Neurotech

Examining Neurotech's Efficacy and Safety

evidence book

2023/10/02 v1.2

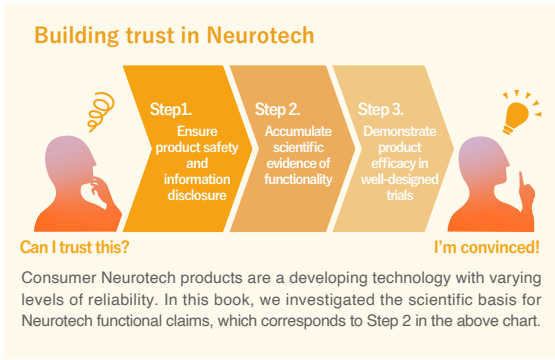
CONTENTS

Preface

This evidence book is written for those interested in the scientific evidence of the efficacy and safety of Neurotech. In recent years, "Neurotechnology," commonly referred to as "Neurotech," has been rapidly growing. Neurotech is the technology that aims to estimate and regulate 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 there any potential risks for ordinary consumers using such products?

The efficacy and safety of Neurotech products available to the general public are still not fully understood. Many of these products lack a solid scientific foundation and often rely on a few academic papers to support their claims [1]. However, citing several papers does not guarantee the reliability of their effectiveness and safety. The product lacks proper scientific evidence if the quality of the trials conducted in cited papers is poorly designed. Unfortunately, it can be challenging for general consumers to accurately grasp the certainty of the claimed efficacy.

To address these concerns, we have compiled the evidence book to provide the public with an accurate overview of the efficacy and safety of Neurotech. The



Consumer Neurotech products are a developing technology 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.

contents are based on the results of systematic reviews, which examine the scientific evidence related to the effects often claimed for Neurotech products and the safety of their usage. In this book, we have posted 12 questions about the commonly claimed effects of Neurotech products, such as "Can neurofeedback training improve motor performance?" We have answered these questions based on the results of systematic reviews. The first edition contains answers to four questions, with the remaining eight to be released after the systematic reviews are completed.

This book was developed by an Evidence Evaluation Committee composed of twelve researchers specializing in neuroscience. The systematic reviews were conducted by a systematic review 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, the systematic review process, the correctness of the contents of this book, and the transparency of the disclosure of conflicts of interest were reviewed by an External Review Board consisting of various experts. For basic knowledge of Neurotech, please refer to the already published Neurotech Guidebook [2].

<Guidebook>
- For those interested in Neurotech products.
- Created by a committee of researchers, physicians, industry persons who are well-versed in the field of neuroscience.
- Provides correct knowledge and perspectives that are currently available as well as information on how to approach Neurotech.

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

This book provides straightforward answers, especially in the headline section of each question, to make it understandable for general consumers. The appendix summarizes the foundational knowledge required to understand this book. For those with scientific and technical expertise–such as business people promoting the sales or development of Neurotech products and services, as well as researchers and medical personnel–this book contains specialized information. While some parts may be complex for ordinary consumers, we believe the scientific perspective acquired through this book will help mitigate potential drawbacks and health risks associated with the use of Neurotech products. We hope this book fosters a scientific understanding of Neurotech and supports its development as a reliable technology.

October 2023
By Evidence Evaluation Committee

Preface

Disclaimer: Please read carefully

The authors of this book have carefully checked that the matters and analysis described are accurate. Furthermore, its contents have been verified by an external review board consisting of professionals in medicine, neuroscience, law, and experts in medical publishing and neuroethics. However, the accuracy of the content cannot be completely guaranteed due to a number of uncertain factors, including future technological developments, the unique complexity of researching the brain, changes in social circumstances, differences in opinions due to individual perspectives, differences in physical characteristics and usage conditions of the consumers, and revisions to the legal framework. Consequently, we assume no responsibility for any health hazards or legal issues that may arise from the usage of this book. Please note that the positive statements in this book do not serve as scientific evidence for specific products with functional claims. In a similar fashion, the absence of evidence supporting functionality based on literature reviews in this book does not imply that products claiming such functionality lack a scientific foundation. We kindly request that the readers refrain from referring to this book regarding Neurotech intended for minors or for medical purposes, such as the diagnosis or treatment of illnesses, as these areas fall outside the scope of this book.

This evidence book was produced 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, Japan Science and Technology Agency and the Cabinet Office, are not involved in any part of this book.

RQ1 Can neurofeedback training improve motor performance?

Answer

The use of neurofeedback for seven days or more possibly improves motor performance. However, due to the limited number of research, it is currently unclear to what extent and in what categories of motor performance these effects occur.

When healthy adults* engage in neurofeedback training for seven days or longer, their motor performance possibly improves immediately after training. However, due to the small number of studies, evidence is too premature to draw any definite conclusion on the specific category of motor performance (e.g., balance, endurance) and to what extent it is effective. In addition, the optimal frequency and duration of daily training necessary to achieve an effect have yet to be fully clarified.

*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 in the experiment.

Background and Purpose

There is growing interest in neurofeedback training (NFT) as a potential alternative to general motor training and a method to enhance the effectiveness of mental imagery. Several studies have reported positive effects of NFT on golf putting and fine motor skills [3,4], while a meta-analysis revealed no significant impact of NFT on motor performance among athletes [5]. This prompts the question, how safely and reliably can NFT improve motor performance in healthy adults?

Results - Safety

The safety of NFT could not be determined due to the limited number of studies discussing potential adverse events. To date, no adverse events have been reported. Out of the 33 studies that utilized NFT to enhance motor performance in healthy adults, only five studies (with a total of 129 subjects) assessed adverse events. Thus, it was not possible to draw conclusive statements regarding the safety of NFT. However, it is worth noting that none of the five studies focusing on adverse events reported negative effects.

Results - Effectiveness

- The use of NFT for seven days or more 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 subjects in the studies conducted.
- The effectiveness of NFT on specific motor performance, such as movement accuracy, reaction time, hand dexterity, whole body balance, and endurance, could not be adequately evaluated due 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 subjects in the studies conducted to date and the inconsistency of the results, scientific evidence remains inconclusive.
- Four studies repeatedly assessed motor performance after NFT. Further research is needed to confirm the duration of the training effects. Also, the training intervals required to maintain or improve performance need to be revealed.

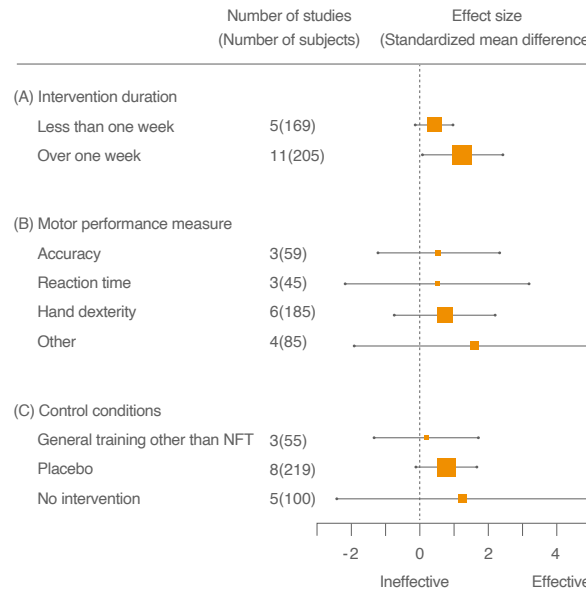


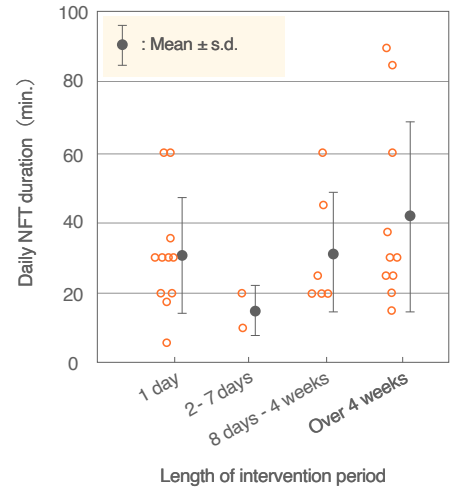
Figure 1. Results of the effectiveness assessment. (A) Effects of intervention duration. (B) Differences in effects by the targeted motor performance. (C) Superiority of NFT by control conditions.

Can neurofeedback training improve motor performance?

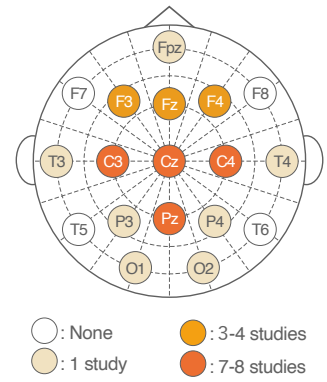
Study characteristics

- Intervention period (Fig. 2A): Thirteen studies lasted only one day, four studies lasted from two to seven days, five studies lasted from eight days to four weeks, and 11 studies lasted longer than four weeks. The longest training time per day was 90 minutes, and the shortest was six minutes. There was no apparent trend that suggested a shorter training time per day was associated with longer training periods.
- Intervention frequency: Daily for training periods of less than four days and every two to seven days for longer 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, 11 recorded EEG from the central region (C3, Cz, and C4). The subsequent most common measurement was from the parietal region (Pz: 5 studies).
- Frequency band(s) targeted by EEG-based NFT study (Fig. 2C): The most common frequency band used for NFT was alpha (14 studies), followed by theta (12 studies) and beta (12 studies). 11 studies used a combination of theta, alpha, and/or beta. In addition, nine studies used a component called sensorimotor rhythm (SMR)[#1], and four studies used the power ratio between theta and beta oscillations.
- Types of control condition: Placebo (18 studies), no intervention (10 studies), and general motor training other than NFT (8 studies). Placebos used methods such as feedback of 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[#2] (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 targets by NFT studies

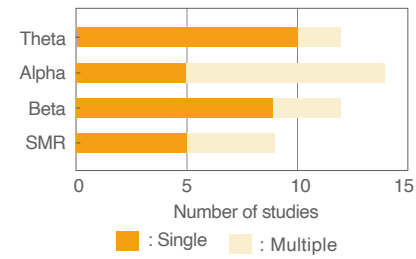


Figure 2. Study characteristics.

RQ1 Can neurofeedback training improve motor performance?

Systematic review processes

- Five databases were used to search for studies that conducted NFT to improve motor performance in healthy adults aged 18-64 years [6].
- 2,325 papers found through our search and other sources were screened according to predetermined inclusion criteria. The 33 selected articles were used to summarize the characteristics of studies conducted to date.
- Of the 33 papers, 13 were randomized controlled trials that could calculate effect sizes related to motor performance and had a low to moderate risk of bias. These papers were used for statistical analyses to evaluate the effectiveness of NFT.

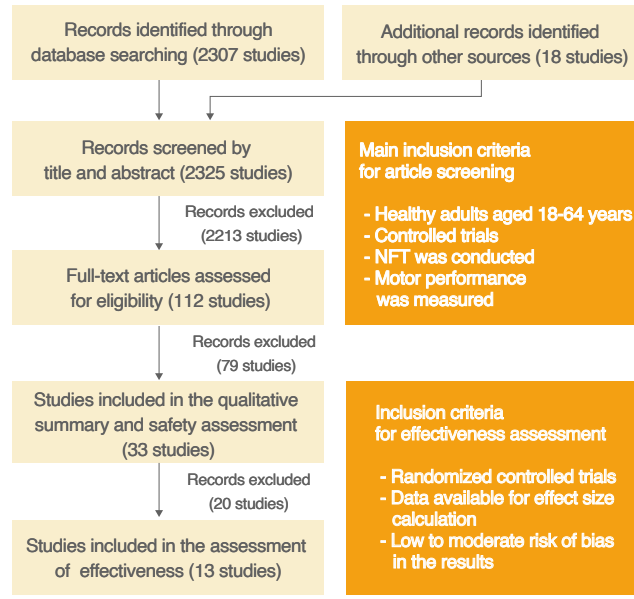


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Sensorimotor rhythm (SMR): SMR refers to the EEG component around 12-15 Hz measured from the central region. Previous studies considered the SMR signal sources as 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 [7].

#2. Reaction time: Reaction time is the time between receiving a cue and beginning movement, like responding to the cue "on your mark, get set, go!".

RQ2

Can neurofeedback training improve sleep quality?

Answer

Due to the limited amount of research, there is currently no evidence to support the claim that neurofeedback improves sleep quality in healthy adults.

Currently, there is insufficient scientific evidence to determine if neurofeedback training can improve the sleep quality of healthy adults. Few studies have been conducted on this topic, and the effectiveness and safety of neurofeedback for enhancing sleep quality are still being investigated. Further research is needed to better understand the specific aspects of sleep that can potentially benefit from neurofeedback. In the meantime, if the reader wants to improve their 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].

*In this RQ, healthy adults were defined as those aged 18 years or older 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

Various methods are available to maintain good sleep and improve its 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]. Neurofeedback training (NFT) has recently emerged as another potential method to improve sleep quality [9]. So, how safely and reliably can NFT be expected to improve sleep quality in healthy adults without sleep disturbances?

Results - Safety

Assessing the safety of NFT is currently difficult as no studies reported any potential adverse events. While four studies have investigated the impact of NFT on sleep quality in healthy adults, none of them provided information about any associated adverse events linked to the intervention.

Results - Effectiveness

- Studies on the effectiveness of NFT have shown varying results. Currently, no scientific evidence supports the claim that NFT improves sleep quality in healthy adults (Fig. 1A). One reason for this uncertainty could be attributed to the inconsistent methods[#1] used to assess sleep quality.
- The impact of NFT on daytime napping and nighttime sleep (Fig. 1B) and the differences in the effects of different EEG components used in NFT (Fig. 1C) cannot be determined due to the insufficient amount of research.
- Additionally, the required training duration and hours per day for NFT to affect sleep remains unknown.

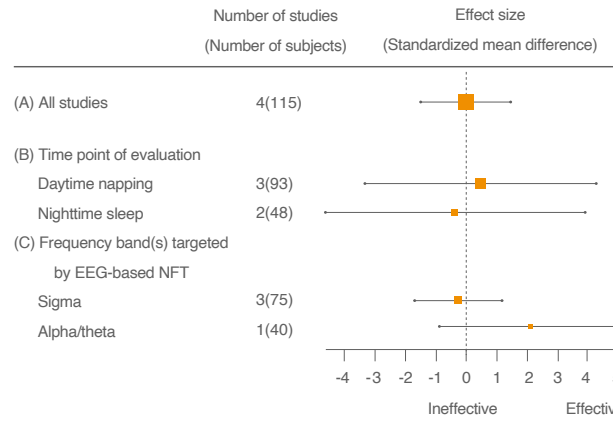


Figure 1. Results of the effectiveness assessment. (A) Overall effects. (B) Comparison between daytime nap and nighttime sleep. (C) Comparison in frequency band(s) targeted by EEG-based NFT.

Can neurofeedback training improve sleep quality?

Study characteristics

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

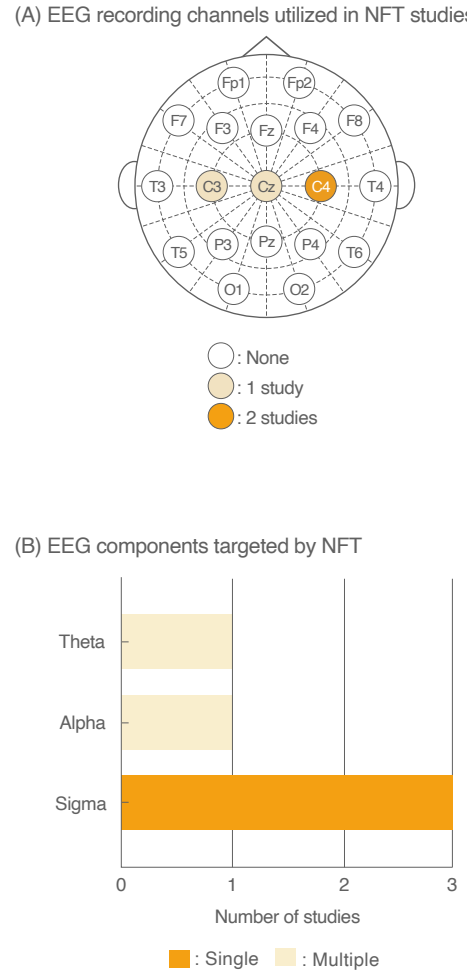


Figure 2. Study characteristcs.

RQ2

Can neurofeedback training improve sleep quality?

Systematic review processes

- Four databases were used to search for studies that conducted NFT to improve sleep quality in healthy adults 18 years of age and older [10].
- 1,285 papers found through our search were screened according to predetermined inclusion criteria. The four articles selected as a result were used to summarize the main characteristics of studies to date.
- These studies were used for statistical analyses to evaluate the effectiveness of NFT.
- To assess these papers, we employed widely accepted sleep quality indices, including the proportion and duration of N3 sleep stages#2, the amplitude of sleep EEG#3 (like sigma and delta waves), sleep efficiency#4, sleep latency#5, and wake time after sleep onset#6.

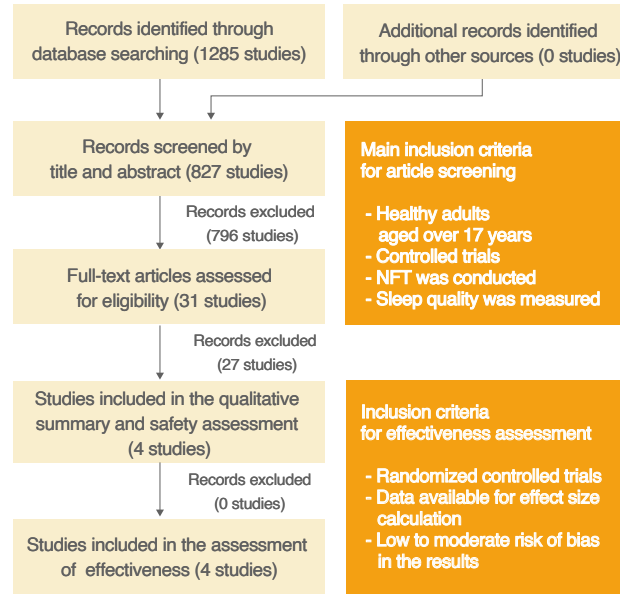


Figure 3. Flowchart of the systematic review process.

Keywords

#1. Methods for assessing sleep quality: Currently, it is evaluated through various indices [11]. Through polysomnography and actigraphy, evaluations can be conducted based on objective indicators such as sleep EEG and sleep latency. On the other hand, subjective sleepiness is also evaluated through questionnaires or interviews. Sleep quality is then evaluated based on an integration of these results. However, there has yet to be a consensus among experts on a standard approach for evaluating sleep quality.

#2. Sleep Stages: Sleep is categorized into two main stages: non-REM and REM sleep. Non-REM sleep is then subdivided into three stages, referred to as N1, N2, and N3. N1 denotes the state of dozing off, while N3 represents a state of deep sleep. During N3, external sounds are less likely to wake an individual up.

#3. Sleep EEG: Theta oscillations are commonly observed during the initial stage of non-REM sleep, known as N1. As one progresses to N2, sleep spindles are present, indicating a deeper stage of sleep. The presence of sleep spindles is a reliable indicator of stable sleep. The deepest non-REM stage, N3, is characterized by slow waves with a frequency of 0.5 to 4 Hz.

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

#5. Sleep latency: This refers to the time from turning the light off to the first onset of any stage of sleep.

#6. Wake time after sleep onset: It is the amount of time between falling asleep and getting up that is considered being awake.

RQ3

Can neurofeedback training enhance attentional functions?

Answer

It likely enhances attentional performance, but whether its effects are greater than those of other general training methods remains unclear.

Attentional functions are classified into three elements: "executive control" (also called the central executive), which focuses 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]. After neurofeedback training, healthy adults* likely experience immediate improvement in executive control and spatial orientation. While these observed effects are greater than those of doing nothing, it remains unclear whether they surpass those of placebos and general training methods, such as meditation or tasks mimicking playing video games (e.g., Tetris or Concentration). Note that the effects of neurofeedback on Attention-Deficit Hyperactivity Disorder (ADHD) have already been summarized elsewhere [13] and are not within 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, mental, or neurological disorder or disease at the time of participation in the experiment.

Background and Purpose

There is growing interest in Neurofeedback Training (NFT) as a training method to enhance attentional functions. For example, several studies have reported the effectiveness of NFT in improving attentional functions by using specific EEG components such as sensorimotor rhythm (SMR) or beta [14,15]. However, contrasting reports suggested that NFT might only change brain activity and did not affect behavioral aspects such as correct response rate or reaction time [16]. Then, what types of attentional functions can NFT reliably enhance in healthy adults, and to what extent?

Results - Safety

The safety of NFT could not be determined due to the limited number of studies discussing adverse events. To date, no adverse events have been reported. Out of the 41 studies that utilized NFT to improve attentional functions in healthy adults, only two studies with a total of 124 subjects assessed adverse events. These studies did not indicate any serious adverse events that necessitated medical intervention or other unfavorable circumstances.

Can neurofeedback training enhance attentional functions?

Results - Effectiveness

- NFT may enhance attentional functions (Fig. 1A).
- Among attentional functions, NFT showed 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, the scientific evidence supporting this claim is insufficient due to the risk of bias in the results and the total number of subjects in the studies (Fig. 1B).
- No effect of NFT on arousal was found (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 unclear whether NFT has advantages (Fig. 1C).
- The difference in the enhancement of attentional functions between NFT and placebo remains unknown (Fig. 1C).
- Only two studies assessed the effect of NFT on attentional functions over time. Thus, the duration of the training effect is not evident. Nor could we determine the training intervals required to maintain or improve the performance.

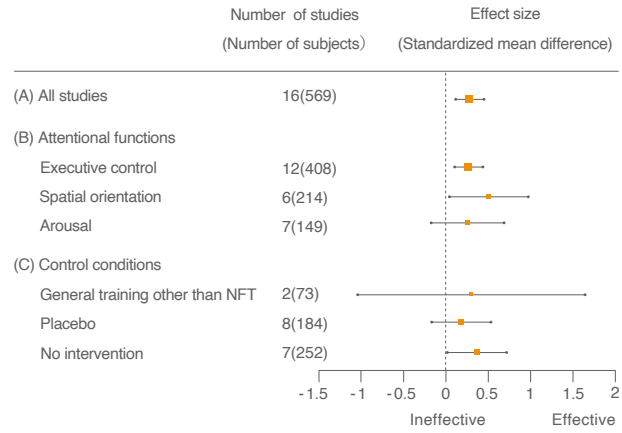


Figure 1. Results of the effectiveness assessment. (A) Overall effects. (B) Differences in effects by attentional functions. (C) Superiority of NFT by control conditions.

Study characteristics

- Intervention period and duration: Three studies lasted only one day, four studies from two to seven days, 15 studies from eight days to four weeks, and 13 studies longer than that, the longest being about 13.5 weeks; the duration of training per day was about five minutes in one study, 10 to 20 minutes in eight studies, about 20 to 60 minutes in 20 studies, and longer than that in five studies, the longest being 136 minutes.
- Intervention frequency: Our survey of studies conducting NFT for three or more days revealed that seven studies performed it daily, four studies performed it four to five days a week, 12 studies performed it two to three days a week, and seven studies performed it less than two days a week.
- Methods to measure brain activity: EEG (33 studies), fMRI (4 studies), NIRS (3 studies), and MEG (1 study).
- Channels recorded for EEG-based NFT (Fig. 2A): There were 24 studies in the central region (C3, Cz, C4), 12 in the frontal region (F3, Fz, F4), 11 in the parietal region (P3, Pz, P4), 7 in the occipital region (O1, Oz, O2), and 5 in the frontal pole (Fp1, Fpz, Fp2).
- Frequency band(s) targeted by EEG-based NFT study (Fig. 2B): Theta and beta frequencies were the most commonly utilized (13 studies), often combined together. Alpha waves were individually used in more than half of the studies (6 out of 11). SMR was used in 10 studies, and only 2 studies incorporated event-related potentials, including P300.
- Types of control conditions: Placebos (8 studies), no intervention (7 studies), and general training methods other than NFT (2 studies). The feedback for the placebo included brain activity from non-target regions, EEG components of other individuals, or random information unrelated to brain activity.
- Targeted attentional functions (Fig. 2C): Executive control (25 studies), spatial orientation (13 studies), and arousal (19 studies), with some studies targeting multiple attentional functions.

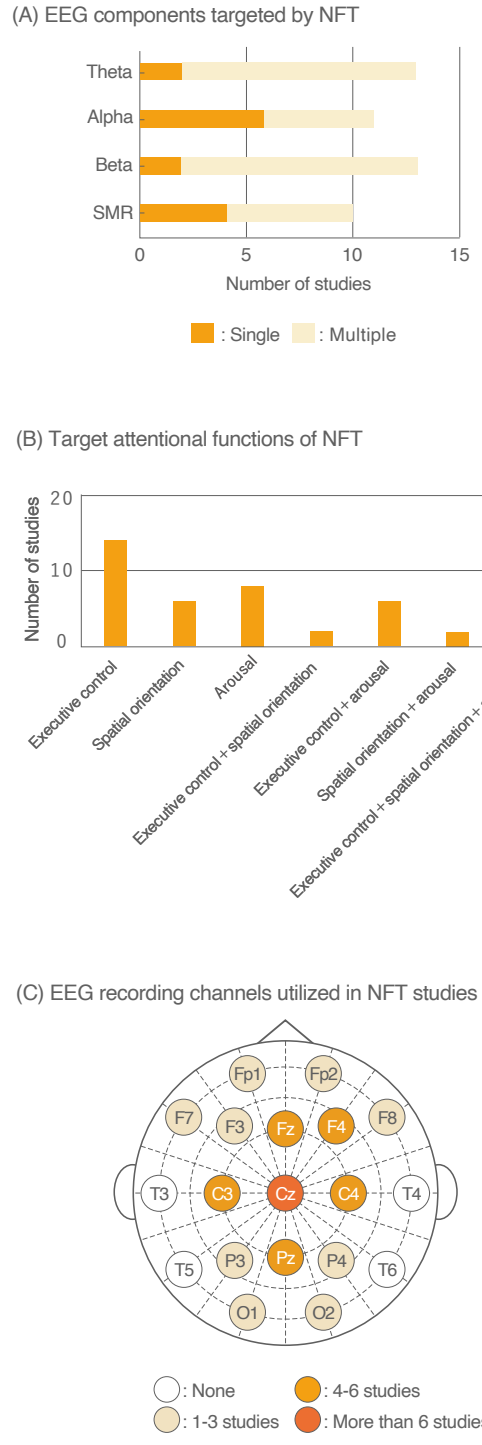


Figure 2. Study characteristics.

Can neurofeedback training enhance attentional functions?

Systematic review processes

- Six databases were used to search for studies that conducted NFT to enhance attentional functions in healthy adults aged 18-65 years[18].
- 3,337 papers found through our search were screened according to predetermined inclusion criteria. The 41 articles selected as a result were used to summarize the main characteristics of studies to date.
- Of the 41 papers, 15 were randomized controlled trials that could gather numerical data on attentional functions and had a low risk of bias in the results. These studies were used for statistical analyses to evaluate the effectiveness of NFT.

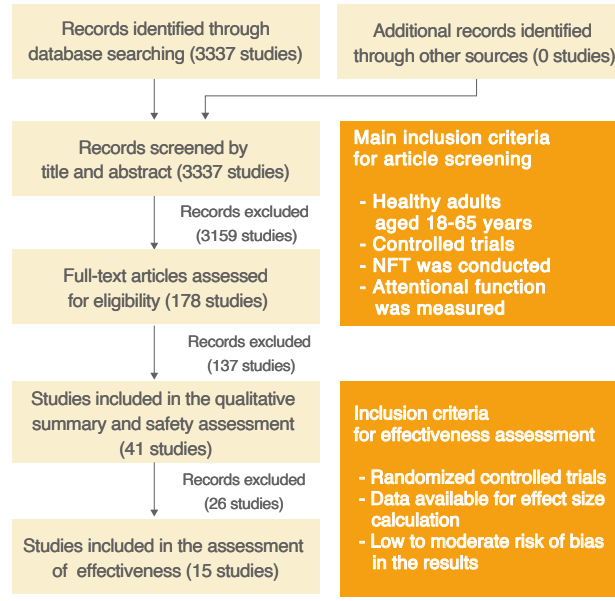


Figure 3. Flowchart of the systematic review process.

RQ4

Can neurofeedback training enhance memory aptitudes?

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

RQ5

Can non-invasive brain stimulation improve motor task performance?

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

RQ6

Can non-invasive brain stimulation improve sleep quality?

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

RQ7

Can non-invasive brain stimulation enhance attentional functions?

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

RQ8

Can non-invasive brain stimulation enhance memory aptitudes?

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

RQ9

Is EEG a biomarker of relaxation?

Answer

The amplitude of alpha oscillations in EEG possibly indicates the level of relaxation, depending on where they are measured. However, interpreting the results requires caution.

For healthy adults*, the amplitude of alpha oscillations in the frontopolar region may indicate their level of relaxation. However, alpha oscillations measured from other areas or other EEG components (such as delta, theta, beta, gamma, and other indices) do not indicate relaxation. These results suggest that although the common belief that alpha oscillations signify a level of relaxation may be partially correct, using alpha oscillations as a biomarker of relaxation requires careful consideration. In actuality, the amplitude of alpha oscillations is influenced not only by the level of relaxation but also by several other factors, including sleepiness, fatigue, and attention [19-23]. Additionally, It should be noted that gold standards of a relaxation index#1 have yet to be 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 disorder or disease at the time of participation in the experiment.

Background and Purpose

Within the general public, alpha oscillations in EEG are often equated with a relaxed state, as seen in products like "alpha oscillation-producing music CDs" marketed for relaxation effects. Some researchers also believe that alpha oscillations become stronger when we relax. However, there is no consensus on the relationship between relaxation indices and various EEG components, including alpha oscillations. 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). So, to what extent are EEG measurements and relaxation actually related?

Results - Safety

EEG measurements are widely considered safe, so EEG could be a safe way to evaluate relaxation levels. EEG measures weak electrical signals through electrodes placed on the scalp and does not induce electric currents in the head. Skin rashes may occasionally develop from the tape used to attach electrodes, but the risk is comparable to that of using adhesive bandages on the skin. While the studies reviewed did not include any safety statements, it is generally believed that no inherent adverse events are associated with EEG measurement.

Results - Validity

- A strong positive correlation of r = 0.74 was found between relaxation indices and the amplitude of alpha oscillations in the frontopolar region (Fig. 1A).
- A weak positive correlation of around r = 0.2 was also found between relaxation indices and the amplitude of alpha oscillations in the frontal and central regions (Fig. 1A).
- No significant correlation was found between relaxation indices and the amplitude of alpha oscillations in the parietal and occipital regions (Fig. 1A).
- No significant correlations were found between relaxation indices and delta, theta, beta, and gamma oscillations, as well as other EEG indices (Fig. 1B).

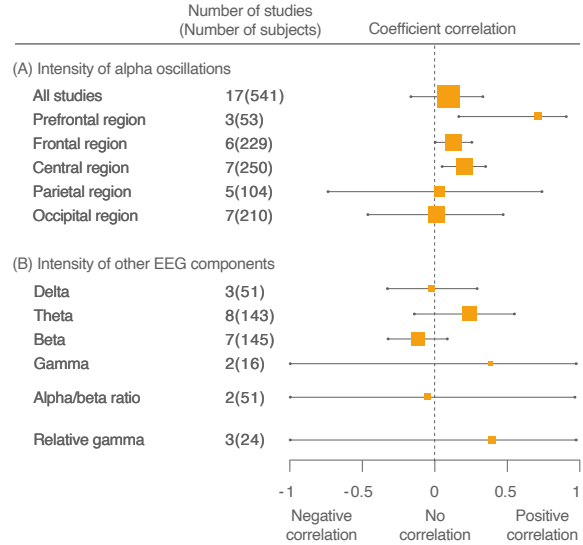
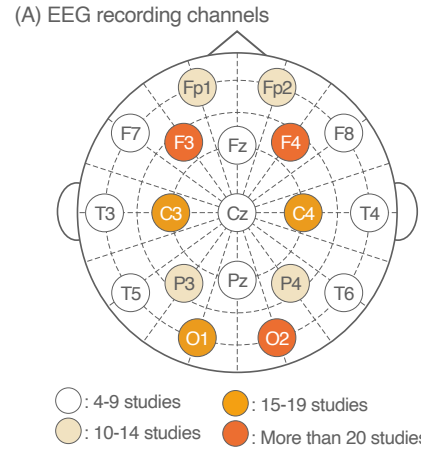


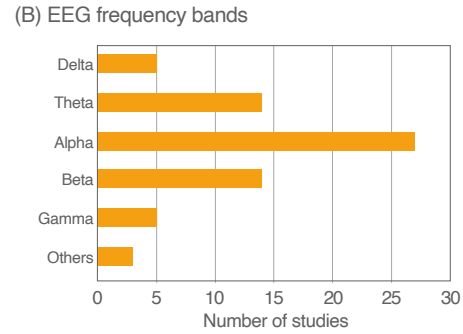
Figure 1. Results of the validity assessment. (A) Correlation between the intensity of alpha oscillations and relaxation indices. (B) Correlation between the intensity of other EEG components and relaxation index.

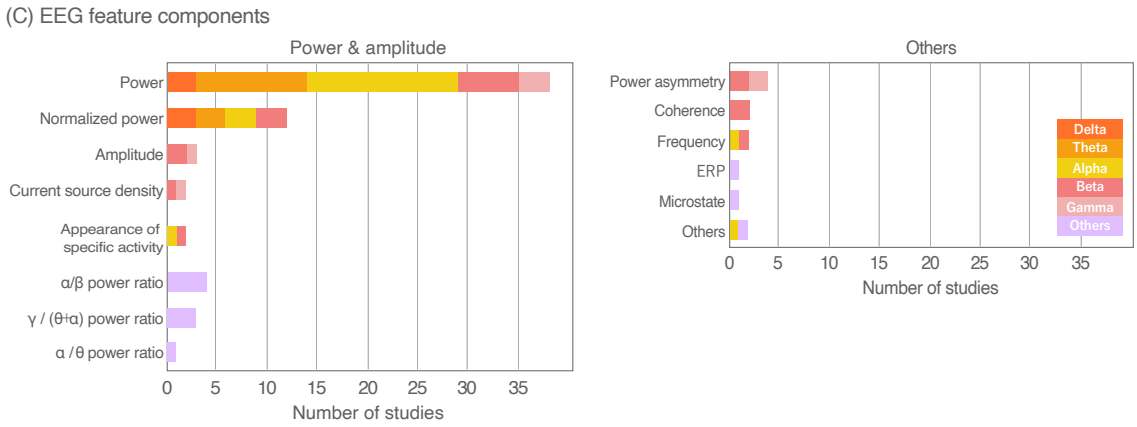
Is EEG a biomarker of relaxation?

Study characteristics

- Proportions of EEG recording channels (Fig. 2A): Measurements from the frontal region (F3, F4) were the most common (21 studies), followed by occipital (O1: 19; O2: 20 studies) and central (C3: 15; C4: 16 studies) regions. More than 10 studies were recorded from the frontopolar (Fp1, Fp2) and parietal (P3, P4) regions, respectively.
- EEG frequency bands (Fig. 2B): Alpha oscillations were the most commonly used EEG index (27 studies), followed by theta and beta (14 studies for each). A few studies used delta and gamma oscillations.
- EEG feature components (Fig. 2C): Most studies used power or normalized power for each frequency band. A few studies 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. Many subjective measures of the level of relaxation were also used, such as the Profile of Mood State (POMS) test. Some studies used salivary indices such as the cortisol test.







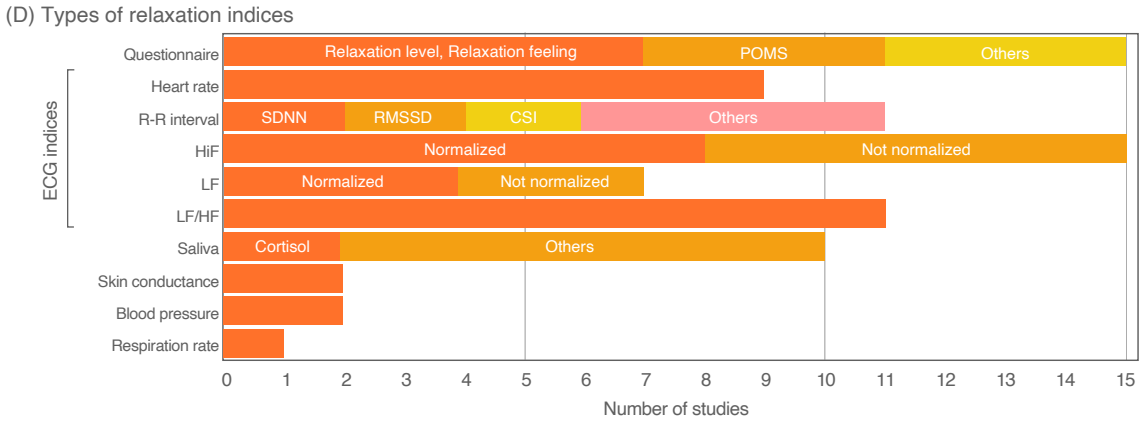


Figure 2. Study characteristics.

Is EEG a biomarker of relaxation?

Systematic review processes

- Five databases were used to search for studies that measured EEG and relaxation indices (e.g., ECG-related indices associated with parasympathetic nervous system activity and subjective indices of relaxation) in healthy adults aged 18-65 years [24].
- 3,295 papers found during our search were screened according to predetermined inclusion criteria. Then, 39 articles were selected to summarize the main characteristics of studies conducted to date.
- Of the 39 papers, 30 provided correlation values between EEG and relaxation indices and had 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 exist: subjective indices obtained through questionnaires and ECG-related indices. Because some indices increase as relaxation deepens while others decrease, adjustments were made to ensure the value consistently rises as relaxation increases. For instance, the signs of subjective indices like nervousness and heart rate were reversed, as smaller values indicate a more relaxed state.

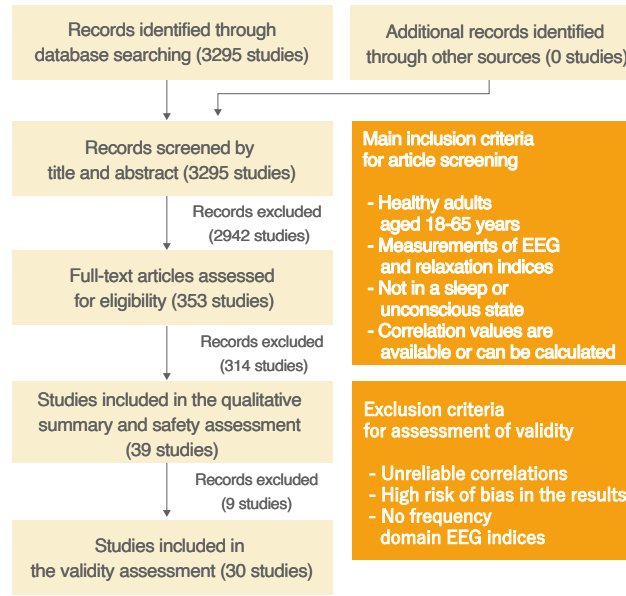


Figure 3. Flowchart of the systematic review process.

Keywords

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

#2. Autonomic nervous system: This refers to the nervous system that controls involuntary functions such as breathing, sweating, and temperature regulation, as well as metabolism. It supports our bodies by balancing the sympathetic nervous system that predominates in quiet "rest and digest" conditions and the parasympathetic nervous system that drives the "fight or flight" response in stressful situations.

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

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 a constantly changing waveform (see 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 one second; for example, if it repeats ten times per second, its frequency is 10 Hz. The types of oscillations in EEG are classified from lowest (fewer waves) to highest frequency as delta, theta, alpha, beta, and gamma (Table1). Delta and theta oscillations, which have lower frequencies, are classified as slow waves, while beta and gamma oscillations, which have higher frequencies, are classified as fast waves, with alpha oscillations serving as the intermediate. The amplitudes of alpha and slow waves are larger than those of fast waves (Fig.1).

Since the physiological significance of EEG rhythms differs depending on their frequency, it is believed that the state of brain activity can be roughly determined by examining the changes in signal amplitude at each frequency range (Table1). However, it is not easy to make a one-to-one match between EEG frequencies and the functions they reflect. Moreover, the criteria for the frequencies that delimit wave types are not always consistent. For instance, an 8 Hz wave can be classified as either alpha or theta, given that it may reflect function and states associated with both. It is also known that the relationship between EEG rhythms and functions varies slightly with age, gender, and exercise habits [25-27].

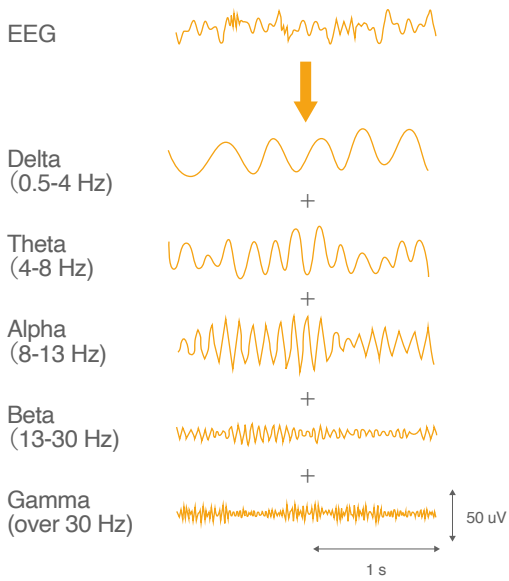


Figure 1. EEG and the multiple waves that make up an EEG. An EEG is a superimposed figure of multiple waves oscillating at various rhythms.

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

Types	Frequencies	Functions and states
Delta	0.5-4 Hz	It is observed during deep sleep.
Theta	4-8 Hz	It is believed to be associated with cognitive function and concentration.
Alpha	8-13 Hz	It is believed to be related to relaxation and visual function.
Beta	13-30 Hz	It is known to be associated with motor function.
Gamma	Over 30Hz	It is believed to be 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 Review Question for an explanation of whether the theta oscillations actually indicate a concentration or the alpha oscillations indicate a level of relaxation.

Basic knowledge of EEG

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 measurement from approximately the same brain region, regardless of head size, and ensures that the recording electrodes are consistently placed when measuring EEG from the same person. However, EEG recordings from the scalp do not exclusively reflect activity from the brain region directly under the recording electrode. Since brain activity is measured through multiple tissues and substances (including the skull, dura mater, and cerebrospinal fluid), the resulting EEG contains a mixture of activity from various brain regions.

The International 10-20 system uses letters of the alphabet 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. It is important to note that 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)

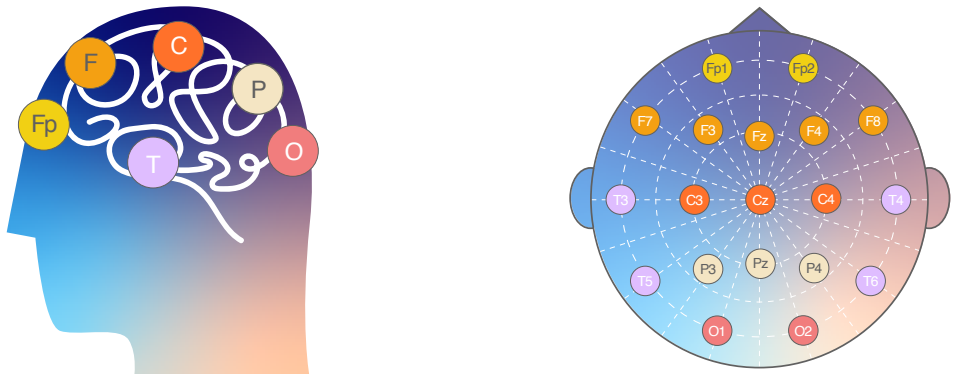


Figure 2. Electrode positions based on the International 10-20 system.

Appendix 2

Design and role of placebos in Neurotech

In general, when conducting clinical trials to test the effectiveness of a drug, participants are allocated into two groups. One group receives the actual medication, while the other group receives a placebo that looks and tastes like the actual drug but does not contain the active therapeutic ingredient. The aim is to compare changes in symptoms between the two groups. However, why is it important to administer the placebo under such circumstances? One may argue that it is enough 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 receive a veritable drug or a 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. That's why clinical trials are conducted in the double-blind manner, that is a trial with physicians, evaluators, and participants not knowing whether a given subject takes a medication containing an active ingredient or a placebo. This approach reduces the risk of unconscious assumptions from those involved in the trial that would influence the results, making the evaluation of the drug's efficacy more reliable.

When testing the efficacy of Neurotech products, it is recommended to compare it to a placebo condition, as is done in drug efficacy studies. In noninvasive brain stimulation, electrodes placed on the scalp are often used to stimulate the brain. To mimic the stimulus being tested, a sham stimulation is used as a placebo condition (Fig.1A). The typical placebo stimulus lasts for a few seconds to a few dozen seconds, after which no stimulus is given (Fig.1B). This method provides the subject with a sensation similar to that of actual stimulation, even though not enough stimulation is actually delivered. Suppose veritable stimulation is more effective than placebo stimulation. In that case, it means that sustained stimulation is necessary to induce changes in motor performance and memory and that the stimulated sensation alone cannot induce such changes.

Other placebos stimulate brain regions that are different from those associated with specific functions and performance (Fig.1C). If actual stimulation is highly effective compared to this placebo, it means that stimulation to a particular brain region is essential for inducing changes in function and performance.

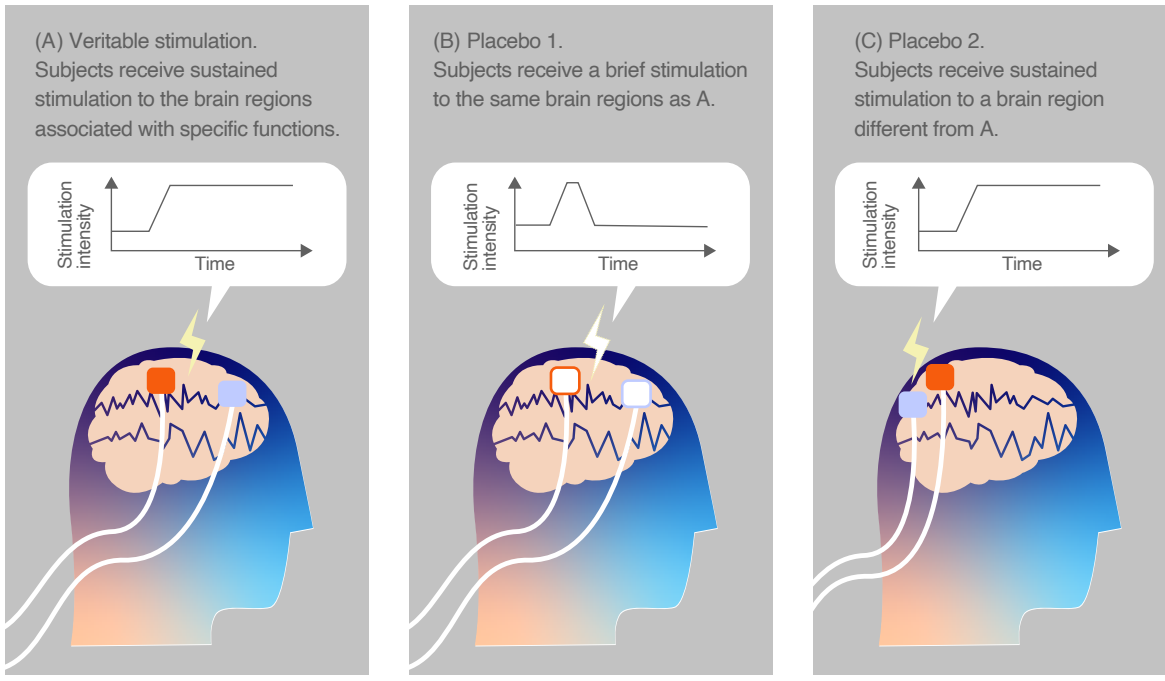


Figure 1. Schematic diagram of noninvasive brain stimulation and its placebo condition.

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) provides subjects with random information that resembles brain activity. The second placebo (Fig.2C) presents subjects with biometric information other than brain activity, such as heart rate. If veritable neurofeedback is more effective than these placebos, this indicates that feedback of brain activity information, such as EEG, is crucial in inducing changes in functions and performance.

The third placebo (Fig.2D) gives subjects brain activity indices calculated from non-target brain regions and other components. If veritable neurofeedback is highly effective compared to this placebo, it proves that feedback of the targeted brain activity is essential in inducing changes in function and performance. This method measures brain activity in the same way as the first and second placebos. Still, it differs in feeding back the brain activity index, validating more precisely the importance of feeding back brain activity in specific brain regions and at the particular frequency of EEG activity [28].

The fourth placebo (Fig.2E) is a method where brain activity indices identical to veritable neurofeedback are calculated from the previously recorded brain activity of others, such as EEG, and presented to subjects. If veritable neurofeedback is more effective than this placebo, it suggests that regulating brain activity through neurofeedback is crucial in inducing changes in function and performance.

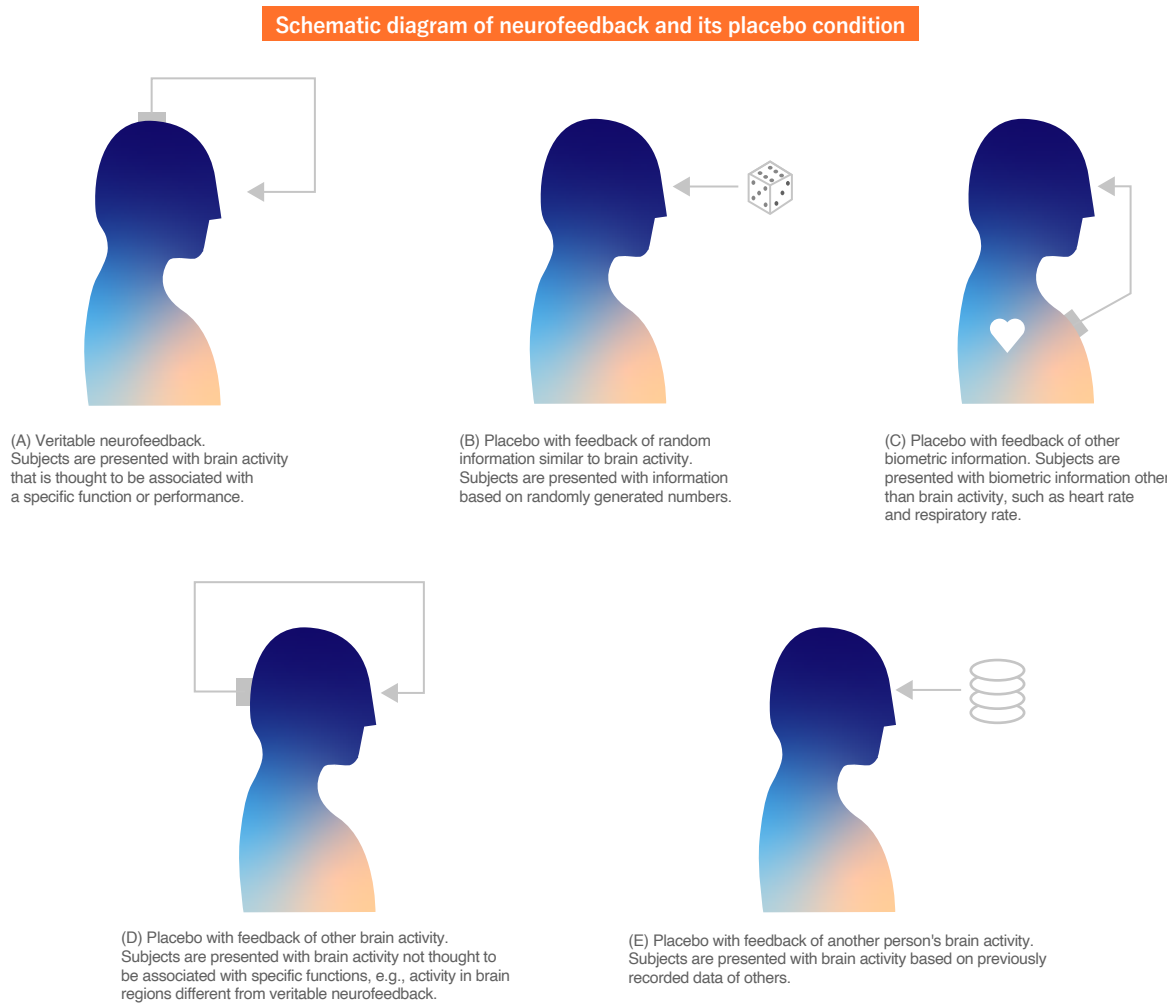


Figure 2. Schematic diagram of neurofeedback and its placebo condition.

Appendix 3

Adverse events reported in the use of Neurotech

An adverse event is an undesired medical event, other than the intended effect, that occurs during or after using Neurotech products [29]. Take the example of antihypertensive drugs. The intended effect of antihypertensive medications is to lower blood pressure at an appropriate level. To this end, some antihypertensive drugs dilate blood vessels or suppress the sympathetic nervous system. However, dilating blood vessels may cause the body to feel hot, and suppressing the sympathetic nervous system too much may cause bradycardia. In addition, some people may feel dizzy if their blood pressures drop too low or they experience allergic reactions.

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

Accumulating research data is now beginning to reveal which usage of Neurotech products or types of participants is more likely to have adverse events with Neurotech products. Table1 shows the adverse events mentioned in the studies examined in the development of the evidence book. Please be aware that studies using noninvasive brain stimulation are conducted following the guidelines published by the relevant academic societies [30,31] and are planned with consideration of the safety of the subjects. Using noninvasive brain stimulation not following these guidelines may result in a higher risk of adverse events.

Serious adverse events are adverse events that fall under the following (1) to (6) [29].

(1) Those leading to death.
(2) Those potentially leading to death.
(3) Those requiring hospitalization or prolonged hospitalization for treatment.
(4) Those causing permanent or significant disability or dysfunction.
(5) Those transmitted to the next generation of children or grandchildren as a congenital disease or abnormality.
(6) Those judged to be medically significant in addition to the above.

Possible non-serious adverse events that may be caused by the methods investigated in this book include (1) temporary fatigue, (2) sick feeling, (3) pain or burning sensation at the site of stimulations, (4) headache, (5) dizziness or nausea, and (6) drowsiness [32]. Note that adverse events not only vary to individuals but also may vary depending on the physical condition of the day and the patient's mental state, such as tension level, and do not always occur.

A similar term to adverse events is side effects. These refer to harmful effects on the user that may have occurred directly due to using the Neurotech products [29].

Appendix 3

Adverse events reported in the use of Neurotech

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

	Intervention methods	Number of papers mentioning the presence or absence of adverse events	Serious adverse events	Non-serious adverse events
RQ1	Neurofeedback	5 of 33 papers	No occurrence	No occurrence
RQ2	Neurofeedback	0 of 4 papers	Unclear	Unclear
RQ3	Neurofeedback	2 of 41 papers	No occurrence	No evaluation
RQ4	Neurofeedback	Under investigation		
RQ5	Non-invasive brain stimulation	Under investigation		
RQ6	Non-invasive brain stimulation	Under investigation		
RQ7	Non-invasive brain stimulation	Under investigation		
RQ8	Non-invasive brain stimulation	Under investigation		
RQ9	EEG measurement	1 of 39 papers	No evaluation	No occurrence
RQ10	EEG measurement	Under investigation		
RQ11	EEG measurement	Under investigation		
RQ12	EEG measurement	Under investigation		

Supplementary Information

Evidence Book Creation Process

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 its activities to develop "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 although the number of products is increasing, most have not been sufficiently verified for their efficacy and safety. As a result, we thought that the development of the BMI Usage Guideline was not appropriate at this time due to the lack of reliable sources.

Meanwhile, 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 is worthwhile. 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 considering entering the Neurotech market. Therefore, the Guidebook Development Committee has decided to produce 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 of the external review board members, who conduct the content audit of the deliverables, were selected from those with no conflict of interest in the Moonshot Kanai Project.

To create the evidence book, NTT Data Institute of Management Consulting, Inc., commissioned by the development committee, first conducted a market survey of the effectiveness widely advocated for Neurotech products. Next, based on the results, the Evidence Evaluation Committee established 12 review questions (RQs) that should be scrutinized for effectiveness, safety, and reliability. Each RQ was assessed by 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 [33]. If any issues were raised during this external review, SR processes were revised until the SR external review board approved that all the steps had been appropriately conducted. After completing an external review of the SR process, the two Evidence Evaluation Committee members were responsible for compiling answers of the RQ. Additionally, volunteer SR members wrote appendices that provide complementary information to help read through the evidence book.

Once a draft of the evidence book was ready, it underwent its first external review by medical science experts. For this review, a modified version of AGREE II [34], originally developed to evaluate the quality of clinical practice guidelines, was used. Based on the results, the text was revised and then reviewed from a legal perspective by jurists and attorneys. The revised text was further polished after a second external review by all evidence book external review board members. The external review results and responses from the Evidence Evaluation Committee members can be found at the end of the Japanese version of the evidence book [2].

Future Revision Plans

The evidence book will be published in three separate editions. The first edition includes the answers to four of the 12 RQs. The second edition, planned to be available in May 2024, will have the answers to additional five RQs. The third edition will have answers to all the 12 RQs and will be available in December 2024. In addition, we plan to update the evidence book every three to five years to reflect the latest research status regarding Neurotech's effectiveness, safety, and reliability. To do so, we have begun discussions with related academic societies and international organizations to establish a system to update this document even after the Moonshot Kanai Project ends in 2025. We believe that consistently providing reliable information to the public will lead to building public trust in Neurotech.

Moreover, the Guidebook Development Committee is currently working on the second version of the Neurotech Guidebook. In contrast to the first version of the guidebook, which was written for the general public, the second version will be written for the private sector and those interested in developing and selling Neurotech products or incorporating them into their own businesses. The second version will emphasize responsible product development, sales, and application. For instance, it will include information on how to ensure the safety of Neurotech products. This will involve distinguishing between device safety (electrical and mechanical) and biological safety (effects on the body and psychological state). Additionally, it will outline the need for monitoring potential side effects, such as headaches, dizziness, and anxiety, for an appropriate period. The guidebook will also highlight the importance of conducting unbiased studies to assure product effectiveness and the methodology for designing such studies.

Management of COI

Conflict of interest (COI) is divided into economic COI, which is related to financial relationships and acquisition of research funds with specific companies/organizations, and COI, such as academic COI (research activities and expertise) that are non-economic in nature (hereinafter referred to as "academic COI"). 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 the committee members belong may also affect evidence book development [35]. Therefore, the Guidebook Development Committee formulated a method of managing COI before developing the evidence book under the Minds Manual for Guideline Development 2020 ver. 3.0 [35] and published a guideline regarding COI [2]. Specifically, the members of the Evidence Evaluation Committee, Systematic Review Team, Secretariat, and External Review Boards are obliged to report their financial COI for the three years prior to their appointment. Apart from this, they are also requested to declare academic COI for the three years prior to the start of the systematic review. In addition, we ask them to report both financial and academic COIs during the previous year if any COI exceeds our set standards. Suppose it is found that there is an error in previously self-reported information. In that case, they must notify the secretariat and promptly file a revised report.

Based on the COI declarations submitted by members, we checked for conflicts of interest and, if any, evaluated whether a management plan was necessary. The declaration criteria for economic and academic COI are published on the website. In addition, the declarations' contents will be made public at the same time as the evidence book is published. Through these efforts, we are striving to ensure that the content of the evidence book is neutral and appropriate and to earn 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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Shiho Tenmoto: Director. Knowledge Mobility based System Institute.
Seiko Fujiwara: Part-time Clerk. Keio University.
Yumiko Kakubari: ARAYA Inc.
Ayumi Kusano: ARAYA Inc.

Editing

Ririko Sano (Illustration & Design), Kairi Sugimoto (Editing), Hiroki Takeuchi (Editing), Tatsuro Fujimaki (Editing),
Jacob Faller (English proofreading), Isabel Bandes (English proofreading)

Acknowledgements

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Dr. Yoshihito Goto and Dr. Yuko Masuzawa: for their lecture on systematic reviews and guideline development.

Dr. Keigo Komamura, Dr. Yoshinori Oshima, Dr. Takeyuki Matsuo, Dr. Masahiko Sudo, and Dr. Masatoshi Kokubo: for their efforts in refining the text from a legal perspective.

Contact for the Neurotech Evidence Book

Neurotech Guidebook Development Committee Secretariat
E-mail: info_guideline@brains.link

List of Financial COI

Evidence Evaluation Committee

*Affiliations, positions, grades, qualifications, etc. are as of April 1, 2023, and COI details, in principle, are based on declarations as of February 1, 2023.

Name	Affiliation	Occupation	Qualifications and Expertise	Specialty	Academic societies in hold positions, etc.	Details of Self-reported Financial COI								
						1. . Employment as an officer/director/adviser in a company or any for-profit organization directly related to the research and amount of remuneration	2. Profit on equity	3. Patent royalty	4. Daily allowance (Remunerations, lecture fee, etc.)	5. Manuscript fees	6. Research funding, grants, etc.	7. Scholarship (Incentive) Donations, etc.	8. Endowed courses offered by a company/organization/institution	9. Others (travel expenses, receipt of gifts, etc.)
Mitsuaki Takemi	Graduate School of Science and Technology, Keio University	Project Assistant Professor	Ph.D.	Neuroscience, Motor system	Councilors,The Japan Neuroscience Society. Working Group 4 member, Industry-Academia Collaboration Advisory Committee, Union of Brain Science Associations in Japan. Program committee member, The Japanese Society for Motor Control (2023).	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kaoru Amano	Graduate School of Information Science and Technology, The University of Tokyo	Professor	Ph.D.	Non-invasive brain function measurement, non-invasive brain stimulation	Committee Members, Industry-Academia Partnership Committee, The Japan Neuroscience Society. Caretaker, Vision Society of Japan. Director, Japanese Neural Network Society.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Aya Ihara	Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology (NICT)	Senior Researcher	Ph.D.	Cognitive Neuroscience, Brain functions involved in language	Evaluation panel member, The Strategic International Brain Science Research Promotion Program, Japan Agency for Medical Research and Development.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rieko Osu	Faculty of Human Sciences, Waseda University	Professor	Ph.D.	Cognitive neuroscience	Committee, Technical Committee on Neurocomputing (NC), Institute of Electronics, Information and Communication Engineers (Through March 2022). Director, The Japanese Society for Motor Control.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jun-ichiro Kawahara	Graduate School of Humanities and Human Sciences, Hokkaido University	Professor	Ph.D.	Cognitive Psychology	Executive Director and Vice President, The Japanese Psychological Association. Managing Director, The Japanese Society for Cognitive Psychology. Chairman of the Editorial Board, The Japanese Psychological Association.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1. NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc., Applicable to: individual, Period: September 2019 to present. 2. Universal Communication Design Association, Applicable to: individual, Period: April 2019 to present.
Akifumi Kishi	Graduate School of Medicine, The University of Tokyo	Project Lecturer	Ph.D.	Educational Physiology	Councilor, Japanese Society for Chronobiology.	N/A	N/A	N/A	N/A	N/A	N/A	1. Toppan Inc., Applicable to: individual, Period: October 2019 to present. 2. JMDC Inc., Applicable to: individual, Period: July 2020 to present.	N/A	N/A
Masako Tamaki	RIKEN Center for Brain Science (CBS), RIKEN Hakubi Team Leader Cognitive Somnology RIKEN Hakubi Research Team	RIKEN Hakubi Team Leader	Ph.D.	Sleep Reserch, Cognitive Neuroscience	Committee, Future Vision Board, The Japanese Society of Sleep Research. Committee, Ethics Board, The Japanese Society of Sleep Research.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nobuhiro Hagura	Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology (NICT)	Senior Researcher	Ph.D.	Cognitive Neuroscience	Program committee member, The Japanese Society for Motor Control (2021 to 2022). Board Member, The Japanese Society for Motor Control (2023).	N/A	N/A	N/A	NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc., Applicable to: individual, Period: September 2019 to present.	N/A	N/A	N/A	N/A	N/A
Koichi Hosomi	Graduate School of Medicine, Osaka University	Specially Appointed Associate Professor	M.D., Ph.D.	Functional Neurosurgery	Councilor, Japan Neuromodulation Society. Delegate, Japanese Association for Study of Pain. International Relations Committee Member and Member of Academic Committee, Japan Society for Stereotactic and Functional Neurosurgery. Member of Subcommittee on brain stimulation, Japanese Society of Clinical Neurophysiology.	N/A	N/A	N/A	N/A	N/A	DAIICHI SANKYO COMPANY, LIMITED, Applicable to: individual, Period: from April 2019 to December 2020.	N/A	Teijin Pharma Limited, Applicable to: individual, Period: from before January 2019 to March 2021. *Not an endowed chair, but a joint research chair.	N/A
Maro Machizawa	Center for Brain, Mind and KANSEI Sciences Research, Hiroshima University Xiberlinc Inc. (April 1, 2022 to present)	Specially Appointed Associate Professor CEO	Ph.D.	Cognitive Neurology	N/A	N/A	N/A	N/A	N/A	N/A	CAINZ Digital Innovation Foundation, Period: from April 2020 to March 2021.	N/A	N/A
Takufumi Yanagisawa	Institute for Advanced Co-Creation Studies, Osaka University	Professor	M.D., Ph.D.	Neuroscience, Neurosurgery, Epilepsy, Clinical Neurophysiology	Councilor, Japanese Association for the Study of Pain. Councilor, The Japanese Society of Aromatherapy (Through FY2021).	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Natsue Yoshimura	School of Computing, Tokyo Institute of Technology	Professor	Ph.D.	Brain Information Decoding, Brain Machine Interfaces	Delegate, Japanese Neural Network Society. Board Member, The Japanese Society for Motor Control (2023).	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Systematic Review Team

*Affiliations, positions, grades, qualifications, etc. are as of April 1, 2023, and COI details, in principle, are based on declarations as of February 1, 2023.

Name	Affiliation	Occupation	Qualifications and Expertise	Specialty	Academic societies in hold positions, etc.	Details of Self-reported Financial COI								
						1. . Employment as an officer/director/adviser in a company or any for-profit organization directly related to the research and amount of remuneration	2. Profit on equity	3. Patent royalty	4. Daily allowance (Remunerations, lecture fee, etc.)	5. Manuscript fees	6. Research funding, grants, etc.	7. Scholarship (Incentive) Donations, etc.	8. Endowed courses offered by a company/organization/institution	9. Others (travel expenses, receipt of gifts, etc.)
Ryoji Onagawa	Faculty of Science and Engineering, Waseda University	Research Fellow (PD), Japan Society for the Promotion of Science	Ph.D.	Motor Control, Decision-making	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Isabel Bandes	Department of Information and Communications Engineering, Tokyo Institute of Technology	Second-year doctoral student	-	Brain decoding associated with movement and the design of online brain computer interface	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Seitaro Iwama	Faculty of Science and Technology, Keio University	Assistant Professor	Ph.D.	Neuroscience	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Naotsugu Kaneko	Graduate School of Arts and Sciences, The University of Tokyo	Assistant Professor	Ph.D.	Neurophysiology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ikko Kimura	Laboratory for Brain Connectomics Imaging, RIKEN	Special Postdoctoral Researcher (SPDR)	M.D., Ph.D.	Neuroscience, Neurology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
XU Yuting	Graduate School of Information Science and Technology, The University of Tokyo	First-year doctoral student	-	Cognitive Neuroscience	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hideaki Kurashiki	Graduate School of Science and Technology, Keio University	Completed master's degree (March 2023)	-	Brain-machine Interface	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Atsushi Sasaki	Graduate School of Engineering Science, Osaka University	Research Fellow (PD), Japan Society for the Promotion of Science	Ph.D.	Neurophysiology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kairi Sugimoto	Faculty of Science and Engineering, Waseda University Waseda University Honjo Senior High School	Third-year doctoral student Research Fellow (DC1), Japan Society for the Promotion of Science Part-time lecturer	Type 1 High school teaching license for Informatics	Cognitive psychology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hiroki Takeuchi	Graduate School of Education, The University of Tokyo	Project Researcher	-	Educational physiology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hiroki Noyama	Graduate School of engineering, The University of Tokyo	Third-year doctoral student	-	Neuroengineering	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yoshihito Muraoka	Graduate School of Science and Technology, Keio University	Completed master's degree (March 2023)	-	Neuroscience	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Evidence Book External Review Board

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Name	Affiliation	Occupation	Qualifications and Expertise	Specialty	Academic societies in hold positions, etc.	Details of Self-reported Financial COI								
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Yoshikazu Ugawa	Fukushima Medical University	Emeritus Professor	M.D., Ph.D., Board Certified Member of the Japanese Society of Internal Medicine, Neurologist, Clinical neurophysiology's Doctor	Neurology, Clinical Neurophysiology	Auditor, The Japanese Society of Neurology. President, Asian Oceanian chapter of IFCN. Member, Executive Committee of IFCN. Chair, Brain Stimulation Special Interest Group of IFCN. Chair, Movement Disorder in Asia Study Group of International Parkinson and Movement Disorders Society (MDS) . Delegate, The Japanese Society of Neurology to World Federation of Neurology.	N/A	N/A	N/A	CHUGAI-IGAKUSHA, Applicable to: individual, Period: from April 2019 to March 2022.	N/A	1. Association of Radio Industries and Businesses, Applicable to: individual, Period: from April 2019 to March 2023. 2. Tokyo Metropolitan Institute of Medical Science, Applicable to: individual, Period: from April 2019 to March 2023.	N/A	1. Takeda General Hospital, Applicable to: individual, Period: from April 2020 to March 2024. 2. Aidu Chuo Hospital, Applicable to: individual, Period: from April 2019 to March 2022.	N/A
Fumihiro Uno	Dobunshoin, Inc.	Chief Executive Officer (CEO)	-	Financial Management	Publisher, Natural Medicine database Japan. Executive Secretary, Japanese Association of Nutritional Science Education.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Noriko Osumi	Tohoku University. Tohoku University Library. Tohoku University Graduate School of Medicine. Center for Neuroscience.	Vice President. Director. Professor. Chair.	Ph.D., DDS	Molecular Biology, Developmental Biology, Neuroembryology, Science Communication	Councilor, The Japanese Society of Neuropsychopharmacology. Councilor, Union of Brain Science Associations in Japan. Director (Through December 2022),Councilor (From January 2023), The Japan Neuroscience Society. Councilor, The Japanese Society for Neurochemistry. Delegate, The Japan Society of Developmental Origins of Health and Disease. Director, BRAINTECH CONSORTIUM. Director, The Naito Foundation. Councilor, Astellas Foundation for Research on Metabolic Disorders.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Takayoshi Sugawara	Sedgefield Kobayashi and Partners. Faculty of Law, Keio University.	Attorney at Law. Professor.	Attoney at Law	Civil law, commercial and corporate law, Information Law, Aviation and Space Law, and Economic Law, Risk Management	Director, The Air Law Institute of Japan. National Governance PT Member, KEIZAI DOYUKAI<Japan Association of Corporate Executives>. Trustee, The Tokyo Bar Association Scholarship Foundation. Director, Corporate Law Section, Legal Research Department, Tokyo Bar Association. Member, International Transaction Law Department, Legal Research Division, Tokyo Bar Association. Academic member, Specialist Committee on Economic Law and Regulations, The Japan Chamber of Commerce and Industry.	1. Keio University. Applicable to: individual, Period: from April 2019 to March 2022. 2. ANA Strategic Research Institute Co.,Ltd., Applicable to: individual, Period: from April 2019 to March 2021.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Takeo Nakayama	Graduate School of Medicine and Faculty of Medicine, Kyoto University	Professor	M.D., Ph.D. Public Health and Social Medicine Certified Specialist, Japanese Society of Public Health Certified Senior Epidemiologist, Japan Epidemiological Association	Public Health, Epidemiology, Health Informatics, Health Communication, etc.	Vice President, Japan Association of Health Communication. Vice President, Japanese Society for Clinical Knowledge. Vice President, The Japanese Association of Smoking Control Science. Vice President, Japanese Society of Health Science for Children.	N/A	N/A	N/A	1. Janssen Pharmaceutical K.K., Applicable to: individual, Period: from April 2018 to March 2019. 2. Mitsubishi Tanabe Pharma Corporation, Applicable to: individual, Period: from April 2020 to March 2021. 3. Eli Lilly Japan K.K., Applicable to: individual, Period: from April 2020 to March 2021.	N/A	KONICA MINOLTA, INC., Applicable to: individual, Period: from April 2019 to March 2022.	1. Hanshin Dispensing Holdings Ltd., Applicable to: individual, Period: from April 2019 to March 2022. 2. Nakagawa Pharmacy Co., Ltd., Applicable to: individual, Period: from April 2019 to March 2022. 3. YUYAMA Co., Ltd. Applicable to: individual, Period: from April 2019 to March 2022.	N/A	N/A
Yu Nishitsutsumi	Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology (NICT)	Researcher	Ph.D.	Philosophy of Mind, Neuroethics	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Systematic Review External Review Board

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						1. Employment as an officer/director/adviser in a company or any for-profit organization directly related to the research and amount of remuneration	2. Profit on equity	3. Patent royalty	4. Daily allowance (Remunerations, lecture fee, etc.)	5. Manuscript fees	6. Research funding, grants, etc.	7. Scholarship (Incentive) Donations, etc.	8. Endowed courses offered by a company/organization/institution	9. Others (travel expenses, receipt of gifts, etc.)
Masahiro Iguchi	Department of Neurology, Fukushima Medical University	Associate Professor	M.D., Ph.D.	Clinical Neurology	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Masahito Mihara	Department of Neurology, Kawasaki Medical School	Professor	M.D., Ph.D.	Clinical Neurology, Neurorehabilitation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Secretariat

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Name	Affiliation	Occupation	Qualifications and Expertise	Specialty	Academic societies in hold positions, etc.	Details of Self-reported Financial COI								
						1. Employment as an officer/director/adviser in a company or any for-profit organization directly related to the research and amount of remuneration	2. Profit on equity	3. Patent royalty	4. Daily allowance (Remunerations, lecture fee, etc.)	5. Manuscript fees	6. Research funding, grants, etc.	7. Scholarship (Incentive) Donations, etc.	8. Endowed courses offered by a company/organization/institution	9. Others (travel expenses, receipt of gifts, etc.)
Yumiko Kakubari	ARAYA Inc.	-	-	—	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ayumi Kusano	ARAYA Inc.	-	Ph.D.	Molecular genetics	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shiho Tenmoto	Knowledge Mobility based System Institute	Director	-	Science Communication	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Seiko Fujiawara	Keio University	Part-time Clerk	-	—	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tomoya Nakanishi	Neuro Innovation Unit, NTT Data Institute of Management Consulting, Inc.	Consultant	Ph.D., Physical Therapist	Rehabilitation Science, Sports Science Neurophysiology, Neuroscience	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[RQ1] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI					
				1. I have cited my academic papers in systematic reviews of the social questions. However, systematic review articles summarizing the findings of this RQ are excluded.	2. I am a family or relative of another committee member.	3. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	4. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	5. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Mitsuaki Takemi	Graduate School of Science and Technology, Keio University	Project Assistant Professor	Member of Guidebook Development Committee, Chairman of Evidence Evaluation Committee	N/A	N/A	Applicable person: Junichi Ushiba Relationship: My employer	N/A	N/A	N/A
Nobuhiro Hagura	Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology (NICT)	Senior Researcher	Member of Evidence Evaluation Committee	N/A	N/A	N/A	N/A	N/A	N/A
Ryoji Onagawa	Faculty of Science and Engineering, Waseda University	Research Fellow (PD), Japan Society for the Promotion of Science	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
Yoshihito Muraoka	Graduate School of Science and Technology, Keio University	Completed master's degree (March 2023)	Systematic Review Member	N/A	N/A	Applicable person: Junichi Ushiba Relationship: My supervisor	N/A	N/A	N/A

[RQ2] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI					
				1. I have cited my academic papers in systematic reviews of the social questions. However, systematic review articles summarizing the findings of this RQ are excluded.	2. I am a family or relative of another committee member.	3. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	4. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	5. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Akifumi Kishi	Graduate School of Medicine, The University of Tokyo	Project Lecturer	Member of Evidence Evaluation Committee	N/A	N/A	N/A	N/A	N/A	N/A
Masako Tamaki	RIKEN Center for Brain Science (CBS), RIKEN Hakubi Team Leader Cognitive Somnology RIKEN Hakubi Research Team	RIKEN Hakubi Team Leader	Member of Evidence Evaluation Committee	N/A	N/A	N/A	N/A	N/A	N/A
Hiroki Takeuchi	Graduate School of Education, The University of Tokyo	Project Researcher	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
Isabel Bandes	Department of Information and Communications Engineering, Tokyo Institute of Technology	Second-year doctoral student	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A

[RQ3] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI					
				1. I have cited my academic papers in systematic reviews of the social questions. However, systematic review articles summarizing the findings of this RQ are excluded.	2. I am a family or relative of another committee member.	3. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	4. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	5. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Rieko Osu	Faculty of Human Sciences, Waseda University	Professor	Member of Evidence Evaluation Committee	N/A	N/A	N/A	N/A	N/A	N/A
Jun-ichiro Kawahara	Graduate School of Humanities and Human Sciences, Hokkaido University	Professor	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
Ryoji Onagawa	Faculty of Science and Engineering, Waseda University	Research Fellow (PD), Japan Society for the Promotion of Science	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
Ikko Kimura	Laboratory for Brain Connectomics Imaging, RIKEN	Special Postdoctoral Researcher (SPDR)	Systematic Review Member	N/A	N/A	Applicable person: Kaoru Amano Relationship: My supervisor	N/A	N/A	N/A
Hiroki Noyama	Graduate School of engineering, The University of Tokyo	Third-year doctoral student	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A

[RQ9] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI					
				1. I have cited my academic papers in systematic reviews of the social questions. However, systematic review articles summarizing the findings of this RQ are excluded.	2. I am a family or relative of another committee member.	3. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	4. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	5. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Kaoru Amano	Graduate School of Information Science and Technology, The University of Tokyo	Professor	Member of Evidence Evaluation Committee	N/A	N/A	Applicable person: Ikko Kimura, XU Yuting Relationship: My students	N/A	Although I haven't published a paper yet, I am currently researching on the relationship between brain waves and relaxation.	N/A
Mitsuaki Takemi	Graduate School of Science and Technology, Keio University	Project Assistant Professor	Member of Guidebook Development Committee, Chairman of Evidence Evaluation Committee	N/A	N/A	Applicable person: Junichi Ushiba Relationship: My employer	N/A	N/A	N/A
Hideaki Kurashiki	Graduate School of Science and Technology, Keio University	Completed master's degree (March 2023)	Systematic Review Member	N/A	N/A	Applicable person: Junichi Ushiba Relationship: My supervisor	N/A	I previously conducted the studies using the indicators possibly treated in the RQ and am going to published them as a paper.	N/A
Kairi Sugimoto	Faculty of Science and Engineering, Waseda University Waseda University Honjo Senior High School	Third-year doctoral student Research Fellow (DC1), Japan Society for the Promotion of Science Part-time lecturer	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
XU Yuting	Graduate School of Information Science and Technology, The University of Tokyo	First-year doctoral student	Systematic Review Member	N/A	N/A	Applicable person: Kaoru Amano Relationship: My supervisor	N/A	N/A	N/A

[Appendix] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI					
				1. I have cited my academic papers in systematic reviews of the social questions. However, systematic review articles summarizing the findings of this RQ are excluded.	2. I am a family or relative of another committee member.	3. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	4. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	5. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Seitaro Iwama	Faculty of Science and Technology, Keio University	Assistant Professor	Systematic Review Member	N/A	N/A	Applicable person: Junichi Ushiba Relationship: My supervisor	N/A	N/A	N/A
Naotsugu Kaneko	Graduate School of Arts and Sciences, The University of Tokyo	Assistant Professor	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A
Ikko Kimura	Laboratory for Brain Connectomics Imaging, RIKEN	Special Postdoctoral Researcher (SPDR)	Systematic Review Member	N/A	N/A	Applicable person: Kaoru Amano Relationship: My supervisor	N/A	N/A	N/A
Atsushi Sasaki	Graduate School of Engineering Science, Osaka University	Research Fellow (PD), Japan Society for the Promotion of Science	Systematic Review Member	N/A	N/A	N/A	N/A	N/A	N/A

[Evidence Book External Review Board] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI				
				1. I am a family or relative of another committee member.	2. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	3. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	4. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Yoshikazu Ugawa	Fukushima Medical University	Emeritus Professor	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A
Fumihiro Uno	Dobunshoin, Inc.	Chief Executive Officer (CEO)	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A
Noriko Osumi	Tohoku University Tohoku University Library Tohoku University Graduate School of Medicine Center for Neuroscience	Vice President Director Professor Chair	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A
Takayoshi Sugawara	Sedgefield Kobayashi and Partners Faculty of Law, Keio University	Attorney at Law Professor	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A
Takeo Nakayama	Graduate School of Medicine and Faculty of Medicine, Kyoto University	Professor	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A
Yu Nishitsutsumi	Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology (NICT)	Researcher	Evidence Book External Review Board	N/A	N/A	N/A	N/A	N/A

[Systematic Review External Review Board] List of Academic COI

Name	Affiliation	Occupation	Function	Details of Self-reported Academic COI				
				1. I am a family or relative of another committee member.	2. I have a close mentor-pupil relationship or direct employment relationship with another committee member.	3. Endowed courses related to BMI are offered by a company or a for-profit corporate organization or group in the department, division, etc. at the university, national research institute, or other research institution to which I belong, or at the same company.	4. Not applicable to the items above, but there are events in which a conflict of interest is assumed.	In particular：
Masahiro Iguchi	Department of Neurology, Fukushima Medical University	Associate Professor	Systematic Review External Review Board	N/A	N/A	N/A	N/A	N/A
Masahito Mihara	Department of Neurology, Kawasaki Medical School	Associate Professor	Systematic Review External Review Board	N/A	N/A	N/A	N/A	N/A