the Evidence Evaluation Committee to derive answers to RQs.)

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