Guidelines for Ethical Planning and Conduct of Brain and Neuroscience Research Involving Human Subjects
(Amended in 2025)

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1. Introduction

In the past, localized functions of the human brain have been conjectured by closely observing the clinical signs in patients who incurred insults to parts of the brain as a result of trauma or cerebrovascular disorders. These clinical signs include neurological deficits (negative signs) such as motor paralysis, sensory disturbance, aphasia, and memory deficit, as well as positive signs (e.g. convulsions), which can be observed as partial signs of epileptic seizures. Localization of brain function has also been conjectured by examining the phenomena triggered by electrostimulation applied to the surface of the cerebral cortex during surgical treatments for patients with intractable epilepsy. However, while simple comparison of these clinical signs and lesion areas has made it possible to speculate upon how a certain area of the brain plays an important part in a given function, it has been difficult to determine the actual functional connections or network mechanisms that exist

among the different structures inside the brain. In particular, it has been extremely difficult to carry out research on the mechanisms of functional compensation and remodeling during recovery from neurological deficits by relying solely on clinical observations, despite the fact that clinically this is the most critical issue.

Thanks to the development of various new technologies in the past 30 years, it has become possible to conduct research with methods that make human brain function visible to the eye. These methods include: electrophysiological methods, whereby brain potentials are detected from the scalp by electroencephalography (EEG) or magnetoencephalography (MEG), allowing for analysis of the cortical electrical activities that are triggered by various brain functions; non-invasive brain stimulation (NBS) by transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), whose use has been expanding recently; nuclear medical methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), which use radioactive isotopes; functional magnetic resonance imaging (fMRI), which has lately become especially popular; and optical imaging, which uses near infrared spectroscopy. These research methods are more or less minimally invasive to research subjects,[1] and are therefore termed non-invasive methodologies. Each of these testing methods has unique characteristics. In particular, electrophysiological methods, including magnetic stimulation methods, provide relatively detailed temporal information of brain function; other imaging methods provide relatively precise spatial information.

In recent years, the Japan Neuroscience Society has continuously established and revised guidelines to be followed by its members, in response to growing awareness of research subject protection in medical and psychological research involving human subjects and legislation regarding medical and biological research involving human brain. During this period, “Ethical Guidelines for Medical and Health Research Involving Human Subjects” (2014, the Ministry of Education, Culture, Sports, Science and Technology [MEXT] and the Ministry of Health, Labour and Welfare [MHLW], partially revised on February 28, 2017) have been developed, which combine “Ethical Guidelines Concerning Epidemiological Research” (Notification No. 1 from MEXT and MHLW in 2007) and “Ethical Guidelines Concerning Clinical Research” (Notification No. 415 from MHLW in 2008). The new guidelines specify the rules that all parties involved in medical research involving human subjects must follow. The Clinical Trial Act, promulgated in 2017, stipulates the procedures and information disclosure systems for clinical trials, defining such trials as research to clarify the efficacy or safety of pharmaceuticals by administering them to humans. Furthermore, in 2021, “Ethical Guidelines for Medical and Health Research Involving Human Subjects” and “Ethical Guidelines for Human Genome/Gene Analysis Research” were combined into “Ethical Guidelines for Medical and Biological Research Involving Human Subjects.” Compliance with “Ethical Guidelines for Medical and Biological Research Involving Human Subjects” is required in studies aiming at the acquisition of knowledge contributing to maintaining and promoting people’s good health, advancing the recuperation of patients from injury and disease, or improving the patient’s quality of life. Because the guidelines stipulate only the basic principles for various forms of medical research, specific and appropriate guidelines based on these principles are desired for each field. In fact, as neuroscience advances, non-invasive research on human brain function increasingly overlaps with medical research subject to the “Ethical Guidelines for Medical and Biological Research

Involving Human Subjects" or the "Clinical Trials Act," as seen in research on neurofeedback and the Brain-Machine Interface. Since the development of guidelines and regulations reflects Japan's drive to advance brain science research, it has become necessary to clarify management systems for non-invasive research on human brain function at each facility to foster public understanding. Furthermore, the Act on the Protection of Personal Information was significantly revised in 2015, and the revision took effect in 2017. To address such circumstances, these guidelines were amended in 2020 (the 2020 version), followed by publication of a further revised version in 2022 (the 2022 version) to reflect the contents of "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" published in 2021 (hereinafter, abbreviated as "Guidelines for Medical and Biological Research 2021" in appropriate cases).

On the other hand, from a global perspective, advancement of technologies to reduce invasiveness in research involving human brain is remarkable. In particular, results of human brain research utilizing minimally invasive methods represented by miniature or wireless implanted electrodes, intracranial electrodes, implanted ultrasound sensors, intravascular electrodes and others have been published one after another. Considering advancement and widespread use of these technologies, the current guidelines need revision to comprehensively cover ethical planning and conduct of brain and neuroscience research involving human subjects to include research utilizing invasive methods. For these reasons, the guidelines revised in 2024-2025 additionally referred to invasive BMI using intracranial electrodes. They also covered brain stimulation methods for the treatment of epilepsy and neurological diseases as well as human brain and neuroscience research utilizing recording devices. Based on these revisions, the guideline title was changed from "Guidelines for Ethics-related Problems with 'Non-invasive Research on Human Brain Function' (2022)" to "Guidelines for Ethical Planning and Conduct of Brain and Neuroscience Research involving Human Subjects (2025)."

In "Ethical Guidelines for Medical and Biological Research Involving Human Subjects," the terms such as "invasiveness" or "intervention" are clearly defined. These definitions are adopted in these Guidelines as well. Namely, "intervention" is defined as "a practice for investigational purposes to control the presence or absence of factors that can affect a variety of events occurring in relation to human health (including activities to maintain and promote good health and medical practices, such as medication and examinations for prevention, diagnosis, and treatment of patients), or the degree of such factors." The above-defined intervention also includes medical technique beyond usual medical practice that are conducted for investigative purposes. "Invasiveness" is defined as "to cause injuries or distress to the body and/or mind of a research subject by conducting a procedure for investigational purposes, such as puncture, incision, administration of drugs, irradiation, and questions related to a subject's mental trauma, etc." Of various types of invasiveness, one causing minor injury and/or distress to the body and/or mind of a research subject is called "minor invasiveness."

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[1] Research subjects refer to participants in research studies and candidates for such participation. Here, candidates refer to potential participants in research studies who have responded to recruitment but have not decided to participate.

2. Purpose of brain and neuroscience research involving human subjects and its scientific and social significance

The purpose of brain and neuroscience research, as covered by the current guidelines, is to shed light on the mechanisms of the human brain. Focusing on memory, one of the most important high-level brain functions, our purpose is to clarify how information from the external/internal worlds is stored and retrieved as needed. To be able to gain new knowledge about the function of the brain is extremely important in itself from a scientific point of view; yet we also expect that it will lead us to be able to recognize signs and symptoms triggered by various neuropsychiatric disorders, unravel their pathogenic mechanism, and develop more effective treatment methods. In other words, to use the example of memory, if a patient who has suffered a lesion to a certain area of the brain incurs memory impairment, it would be possible to determine the stage in the memory process where the damage has occurred based on the knowledge obtained by studying the neurological networks associated with memory in healthy subjects. Another example is use of the resting state functional connectivity that is calculated based on MRI images, as well as the neurological network data obtained by diffusion tractography, it might be possible to determine which regions contain the information transduction pathways that are affected by the disease; this would in turn make it possible to plan treatments and measure their effects. Moreover, if details of the neurotransmitters and their receptors, which are necessary for information transmission in the given neural pathways, could be elucidated by using neurotransmission imaging methods with PET, there is a possibility of developing therapeutic agents. In addition, NBS may be applied to the relevant neural network to yield information that is useful for establishing policies regarding functional recovery and rehabilitation. If the physiological adjustment mechanisms relevant to the recovery of impaired brain function can be elucidated, there is a possibility that this will lead to the development of effective drugs or rehabilitation training. In particular, these avenues of research carry huge social significance in the 21st century, where an increase in the number of patients with dementia or mobility impairment is increasing as a result of an aging society. This remains true even after the scope of the current guidelines is extended to include research involving invasive methods.

However the gain of new knowledge of brain function, as mentioned above, increases the danger of proliferation of inaccurate or over-interpreted information to the general public, causing spread of superstitions that are not scientifically proven, or generating suspicions about the reliability of neuroscience. The basis of development and progress in neuroscience requires the firm trust from society, starting with research subjects and various related parties, and more general recognition of the social effectiveness and significance of research. Moreover, since research, regardless of invasiveness of the method used, also covers areas of the “mind”, that is directly linked to human dignity, it entails special care so as not to trigger social concerns that lack scientific bases at the current level of technology, such as “Are they going to manipulate my mind?” or “Are they going to read my mind?” not in the laboratory but in general society. Precautions must be taken in order to ensure that results of research on brain functions are not used to discriminate or ostracize certain people, and thereby cause an invasion of human rights.

With recent advancements in artificial intelligence and autonomous systems, including robots and neurotechnologies, the ethical aspects of brain science are increasingly being debated worldwide, prompting domestic debate on this topic.[1,2,3)] There is growing concern regarding the

potential erosion of self-identity (physical and mental integrity), diminishment of agency (ability to choose one's own behavior), and invasion of individual privacy, which are basic human rights. For this reason, informed consent prior to participation in experiments is emphasized more now than in the past as a means of protecting the basic human rights of research subjects. Sufficient attention should also be paid to possible changes in societal norms and to new forms of discrimination related to novel neurotechnologies for extending specific abilities.

As stated in the previous section, brain and neuroscience research currently receives substantial financial support from the government. In such circumstances, it is sought that research results be used in return for the benefit of society. To achieve this, efforts at publicizing research results through the media, such as the press and documents, or through outreach activities, such as public lectures and science cafes, are being encouraged. Yet, in order to ensure that research results are communicated accurately without unintended generation of any pseudo-brain/neuro-science or so-called "neuro-myths" as mentioned above, it is necessary to present research results after considering how they would be perceived by society and verifying how these achievements would ultimately be disseminated by the media. For this, it is advisable to be familiar with the characteristics of the media and society, and as well as to actively facilitate mutual communication with these two parties.

References

1. Rommelfanger KS et al. (2018) Neuroethics Questions to Guide Ethical Research in the International Brain Initiatives. Neuron 100:19–36.
2. Yuste R et al. (2017) Four ethical priorities for neurotechnologies and AI. Nature 551:159–163.
3. Nakazawa E et al. (2022) The way forward for neuroethics in Japan: A review of five topics surrounding present challenges. Neuroscience Research 183: 7-16.

3. Purpose of current guidelines

As stated in the previous section, neuroscience research also covers areas of the human mind. It therefore requires knowledge and application of ethical standards pertaining to research on human subjects; special attention must also be paid to its influence on society. Therefore, in brain and neuroscience research involving humans (the term "human" refers to a biological species) as research subjects, consideration for the welfare of research subjects and related parties must take precedence over scientific and social benefits. Investigators must respect the sanctity of research subjects and related parties and abide by the general principles that protect their human rights. Investigators are also required to draw up a research plan that takes ample account of ethical, legal, and social issues, and to carry out their research accordingly. On the other hand, brain and neuroscience research involving neurotechnology is advancing rapidly. Under these circumstances, it has become more important and necessary than ever for our Society to appropriately identify current ethical problems and timely issues, and to develop practical policies relating to brain and neuroscience research involving neurotechnology.

It should be noted that these guidelines are only sample guidelines set out by our Society and that they do not limit individual research conducted at various research implementing entities and facilities. Each research project should be carried out by following the regulations established at each research implementing entity and facility based on the national laws, ordinances, and guidelines

applicable to each research area listed below, and by obtaining approval of their ethical review committee.

Each method covered by current guidelines has varying level of invasiveness. In accordance with the definitions in the Guidelines for Medical and Biological Research 2021, psychological tests, EEG/MEG, NIRS and others are classified as research not involving "invasiveness," while ordinary MRI research as involving "minor invasiveness." NBS may be generally regarded as involving "minor invasiveness," if the stimulation parameters are within the range described in guidelines published by specialist organizations or in academic journals. However, repetitive high frequency magnetic stimulation previously causing convulsion in healthy subjects requires careful review regarding the level of invasiveness by the ethics committee of each facility. In particular, cases requiring application of stimulation parameters beyond the range specified by the guidelines (e.g., at a higher frequency or intensity) should be regarded as involving "invasiveness." Use of nuclear medical methods such as PET and SPECT (requiring venipuncture and drug administration), implanted, intracranial and other electrodes (requiring craniotomy), and intravascular electrodes (requiring vascular puncture) is research involving "invasiveness." Even though a test method used per se involves no "invasiveness" or involves only "minor invasiveness," research might be regarded as involving "invasiveness" due to extremely prolonged test duration or questions related to a research subject's mental trauma, etc. causing injuries or distress to the body and/or mind of a subject.

In addition, if research involving NIBS, neurofeedback, BMI and other methods includes "control of the presence or absence of factors that can affect a variety of events occurring in relation to human health or the degree of such factors," it is regarded as "interventional" research, whether the research subjects are healthy or affected with neuropsychiatric disorders. If such "interventional" research aims to "clarify the efficacy or safety of pharmaceuticals by using these pharmaceuticals in humans," it is regarded as a "specified clinical trial."

[Clinical trial][2]

Clinical Trials Act (Act No. 16 of 2017)[3]

Ministerial ordinance concerning the standards for implementing clinical studies of drugs and medicines.[4]

[Research, other than clinical trials, that uses human subjects][5]

Ethical Guidelines for Medical and Biological Research Involving Human Subjects[6]

Policies concerning clinical research on gene therapeutic techniques, etc.

Guidelines concerning research that uses extracted human tissues e.g. following surgery

[All research supported by MHLW Grants]

Policies concerning the management of conflict of interest in MHLW-grants assisted research[7]

It should be noted that current guidelines do not apply to studies conducted as interventions, which are solely for the purpose of diagnosis and treatment; they cover practices that are conducted on healthy participants or patients mainly for research purposes. In addition, research articles that are presented in our in-house journal, Neuroscience Research, should take applicable regulations into account and follow the guidelines set out in this document. This stipulation is also indicated in the journal's publication guidelines.

https://www.jnss.org/NSRoffice/NSR-Inst.htm
This applies presentations at conferences such as scientific meetings hosted by our Society.

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[2] Clinical trials refer to research that aims to clarify the efficacy or safety of pharmaceuticals by using these pharmaceuticals in humans. Clinical trials using human stem cells are subject to the Act on Securing Safety of Regenerative Medicine (Act No. 85 of 2013).
[3] https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000163417.html [4]https://www.pmda.go.jp/int-activities/int-harmony/ich/0076.html
[5]https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html
[6]https://www.lifescience.mext.go.jp/bioethics/seimeikagaku_igaku.html
[7]http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html

4. **Ethical characteristics and testing guidelines for each non-invasive research method**

A. **Magnetoencephalography (MEG)**

1) Summary

Magnetoencephalography (MEG) is an imaging technique that uses a measuring device to record changes in the magnetic field produced by the brain. Electroencephalography (EEG), which is widely used, and MEG both directly measure electrical activity generated by the brain but do so by different methods. When areas of pyramidal cells in the cerebral cortex, which have dendritic protrusions at the pointed extremity, are stimulated, they produce a depolarization, which generates electric currents inside and outside the cells. While EEG records the potential derived from electric currents that flow outside the cells, MEG records the magnetic field that is generated by the electric currents inside the cells. Thus, the underlying source of the signal for both EEG and MEG recordings is identical, and since neither technique entails application of stress or direct stimulation to the brain, these methods are considered highly safe.

2) Effectiveness

Compared to EEG, MEG's greatest strength is its high spatial resolution. The space between the brain and scalp is made up of three layers – cerebrospinal fluid, skull and skin – and each has a significantly different electric conductivity. As a result, these layers have a significant impact on the electric field generated by the brain, making it difficult to accurately measure the active area in the cortex from EEG electrodes placed on the scalp, even when a specialized estimation method (such as the dipole tracing method) is used. However, magnetic fields are not affected by electric conductivity, and thus when recording conditions are favorable, MEG can be used to image active areas with 1 mm precision. This is the greatest advantage of MEG. Compared to PET and fMRI, MEG has the advantage of being completely non-invasive; it records the neurons' electrical activity rather than changes in localized cerebral blood flow; and, like EEG, it has a high temporal resolution of 1 msec. However, the biggest problem with MEG is that, as with EEG, when estimating localized brain function, its location must be estimated based on the recorded distribution of the magnetic field (i.e. the inverse problem must be solved). In other words, compared to fMRI or PET, it inevitably yields an indirect estimate of the location. MEG also has three more disadvantages: (1) it is difficult to record activities that are generated in the deep part of the cerebrum (because the spatial

attenuation is large due to the distance of the magnetic field signal); (2) it is difficult to record activities in the cerebral gyrus parallel to the surface of the head (due to technical problems associated with measuring magnetic fields); (3) it is difficult to accurately estimate the location of activities when they are occurring simultaneously in multiple areas (because the algorithm of the analysis software becomes extremely complicated when estimating activities in multiple areas).

3) Ethical problems (Risks involved in testing)

It can be claimed that MEG testing *per se* does not involve any risks. So far, there have been no articles or reports on safety considerations for MEG use. If accidents were to occur, potential causes might include design errors in the MEG measurement equipment or the installation device, or their deterioration; the equipment might also be damaged or fall due to natural disasters such as earthquakes. Yet manufacturing companies take extreme precautions against these possibilities and conduct frequent inspections. Thus far, such accidents, including small-scale accidents, have not been reported. Rather, the problem with MEG concerns the pain research subjects experience during actual testing. Firstly, to achieve high spatial resolution, research subjects should, as much as possible, avoid moving their heads during the test. Remaining still can cause discomfort or pain when the test lasts for long periods. Secondly, since the test is conducted in a sealed room, there is a sense of being isolated and trapped, which can become distressing to research subjects who have tendencies to experience "claustrophobia." Thirdly, when recording functional responses to stimuli, such as tactile, visual, or auditory stimuli (induced magnetic encephalography), experimental protocols can cause discomfort for some research subjects. However, these problematic points are not specific to MEG but are also common to EEG, fMRI, and PET.

A higher risk, beyond the three points mentioned above, is posed by the participation of epilepsy patients in these brain imaging procedures. During MEG testing, the measuring device completely covers the entire head of the test participant, and in the event of the patient having a convulsive seizure, there is the possibility that the head and neck areas of the patient might get severely damaged (though there have been no reports of such incidents so far). To take precautions against this possibility, it is crucial to be familiar with the patient's medical history and current condition before conducting the test, especially when applying visual stimuli to an epilepsy patient.

4) Testing guidelines

1. Before conducting the test, detailed explanations of the general procedures and the risks involved in MEG testing should be provided, and informed consent[7] obtained.
2. When conducting tests on patients, the attendance of a primary physician or an alternative physician is required. However, when the person in charge of the test is a doctor, the attending nurse could be present instead. In both cases, it is essential to make arrangements so that measures can be taken if unforeseen situations arise. Particular care must be taken when the subject is an epilepsy patient, as mentioned above. If a seizure occurs, the test must be aborted immediately, and appropriate measures must be taken against the seizure. The decision to resume the test will be made by the physician in charge at a later date. In cases of retesting, informed consent must be obtained anew to ensure the patient or family understands the procedure.

3. Precautions to be taken during the test
    a. The interior of the sealed room should be monitored at all times by the installation of a television camera. In certain cases, the physician or nurse may need to enter the room to observe the patient's condition.
    b. A microphone should be in place so that the research subject, who is inside the sealed room, is in close contact with the person in charge of the test at all times, who is outside the room. Also, it should be ensured that the research subject can express themselves clearly to the people outside at any time.
    c. While the length of the test is to be determined by the person in charge of the test or by the doctor in charge, as a general rule, each testing session should be limited to 15 minutes or less, and breaks should be offered to the research subject accordingly. During the break, the subject should be able to leave the sealed room. During breaks, clinicians, experimenters, and support staff should talk to the research subject, ask if there are any problems, and attend to those problems.
    d. As a general rule, the entire testing session should be limited to an hour or less.

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[7]Refers to consent to participate in research, provided by and based on the free will of the person asked to undergo the research, after they have received a thorough explanation from the investigator, etc., about the research and have understood its significance, purpose, and methods (for details, refer to 6. of the current guidelines).

5) Explanatory documents for research participants

As a general rule, follow the content stated in Section 6 of the current guidelines. Below, we provide some examples of information that can be provided specifically to the characteristics of MEG testing, which can be used in explanatory documents.

1. <u>What is informed consent?</u>
   Refers to consent to participate in research, provided by and based on the free will of the person asked to undergo the research, after they have received a thorough explanation from the investigator, etc., about the research and have understood its significance, purpose, and methods.
2. <u>What is MEG?</u>
   MEG records the magnetic field emitted by the brain. The recorded wave pattern is called MEG. The test closely resembles EEG but differs in that EEG records the electrical potential generated by the brain.
3. <u>What is the purpose of using MEG?</u>
   MEG can provide detailed information about brain function, and its quality is more than 10 times that of EEG. (In documents provided to patients: "There is a possibility that the test might yield findings that are beneficial to future treatments.")
4. <u>Are there any risks involved in MEG?</u>
   There are no risks because the magnetic field measured is naturally emitted by the brain. There is no need to irradiate anything from the outside or to inject medical substances. We only ask that you do your best not to move, so that accurate test results can be obtained.

5. Types of MEG tests
   Depending on the type of brain function examined in the test, the testing protocol may involve tasks with stimuli and/or participant responses. Sounds would be provided through earphones or speakers for auditory stimuli; light, letters, or moving images for visual tasks; and weak electrical stimulation or other stimuli may be applied to the wrist or ankle for somatosensory (tactile) tasks. There is no need for concern since there are no safety issues associated with these tasks. (In explanatory documents for patients, add the sentence: “A doctor, technician, or nurse will be present at all times during the test.”)
6. Other cautionary notes
   a. Please do not wear anything with magnetic properties, as it cannot be distinguished from the magnetism emitted by the brain, making it impossible to conduct the test. Please be advised that you would not be allowed to enter the test room wearing underwear with metal attachments, belts, watches, keys, coins, bills, or magnetic cards. These should be removed beforehand. Also, if you have any metal implants, such as a pacemaker or a metal device for dental treatments, please inform us before the test begins.
   b. The test will be conducted in a sealed room (a magnetically sealed room). The interior of the room is monitored by a television camera at all times. Also, there is a microphone that allows you to be in constant contact with the person in charge of the test or the doctor outside the room. If you experience any inconvenience or discomfort, please do not hesitate to seek our attention immediately, even during the test.

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Supplementary remarks concerning electroencephalography (EEG)

1/2) Summary and usefulness

Electroencephalography (EEG) is obtained by recording the electrical potential of the brain from electrodes installed on the scalp. Since there is no need to apply direct stimulation or stress to the brain, the procedure is extremely safe and widely used, including in the field of psychology. In recent years, EEG has been increasingly used for various commercial purposes in daily life, heightening the need for accurate communication of results. Neuromarketing is expected to enable the collection of information on consumers' reactions to products in ways not possible with past questionnaire-based surveys. Even when EEG is used solely for basic research, attention should be paid to the fact that the general public may interpret it as being related to such commercial applications. For details on its technical aspects, follow "Revised clinical electroencephalography tests standards 2002,"[1)] which are the guidelines outlined by its specialist organization, the Japanese Society of Clinical Neurophysiology.

3) Problematic points (Risks involved in testing)

While EEG measurement has been widely used, including in neuropsychological studies (see later), there have been no reports of severe accidents specifically associated with EEG. Since skin allergies can be triggered in reaction to procedures on the scalp or electrode paste, which are applied in preparation for the test, it is advised to inquire about the past medical history of drug allergy before testing.

4) Testing guidelines

Follow the guidelines set out for MEG. Since a sealed room is not required for measuring EEG, the procedure is less stressful for the examined research subject. Also, because of its minimally invasive nature, the test might be conducted continuously, and might last for a week or longer, depending on its purpose (e.g. research on sleep or epilepsy).

5) Explanatory documents for research participants

In principle, Section 6 of the current guidelines should be followed.

References

1. Japanese Society of Clinical Neurophysiology, Clinical Electroencephalography Tests Standards Revision Committee: Clinical Electroencephalography Tests Standards 2002. Clinical Neurophysiology 31: 221-42, 2003
http://jscn.umin.ac.jp/files/guideline/ClinicalEEGtest.pdf

B. **Non-invasive brain stimulation (NBS)**

There are two methods of NBS, one using magnetic stimulation and the other using electric stimulation.

B-1. NBS using magnetism

1) Summary

Transcranial magnetic stimulation (TMS) is a method that stimulates the brain of a person by generating a magnetic field with a coil placed on the outside of the skull (on the scalp). It was developed by Barker et al in 1985.[1)] Because the skull has high electric resistance, the brain, which is located inside the skull, cannot be easily stimulated by applying an electric current from outside. TMS uses a magnetic field that is not weakened by the skull. A varying magnetic field is generated by applying a time-varying electric current to a coil placed on the scalp, and this magnetic field reaches the brain tissues beneath the skull without weakening. This time-varying magnetic field in brain tissue induces an eddy current that electrically stimulates neural circuits. Since the method involves stimulating the human brain, there were initially quite a few debates about its safety. Experiences to date show that its safety standards have become clearer, at least with regard to single-pulse stimulation.

Because human brain can be stimulated externally, TMS has been used for physiological research on healthy participants as well as for tests on patients. While TMS can stimulate many parts of the cerebral cortex and has reportedly been used to stimulate the cerebellum or brainstem, this method is most frequently used to stimulate the motor cortex, where stimulation effects can be more easily assessed. Stimulation methods include single magnetic stimulation and repetitive magnetic stimulation. Use of the latter requires careful consideration of safety. Moreover, repetitive magnetic stimulation has already been used for healthcare purposes, specifically for the treatment of neuropsychiatric diseases such as depression.[2)] With both single and repetitive magnetic stimulation, it is advisable that all tests follow the guidelines set out by the Japanese Society of Clinical Neurophysiology, which is an academic organization specializing in research methods used in clinical neurophysiology, including TMS.[5,6)] At the same time, it is desirable that tests involving repetitive magnetic stimulation follow international guidelines.[3,4)] When the purpose is performing primary or supplemental diagnosis of diseases, the “Guidelines for Medical and Biological Research 2021” must be followed. In cases of “specified clinical trials,” defined in the “Clinical Trials Act” as those which involve therapeutic intervention, the “Clinical Trials Act” must be followed.

Studies involving healthy participants require particular attention to close adherence to safety standards, as there are no benefits, including treatment effects, for the research participants. Moreover, repetitive magnetic stimulation should not be used without preparing for the possibility of seizure, which is a significant adverse reaction.

2) Effectiveness

TMS is characterized by its ability to stimulate human brain without pain. Therefore, its greatest scientific contribution is in the investigation of the physiological functions of healthy brain. It has the advantage of a high temporal resolution of 1 msec. By combining it with other high-resolution imaging technologies, it becomes possible to analyze which part of the human brain functions during which time interval. In particular, TMS can measure behavioral and cognitive changes resulting from neural activity and thereby clarify the causal relationship between neural activity and behavior/cognition. This is the major advantage of TMS. A second advantage concerns its use as a diagnostic device. Currently, TMS is especially useful for assessing lesions of the pyramidal tract and identifying their location. It is also used to assess disorders of motor control from the cerebellum

and basal ganglia. A third advantage concerns its use as a treatment device. It has attracted attention for the treatment of mental disorders, including depression, and neurological disorders such as Parkinson's disease. A medical device used for TMS treatment of depression was approved in September 2017 in Japan. The Japanese Society of Psychiatry and Neurology developed relevant guidelines.[13)]

3) Ethical problems (Risks involved in testing)

When considering the risks of TMS, it is necessary to divide the methods into repetitive magnetic stimulation (repetitive TMS, rTMS) and single- or paired-magnetic stimulation, and to consider the risks of each. In particular, high frequency rTMS should be considered separately. For descriptive purposes, high frequency rTMS is defined as the repetitive application of stimuli at a frequency exceeding 1 Hz, patterned repetitive magnetic stimulation, including theta-burst stimulation protocols and quadro-pulse stimulation (QPS), lately becoming widely used, is handled in the same manner as high frequency rTMS, if it enhances cortical excitability. The stimulation parameters of high frequency rTMS and patterned repetitive magnetic stimulation should be specified in accordance with the latest guidelines developed by the Japanese Society of Clinical Neurophysiology[6)] and Rossi et al.'s report on international standards.[7)]

Risks common to both single and repetitive magnetic stimulation are listed first; problems with each method are then described.

1. General risks

a. Auditory disorders

With TMS, when an electric current flows through the coil, the metals inside the coil attract each other, and as a result, generate sounds of metal clanking. These sounds can cause damage to the auditory system.

b. Burn

Metal beneath the coils, such as EEG electrodes, heats up when the coils are activated. Long hours of stimulation can therefore cause burn injuries. When EEG electrodes are in place during testing, the temperature of the coils should be checked periodically, as needed.

c. Decreased levels of concentration

Some reports have indicated a decrease in concentration after TMS. While it is unclear whether this is due to the long test duration or to TMS itself, in all cases, driving an automobile or motorcycle immediately after the test should be avoided.

2. Single or paired pulse stimulation

Based on clinical use to date and assessments of animal and human subjects, single- and paired-pulse stimulation can be considered without major risks, unless these approaches are contraindicated, as described below (minor invasiveness). Initially, epilepsy patients as well as children were excluded from TMS testing, and stimulation to the cervical region was not applied to patients suffering from cervical spondylosis. However, since then, studies have been conducted with these types of patients at several facilities and based on considerable experience in Germany and other countries, the indications have been expanded. Although it is likely that single and paired pulse stimulation are safe for patients with epilepsy (e.g., no possibility of worsening epilepsy), it is still possible that incidental convulsive seizures might occur during or immediately after the stimulation.

It is therefore necessary to explain this possibility to patients in advance, to carefully monitor for convulsions, and to prepare for their occurrence. Additionally, special precautions should be taken when stimulating epilepsy foci and when reducing antiepileptic doses. Indeed, even with healthy participants, since there is a chance that the participant happens to have undeveloped epilepsy, it is necessary to carefully and thoroughly inquire whether the participant has any previous history of febrile convulsion, head injuries, or brain surgery, family history of epilepsy, and any metal devices placed inside the body.

3. Repetitive transcranial magnetic stimulation (rTMS)

Prior to conducting research with repetitive transcranial magnetic stimulation (rTMS), approval of the applicable ethical review committee at each research implementing entity or facility must be obtained. rTMS or patterned repetitive magnetic stimulation, not enhancing cortical excitability, might be considered in the same manner as single or paired pulse stimulation. High frequency rTMS (frequencies exceeding 1 Hz) is used for the treatment of neuropsychiatric diseases and for psychobehavioral testing in healthy participants. However, since some reports have indicated that even healthy subjects can develop seizures during stimulation, safety and non-invasiveness have to be carefully considered. Prior to conducting research with high-frequency rTMS or patterned repetitive magnetic stimulation enhancing cortical excitability, approval of the applicable ethical review committee at each research implementing entity or facility must be obtained unless such use is considered to be established medical practice (such magnetic stimulation methods are currently indicated in Japan only for patients with depression). The stimulation parameters should be within the ranges specified in the latest international safety standards.[3, 4, 6)] Regarding the total number of stimulations, the recommendation by the Japanese Society of Clinical Neurophysiology can be referred to as follows. In the "Guidelines on Safety of Magnetic Stimulation Method (2019 version)",[6)] it is stated that stimulation at a frequency up to 10 Hz with a strength up to 1.2 times the resting threshold in the motor area can safely be repeated up to 15,000 times per week. Regarding patterned repetitive magnetic stimulation, the guidelines state that theta-burst stimulation with a strength not exceeding the resting threshold can be safely repeated up to 3,000 times per week, and QPS with a strength not exceeding the resting threshold can be safely repeated up to 2,880 times per week. It is recommended that high frequency rTMS be performed under physician supervision and responsibility, and that physicians be involved in the decisions on the treatment protocol and parameters.[6)] In principle, stimulation should be implemented by physicians with sufficient knowledge of the applicable device, while there is a notion that healthcare professionals who have sufficient knowledge of the device, who can respond to emergency situations, and who have participated in training sessions organized by academic societies or other organizations, can carry out the monitoring during stimulation. It is essential to perform the stimulation in a setting where the recipient can be transferred to a general hospital in the event of a convulsion or other events. Cases requiring application of stimulation parameters beyond the range specified by the guidelines (e.g., at a higher frequency or intensity) should be regarded as involving "invasiveness."

4) Testing guidelines

1. General precautions

a. The protocols should already have been approved by an ethical review committee at each research

implementing entity or facility. When research is conducted to develop therapies or therapeutic technologies in humans, the research procedures must be determined in accordance with the Clinical Trials Act and other relevant rules and regulations. However, the motor-evoked potential test using single or paired TMS is established as medical practice (covered by insurance), and therefore, ethics review is not necessarily required when it is medically necessary (ethics review would be necessary if research subjects included healthy controls or if the research were conducted as prospective clinical research). Moreover, if research includes "control of the presence or absence of factors that can affect a variety of events occurring in relation to human health or the degree of such factors," it is regarded as "interventional" research requiring ethics review.

b. A thorough explanation of the procedure must be given to each research participant, and informed consent should be obtained. For example, it is desirable to provide explanations such as the following to research participants: "At the time of maximum magnetic stimulation, a magnetic field of 2 tesla is applied at the rate of change of approximately 1000 tesla/sec from a coil placed on the head. The strength of this magnetic field is nearly the same as that used in Magnetic Resonance Imaging (MRI), which is widely used for diagnostic testing.– At this point, you might hear a loud sound, or your body might move slightly, but there is nothing to worry about. In the past, reports have stated that research participants experienced headaches, shoulder stiffness, or fatigue after stimulation, but all symptoms disappeared within a day. Both single and paired pulse stimulation are regularly used as a part of medical practice, and there have been no reports of serious side-effects."

c. Have the research participant wear earplugs.

d. Driving a car or motorcycle immediately after the test should be avoided. If driving a car, have the research participant wait for at least 1 hour after completing testing.

e. Using questionnaires or other tools, research participants should be screened in advance regarding their health status and risks for adverse reactions related to TMS.[8,9)]

2. Contraindications of and precautions related to single or paired pulse stimulation

a. Presence of any metal object in any part of the head other than the intraoral space

b. Past placement of a cardiac pacemaker, an implantable cardioverter defibrillator, an implantable neurostimulator, or a drug delivery pump (people with any of these devices cannot perform the stimulation)

c. Serious heart disease or other conditions judged to be contraindications by a physician

d. Pregnancy or possible pregnancy

e. Caution is required in cases of epilepsy or prior convulsions that are now poorly controlled. In particular, stimulation of epilepsy foci should be avoided as much as possible.

3. Repetitive magnetic stimulation tests (particularly those involving high-frequency stimulation)

Significant precautions are needed when using this method for testing. It is necessary to thoroughly explain the possibility that even healthy participants can develop seizures associated with this methodology. For details, we suggest you refer to References 3, 4, 6, 7, 10, 11, 12, and 13.

A simple summary is provided below:

1. Absolute contraindications

A pacemaker or a metal object adjacent to the stimulation site (cochlear implant, magnetic clip, deep brain or vagal stimulator)

2. Relative contraindications

A metal object not adjacent to the stimulation site (implant-type drug delivery pump, etc.), past epilepsy, an intracranial lesion, current administration of a drug that lowers the threshold for epileptic seizures, pregnancy, or serious somatic disorder

Young individuals aged less than 18 years and patients with clear dementia require caution.

The above are merely general precautions. The investigator must be responsible for implementing the procedures in each research study, and he/she (or the research group) must take responsibility for matters such as ethical review of the research protocol at each research implementation entity or facility and the acquisition of informed consent.

5) Explanatory documents for research participants

As a general rule, follow the contents stated in Section 7 of the current guidelines. In particular, with TMS, given the wide variety of purposes and testing methods, it is impossible to create a single template. It is therefore preferable that these documents be prepared by the investigator himself/herself according to his/her individual research.

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B-2. NBS using electricity

1/2) Overview and effectiveness

NBS methods using electricity are collectively called “transcranial electrical stimulation” (tES). For tES, direct current, alternating current, or random electric stimulation is used. When direct current is used, tES is called “transcranial direct current stimulation” (tDCS). It has been known that when using direct current to stimulate the brain, the firing frequency of neurons sometimes changes according to the polarity of the stimulation. In applying this principle non-invasively, a method that alters brain function by applying a weak direct electric stimulation from the scalp[1)] has been introduced since the latter half of the 1990s. This method has been used for neuroscientific research as well as for the treatment of neuropsychiatric disorders. Unlike TMS, this method does not stimulate the brain as a way to induce neural cell firing *per se* and is a relatively safe method that intends to change excitability of neural cells. There have been no reports of significant accidents as long as the electrodes are placed on the head. However, risks can occur when electric current is intentionally directed toward the heart using an inappropriate stimulation method. When tES uses alternating current, it is called “transcranial alternating current stimulation” (tACS). In this method, alternating current modifies cerebral cortex activity by inducing synchronization of rhythmic brain activities.[2)] Transcranial random noise stimulation (tRNS) is a method based on tACS and is implemented by randomly changing the frequency or strength of alternating current stimulation.[3)]

3) Problematic points (Risks involved in testing)

Existing reports from Europe and the United States concerning the risks involved with tDCS[4,5)] (including the phase I trial in the United States) indicate that there were no serious adverse events

with stimulation parameters up to 2 mA of electrical current and 20 minutes of duration. The 2016 report did not include any serious accidents or adverse reactions.[6] There have been no reports of convulsive seizures with tDCS, although convulsion of unknown cause was reported 4 hours after tDCS in a patient with a history of epilepsy.[7]

Adverse reactions experienced by research participants in response to tDCS include symptoms such as itching and headache during stimulation. However, these symptoms were also observed during sham stimulation and are therefore unlikely to be directly related to electrical stimulation.[8] With daily tDCS, minor skin injuries have been reported.[9] As high resistance in the skin is speculated to be a factor underlying skin injuries, electrode placement should achieve an even distribution of electric current, and the sponge needs to be wetted thoroughly.[8] It is desirable to use physiological saline to wet the sponge; tap water is not suitable.[8),9] Attention should be paid to sponge deterioration, as it may also cause skin injuries.[8] Evaluation of risks associated with tACS did not show serious adverse reactions up to the following stimulation parameters: 5000 Hz, 1 mA, and 10-minute duration (stimulation site, primary motor cortex).[10]

Previously reported adverse reactions to tACS include phosphenes with stimulation of the motor area[11] and dizziness with stimulation of the parietal region.[12] Increase in seizure frequency was also reported in tACS in patients with idiopathic generalized epilepsy and genetic epilepsy.[13]

Because tES transiently improves brain function or enhances the effects of training, depending on stimulation parameters, an expert stated the need to discuss ethical issues surrounding the possible use of tES as a method of neuroenhancement.[14] On the other hand, there has been low reproducibility of related research due to individual differences in efficacy.[15] The relationship between neuroenhancement and tES should be discussed further from both technical and ethical perspectives in the future.

4) Testing guidelines

Regarding tES, there exist both internationally acknowledged guidelines[8),15] and the recommendations of the Committee on Brain Stimulation Methods of the Japanese Society of Clinical Neurophysiology.[16),17] It is therefore desirable to use tES within the range specified in these guidelines and recommendations. However, stimulation parameters can vary, and tES has many aspects that are not fully established when viewed as a neuroenhancement method. Discussions on neuroethics are currently underway. Against this background, even research protocols using stimulation parameters that have not been reported are not uniformly prohibited at present, provided that approval is obtained from the ethical review committee of the relevant research implementing entity or facility. While tES is considered a minimally invasive stimulation method, it involves passing an electric current through the body. Considering this, each research protocol must be reviewed by the ethical review committee at each research implementing entity or facility and implemented without deviation from the approved procedures.

5) Explanatory documents for research subjects

In principle, Section 6 of the current guidelines should be followed.

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C. **Positron Emission Tomography (PET) / Single-Photon Emission Computed Tomography (SPECT)**

1) Summary

Both PET and SPECT are methods that administer a diagnostic agent labeled with a radioactive nuclide into the body and produce a tomographic image of its mode of aggregation. Their characteristic is that they allow various kinds of information on brain function, such as blood flow, metabolism, and neural transmission and function, to be derived from the distribution and behavior of the administered indicator agent within the brain. However, their use has limitations, as they require radioactive nuclides, and there are concerns about their management and radiation exposure for research subjects and the persons engaged in the research.

PET uses radioactive agents tagged with a positron-emitting radionuclide with an extremely short half-life, such as carbon-11 (half-life 20 min), oxygen-15 (half-life 2 min), nitrogen-13 (half-life 10 min), and fluorine-18 (half-life 110 min). It is characterized by its ability to qualitatively measure metabolism or function within an organism, which cannot be measured through other testing methods. Because using these nuclides with extremely short half-lives require setting up a small-scale cyclotron at the test site, PET entails significant expense and manpower for installation and operation. Recently, some products containing fluorine-18 synthesized at the factory and delivered to medical facilities, etc., are available for use.

By contrast, SPECT testing uses gamma-ray-emitting radionuclides with relatively long half-lives, such as technetium-99m (half-life 6 hrs) and iodine-123 (half-life 13 hrs). While the quality of qualitative SPECT measurements is inferior to that of PET, it has the advantage of using radioactive agents commonly used in clinical nuclear medicine tests. In addition, because it uses nuclides with longer half-lives than those used in PET, this method allows their dynamic states to be traced for extended periods and is useful for imaging synaptic receptors and transporters.

2) Effectiveness

Since PET and SPECT allow qualitative measurement of metabolism or function within an organism, they are useful for assessing the brain function of healthy individuals, ascertaining the clinical condition of individuals with various disorders, performing early diagnostics, and determining treatment effects. These methods are used in brain science research to measure blood circulation and metabolism in the brain, assess brain activation (as indicated by cerebral blood flow), and image neural transmission and function.

Because it is thought that changes in cerebral blood flow and glucose metabolism occur in parallel with localized neural activity, it is possible to measure changes in localized brain activity by monitoring changes in cerebral blood flow and metabolism. Brain activity testing, which is indicated by cerebral blood flow, compares cerebral blood flow during task completion with that during a control state to detect areas where cerebral blood flow changes. Assuming that the area with a

significant increase in blood flow plays some part in completing the given task, it is possible to identify the locations where changes in neural activity related to this task have occurred. As a method for measuring cerebral blood flow and metabolism during a test of brain activity, a system that uses oxygen-15-labeled water and PET has been employed frequently, as it allows repeated measurements and provides good spatial resolution. Even today, when tests of brain activation using MRI have become popular, PET/SPECT allows easy physical access to the research subject during testing, enabling various electrical measurements, the assessment of physiological states, and the comprehension of task achievement to be performed with precision. They also allow easy access to the deep structures of the brain and serve as standards for qualitative measurement of cerebral blood flow.

In addition, imaging of various functions associated with neurotransmission becomes possible by administering radioactive labeling agents that uniquely bind to specific receptors and by using PET or SPECT to trace the dynamic distribution within the brain. While mapping of receptors and transporters that exist at neural synapses is being widely practiced, other attempts are also being made, such as using agents to measure the percentage of areas occupied by the receptor, assessing enzyme reactions associated with the synthesis and resolution of specific neurotransmitters, and imaging information transmission functions inside neural cells.

For PET visualization of abnormal proteins that have accumulated in the brains of patients with neurodegenerative diseases, radiolabeled agents that bind to amyloid β-protein have been developed. This visualization is currently widely used for the diagnosis of Alzheimer's disease in clinical trials and research. Radiolabeled agents that bind to the tau protein have also been developed and are being evaluated. These agents will be used to diagnose and evaluate treatments of not only Alzheimer's disease, but also other neurodegenerative diseases associated with the accumulation of tau protein, including progressive supranuclear palsy and corticobasal degeneration.

3) Ethical problems (Risks involved in testing)

For tests using PET or SPECT, it is necessary to consider radiation exposure to research participants and to persons engaged in the research. As a fundamental principle for radiological protection, the International Commission on Radiological Protection (ICRP) issues recommended dose constraints for individuals. ICRP adopts a stance of justification: "Any activities that involve radiation exposure cannot be employed unless they yield benefits that sufficiently cancel out the radioactive damages that are incurred by exposed individuals or societies as a result of such activities."[1)] With radiation exposure, dose constraints are set for three types of exposure: public exposure, workplace exposure, and medical exposure. For persons in charge of the test, radiation exposure incurred during testing procedures is handled as workplace exposure. As tests are conducted as part of a medical practice, taking the patients' benefits into account, the radiation exposure incurred by patients falls under the category of medical exposure. By contrast, ICRP issues additional recommendations[2)] for healthy volunteers or patients who agree to participate in clinical research even though they do not receive any direct medical benefits. In our country, a regulatory body's stance on this issue is indicated only in the Ministry of Health, Labour and Welfare's guidance on "micro-dose clinical trial" which are carried out under the Pharmaceutical Affairs Act. ICRP recommendations, which define three tiers of benefit that research brings to society, allow

research subjects who do not directly receive benefits themselves to be exposed to 10 mSv of radiation in situations that yield the "substantial" benefit to society. MHLW does not indicate dose constraints and requires that effective dose on human should be estimated based on the results obtained from animal testing. Since research subjects undergo tests voluntarily, it may be thought that their radiation exposure should be subject to standards different from those for public radiation exposure. Yet taking into account that these research subjects do not receive direct benefits, considerations should be made: for the ethical review committee at each research implementing entity and facility to set the ceiling of radiation dose constraints; to establish a mechanism that prevents research subjects from participating in multiple studies at the same time or without appropriate intervals between tests; to draw up research plans that accommodate the scientific needs of individual research projects while minimizing radiation exposure; for the ethical review committee to make thorough assessments and to make arrangements at the planning and implementation stage to minimize radiation exposure to research subjects and persons engaged in the research. Safety issues related to radioactive agents used must be carefully reviewed at each facility. Depending on their type and amount, some agents require precautions as they might have pharmacological effects. Therefore, decisions regarding the composition, quality control, and administration of indicator agents should be made under the supervision of a doctor and a pharmacist with specialist knowledge.

Since the research subject is asked not to move his/her head during testing, long-duration measurements can cause discomfort or pain. Therefore, thorough attention should be paid to the research subject's condition, and the measurement duration should be minimized to keep the pain to an absolute minimum. In addition, when measuring functions qualitatively, it may be necessary to collect arterial blood to obtain the input function to the brain. While taking appropriate measures can lower the chances of developing complications occurring, these cases should be dealt with by a medical doctor who is experienced in appropriate well-versed in such techniques.

4) Testing guidelines

All procedures, from the composing of radioactive label agents to measurements using PET or SPECT, should be carried out in radiation-controlled areas. Since radiological protection laws apply to the setup of a small-scale cyclotron to produce positron-emitting nuclides and to the creation of a composite of radioactive agents for labeling, it is necessary to obtain approval from the Ministry of Education, Culture, Sports, Science and Technology.

For quality control of radioactive labeling agents used, each research implementing entity and facility must establish and follow its own standards, either by referring to the guidelines set by the Japanese Society for Nuclear Medicine or by the Cyclotron Nuclear Medicine Usage Special Committee under the Division of Medicine and Pharmacology at Japan Radioisotope Association.[2-4)] Current standards regulate the following aspects of the agents: manufacturing method, properties, confirmation (radioactive nuclides, labeling compound), purity (inclusion of foreign radioactive substances, foreign radioactive nuclides, or other materials), and full weight; and when necessary, their compatibility for thermogenic material testing, aseptic condition, pH, and specific activity.

For SPECT testing, when using agents that have been provided by pharmaceutical companies as radioactive medical products, each agent's usage standards should be followed. When using labeling

agents that have been developed uniquely at each research implementing entity or facility, they should be handled as other labeling agents made of positron nuclides.

When developing a research protocol, considerations should be made to ensure that radiation exposure to research subjects is kept to an essential minimum. The sensitivity and performance of the measuring device should be considered. For the ceiling of dose constraints for radiation exposure to research subjects, ICRP recommendations[1)] can be referred to, as well as Japanese regulations relating to radiological protection.[2-4)] Approval from the ethical review committee at each research institute and facility should then be secured. Selection procedures for research subjects should be reviewed, taking into account factors such as their health condition, current medical symptoms, age, gender, and capacity to provide consent. As a general rule, an individual becomes a research subject and may undergo the test when voluntary consent has been obtained from him or her. However, when consent, which is necessary to carry out the test, cannot be obtained from the research subject, consent can be gained from the subject's family or a representative who can give consent on behalf of the research subject. As a general rule, pregnant women are excluded as participants. All female participants should indicate whether or not they are pregnant. Although children are, in principle, excluded from testing, in cases where there is clinical merit, approval should be obtained from the ethical review committee at each research implementing entity and facility.

Before the test, the experiment's general procedure should be explained to the test participant in detail, including the risks involved, and informed consent should be obtained. In research subject to the Guidelines for Medical and Biological Research 2021, research involving PET or SPECT is classified as research involving "invasiveness." Research evaluating the effectiveness or safety of PET agents meets the definition of clinical trials in the Clinical Trials Act, while, in particular, research on unapproved PET agents or on the usage, effects, and performance of approved PET agents used outside the approved range meets the definition of "specified clinical trials" in the Act;[8] these clinical trials require review by certified review boards. In contrast, research whose intent is not to evaluate the effectiveness or safety of PET agents but rather to monitor the disease state based on PET drug accumulation does not meet the definition of a clinical trial under the Clinical Trials Act. In such cases, however, even the secondary endpoints are not assumed to include the evaluation of the safety or effectiveness of PET agents.

5) Explanatory documents for research participants

In principle, Section 6 of the current guidelines should be followed. The research subject should be provided with thorough explanations about the purpose, content, and method of the test, its possible side effects, and radiation exposure. The research subject's understanding of the protocol should be sought, and his/her informed consent obtained. For matters regarding radiation exposure, concrete descriptions should be provided by comparing them with tests that are more generally familiar.

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[8]Refer to the report of a case survey on the classification of nuclear medicine research into "specified clinical trials" (http://www.jsnm.org/archives/4744/).

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D. **Functional Magnetic Resonance Imaging (fMRI)**

1) Summary

Functional magnetic resonance imaging (fMRI) is a technique that uses MRI to estimate the localized brain activity by measuring changes in blood flow (cerebral blood flow) and oxygen metabolism in blood vessels. Two methods are primarily used: one that measures the relative concentration of deoxygenated hemoglobin in the blood (blood-oxygenation-level-dependent (BOLD) method), and the other that directly measures blood flow.

2) Effectiveness

With fMRI, the spatial distribution of the BOLD signal, or blood flow, as a surrogate marker of neural activity, can be measured with high spatial resolution. Compared with PET, fMRI offers advantages, including the ability to repeat measurements on the same participant, yielding high spatial and temporal resolution. However, it has disadvantages, such as a tendency to produce artifacts due to subject movement and reduced signal and image distortion around the ear and nasal cavities. The research participants must remain still in a magnetic field during measurement. Compared with MEG or EEG, fMRI has a high spatial resolution but a lower temporal resolution.

3) Ethical problems (Risks involved in testing)

The ethical problems of fMRI measurement are basically the same as those of MRI measurement in general. Here, these points are classified into three categories: 1. Effects on the health of the research subjects, 2. Risks of accidents specific to MRI-environment, and 3. Others. 1 and 2 are based on the 2017 version of the Japanese Industrial Standard (JIS) specification (JIS Z4951), translated and supplemented from the 2015 version of the International Electrotechnical Commission (IEC) standard (IEC 60601-33-2, Amd2).

1. Effects of MRI measurements on the health of research subjects.

IEC/JIS standard focus on three aspects. The “operating mode”, which is important to ensure safety, is defined by following limits [details are given in Section 1 under 4) Testing guidelines].

i) Strength of the magnetic field

Moving the head in a static magnetic field can cause dizziness, nausea, and taste disturbance. As the static magnetic field strength increases, more people experience these symptoms. In addition, although various studies have been conducted on the adverse biological effects of high static magnetic field strength, however IEC/JIS specifications have concluded that these effects lack foundation for fields of up to 8 T.

ii) Temporal changes in gradient field strength (dB/dt)

As the magnetic field gradient increases over time, peripheral nerves are stimulated by the electric current accompanying the change in the field, sometimes causing an unpleasant twitching sensation. A greater temporal variation in magnetic field strength may directly stimulate the myocardium.

iii) Radio Frequency (RF) heating

High-frequency RF pulses, which excite and invert spins, can provide heat to tissues and have the potential to cause adverse changes in body temperature or burn injuries. The degree of heat absorption by tissue is measured as specific absorption rate (SAR) and constrained by the device's limitations.

2. Risks of accidents specific to MRI-environment

There is an accident risk, particularly in the MRI environment, induced by the carelessness of experimenters and research subjects, or by natural disasters.

i) Propulsion of magnetic substances caused by a strong magnetic field

Research or medical equipment containing magnetic materials is attracted to a strong magnetic field and collides with research subjects and experimenters, causing physical injury. Fatal accidents have also been reported. In the event of an emergency, rescue personnel and firefighters may enter the scanner room, potentially causing a secondary accident due to magnetic material.

ii) Effects of the magnetic field on medical devices implanted in the body of the research subject

In the case of medical devices containing magnetic components or electronic circuits embedded in the body or on the surface of research subjects, the magnetic field may cause physical tissue damage or malfunction of the electronic circuits. Typical implanted magnetic components are artificial heart valves, stents for blood vessels, artificial joints, and cardiac pacemakers. Even when away from the MRI scanner, there may be adverse effects from magnetic field leakage.

iii) Heating caused by RF energy generated by lead wire, body loop, and magnetic substances inside the body or on the surface of the body

When the wires of the experiment/measurement equipment form a loop on the body surface, if the body of the research subjects forms a loop due to contact with a body part, if the RF coil itself is in close proximity to the body, if there is a magnetic substance (Bullets and pieces of iron) buried in the body, or if there is a magnetic substance (Tattoos, cosmetics, ornaments, chemical patches, contact lenses containing metal, etc.) on the body surface, unexpected heat generation may cause burns on the body and the body surface of the research subjects.

iv) Sounds generated during imaging

The sound of an MRI scan, particularly that of an fMRI scan, is so loud that it can cause hearing impairment in research subjects or experimenters.

v) Quenching

Generally, superconducting magnets that generate the strong static magnetic field in MRI systems

are cooled with liquid helium. In rare cases, liquid helium vaporizes for some reason, causing rapid volume expansion (an explosion) known as quenching. Double safety devices usually operate, but if they fail, it could lead to frostbite and asphyxiation of the research subjects and experimenters due to helium gas leaks.

vi) Claustrophobia

The space inside the MRI scanner (the bore), where the research subject is placed, is very narrow, and the lights are often dimmed during experiments. These conditions might trigger panic when the research subject has claustrophobia or nyctophobia.

vii) Oversight of abnormal conditions inside the scanner

After starting MRI scan, only the research subjects may notice various abnormal situations including those stated above. However, in general, it is not easy to observe the research subject from the operating room, and even if the subject speaks, the sound is drowned out by the imaging sound and cannot be heard, so the experimenter may not notice the subject's body or voice. To prevent such a situation, a buzzer that emits an alarm and notifies of abnormalities is provided to each research subject. Proper functioning of each buzzer should be confirmed in advance.

3. Others

i) Incidental findings

Tumors or other pathologic findings may rarely be detected on MRI images obtained for experimental purposes. In principle, diagnosis is not part of the basic research conducting fMRI experiment. However, it is a humanitarian problem to neglect these incidental findings and to give up the opportunity to treat or save the research subjects, and there is a possibility of being held liable in a lawsuit. On the other hand, if these incidental findings are reported to the research subjects and the examination results are normal, there is a possibility that the experimenters will face the risk of lawsuits from research subjects for unnecessary mental harm.

ii) Others

Because prolonged restriction is considered as invasiveness, a limitation should be imposed on the duration of imaging. In addition, tasks used in fMRI research might require close examination for the potential invasiveness due to trauma imposed on research subjects. When the static magnetic field is strong, many research subjects experience dizziness, nausea, and dysgeusia during head movements. If the experimenters' explanation of the experiment and the relationship of trust with the research subjects are insufficient, rumors about health risks from MRI might develop, leading to unwanted prejudice in society against the entire field of fMRI research. Therefore, providing a thorough prior explanation of the procedure to each research subject and obtaining informed consent is of key importance.

4) Testing guidelines

Before the test, the experiment’s general procedure should be explained to the test participant in detail, including the risks involved, and informed consent should be obtained. In research subject to the Guidelines for Medical and Biological Research 2021, research involving MRI is classified as research involving “minor invasiveness.”

Explanations of these guidelines are given in five categories: 1. MRI equipment and operating mode, 2. Safety management and consideration at the research site, 3. Manuals and training for handling an

emergency situation, 4. Prior screening of research subjects and experimenters, 5. Other. 1 to 4 is based on the IEC/JIS standard, and it is recommended that the experimenters read the latest IEC/JIS standard.

1. MRI equipment and operating mode

In the IEC/JIS standard, three operating modes are defined based on the risk to research subjects during MRI measurements. Each MRI operation mode has different restrictions across three parameters: the strength of the static magnetic field, the time variation of the gradient field strength, and RF heating (SAR). Each mode also has different safety measures that should be in place (such as the need for a medical doctor to monitor and contents that require approval from the ethical review committee).

i) Normal operating mode

This is the safest mode of operation. The strength of the static magnetic field is restricted to 3T or lower. Based on the currently known physiological mechanisms and numerous research findings, the three MRI parameters mentioned above are set and limited to values considered incapable of causing physiological stress on the research subjects. MRI scanners configured for this operation mode do not allow imaging parameters to be set above these limits. However, even at a static magnetic field strength of 3T or lower, some people experience dizziness or nausea from head movement.

ii) First level controlled operating mode

This mode recommends that the operation to be monitored by a medical doctor. The static magnetic field strength is up to 8 T, and the time variation of the gradient field strength and the SAR limit are higher. A static magnetic field strength of 8 T or less is thought to have only minor biological effects, but as the field strength increases the number of people who experience dizziness, nausea, or dysgeusia due to head movement increases. There is the possibility of peripheral nerve stimulation when the time variation of the gradient magnetic field strength is sufficiently intense even within the limit value. For the latter, medical doctors' monitoring of the effects of RF heating is essential for research subjects with reduced thermoregulatory ability (E.g., Patients with febrile diseases, heart disease, dyshidrosis, etc.). In MRI systems set to this operation mode, it is not allowed to set imaging parameters exceeding these limits, and, further, the time variation of the gradient magnetic field intensity and the SAR value can be displayed on the operation console.

iii) Second level controlled operating mode

This mode requires approval by the ethics committee of each facility in accordance with domestic laws and regulations, and is used only for research. This operating mode is entered when the value of any of the three elements exceeds the first level controlled operating mode. There are potential biological effects of static magnetic field strength, myocardial stimulation associated with temporal changes in gradient field strength, and adverse temperature changes and burns associated with RF heating.

It is necessary for the persons conducting experiments to clarify which of the three operating modes will be used. In general, it is used under the first level controlled operating mode. The operating mode should also be included in research applications submitted for ethical review. The IEC/JIS standard requires MRI manufacturers to implement safety settings on MRI scanners to prevent accidental entry into the upper operating mode, which allows greater temporal changes in gradient field strength and SAR.

The static magnetic field strength limit values for the normal and first-level controlled operating modes described above are based on the IEC Standard 2015 (JIS Standard 2017) and may be changed in future revisions. The experimenters should refer to the latest IEC/JIS standard.

2. Safety management and considerations at the research site

MRI scanner sites require the following:

i) Restricted areas

Areas with a static magnetic field strength of 0.5 mT or more should be clearly separated from surrounding areas (e.g., by marking, etc.) as off-limits areas. And markings or other measures should be used to prevent the inadvertent introduction of magnetic materials or the entry of persons implanted with magnetic medical devices or cardiac pacemakers. Although there is no clear evidence for the effects of static magnetic fields on the fetus, it is recommended that pregnant women refrain from unnecessary exposure.

Even experimenters and research subjects who fully understand the prohibition of bringing in magnetic materials that may be adsorbed by a static magnetic field, or electronic equipment (clocks, mobile phones, magnetic cards, etc.) that may be broken, who habitually conducting scans, may enter the restricted area wearing watches or accessories, or with keys, coins, mobile phones, wallets, etc. in their pockets. Persons conducting the scan must systematically check themselves and their pockets on each occasion before entering the magnet room and restricted areas; they must also visually inspect the research subjects and use checklists or metal detectors each time.

ii) Avoiding accidents occurring to research subjects during testing

In order to avoid burn injuries from RF heating, it is necessary for the experimenters to check every time before measurement whether or not there is any magnetic materials (cosmetics, hair dyes, contact lenses, ornaments, clothing containing metals) on the body surface of the research subjects using a visual check list or a metal detector. Also, when the research subjects has been placed inside the scanner for measurement, make sure that the lead wire or the research subject's body should not in any arrangement form a loop, and that the RF coil itself should not close to the body.

To prevent hearing impairment from scanner noise, research subjects must wear earplugs during measurements. In these cases, the experimenters check whether the reduction of the scanner noise is sufficient. In addition, measures such as a checklist should be taken so that research subjects do not forget to wear earplugs or headphones.

A means of communication between operators and research subjects should be established so that research subjects can request that procedures be stopped at any time if they feel any abnormality or discomfort during measurements. A system generating a loud alarm sound (buzzer) in an operation room when a research subject squeezes a valve in his/her hand is commonly used.

In addition, it is necessary to constantly monitor the state of the research subjects through a window or a video monitor during measurement, and to communicate with the research subjects frequently between measurements, and to enter the imaging room and confirm their condition as necessary.

3. Manuals and training for handling an emergency situation

The person responsible for the MRI facility must meet with the MRI manufacturer and relevant departments (Hospitals, fire stations, etc.) as necessary to prepare a manual for the following emergency response: The experimenters must be familiar with this procedure and trained if

necessary. The experimenters must verify the following emergency response with the facility's safety manager and be prepared to actually perform it.

i) Emergency medical procedure

When an accident resulting in injury or a feeling of unwellness occur during an experiment, scan should be aborted immediately, and the research subjects or the experimenters should be quickly removed from the scanner room, transported to the hospital or called an ambulance. If possible, it is desirable to establish a system that enables first-aid treatment and primary life support in the event of cardiopulmonary arrest. In addition, it is desirable to obtain approval from specific hospitals to accept patients for ambulance transport.

ii) Emergency shutdown of magnetic field

When a research subject or experimenter is caught between a scanner and a magnetic object and cannot escape, or when an emergency crew or a fire fighter is expected to enter the scanner room due to a disaster, etc., it is necessary to urgently shut down the static magnetic field of the MRI. The experimenters should be familiar with this operation.

iii) Measures against fire or earthquake

Preparation should be made to take the immediate steps necessary in the event of a fire or an earthquake.

iv) Measures against quenching

In the event of a quench or a malfunction of the safety device, the experimenters should recognize these events by visual observation of white smoke or a decrease in oxygen concentration measured with an oxygen concentration meter, and take the necessary measures.

4. Prior screening of research subjects and experimenters

The person responsible for the safety of the MRI facility and experiments needs to establish a screening system that requires operators and potential research subjects who are at risk from MRI measurements to be entered into restricted areas, as stated below.

i) The following persons are prohibited from conducting or undergoing MRI examination (i.e. they are prohibited from entering restricted areas).

- Persons who have medical devices (Artificial heart valves, artificial joints, vascular stents, cardiac pacemakers, etc.) containing magnetic components or electronic circuits implanted in the body or its surface.

ii) The following persons cannot be research subjects unless there are particularly reasonable grounds.

- Persons who is buried magnetic substance that cannot be removed in the body (Bullets and pieces of iron) or the body surface (tattoos, etc.)
- Pregnant women

iii) It is recommended that the following persons not be included in the research subjects unless there are particularly reasonable reasons. When these persons are made to be a research subjects, it is necessary to carry out the experiment under the supervision of the medical doctor.

- Persons who may experience an attack due to a medical disorder (e.g. ischemic heart disease or epilepsy) during measurement.
- Persons with claustrophobia or nyctophobia.
- Persons who have difficulty in securing a means of communication during MRI measurements.

• Persons with an impaired thermoregulation (Patients with febrile diseases, heart diseases, dyshidrosis, etc.).

iv) It is recommended that the following persons avoid entering restricted areas.

• Pregnant women

5. Others

i) Preparing for incidental findings

When explaining the experiment to research subjects, it should be made clear that the MRI scan is solely for investigational purposes and that this brain imaging cannot achieve the diagnostic precision required. In addition, it is desirable to have the applicant indicate in writing whether or not he/she wishes to be informed of any incidental findings when he/she agrees to participate in the experiment. On that occasion, the investigator needs to explain to the applicant that a life-threatening finding might be notified upon identification, even without his/her prior wish for disclosure of any incidental findings and then obtain his/her consent. The principal investigator should be responsible for disclosing the medical notification. He/she should decide in advance about procedures for handling incidental findings and about methods of notification, and ensure that all members of the research team are fully informed. If the findings warrant close examination, the basic response is to recommend that the research subject consult a medical professional. There are many cases in which it is difficult to decide whether it is actually an abnormal finding (and whether or not to notify the research subjects), and it is desirable to consult an expert who specializes in diagnosis of brain imaging.

While the concepts described above are applied as general rules, there are different opinions. For example, the potential return of incidental findings raises ethical dilemmas: it might bias consent to research participation and render research participation inappropriate. Furthermore, regarding the establishment of a system for addressing and notifying incidental findings upon identification, the decision-making process within a research team may vary depending on whether any physician is on the team. Please refer to “Ethical Guides on Incidental Findings: Countermeasures in Brain Science Research” for details.

5) Explanatory documents for research participants

As a general rule, follow the contents indicated in Section 6 of current guidelines.

Supplement: For the establishment of MRI safety management systems at facilities, refer to the following guideline:

Guidelines for MRI in human subjects for basic research 2018 (Joint Working Group for Examination of Guidelines for MR Imaging Related to Basic Research of the Japan Neuroscience Society and Japanese Society for Magnetic Resonance in Medicine).

http://www.jsmrm.jp/modules/other/index.php?content_id=1

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3. Ethical Guides on Incidental Findings: Countermeasures in Brain Science Research https://neuro-elsi.jp/download/wpdmpro-280/
<Acknowledgement>These guidelines were created with the help of Toshiharu Nakai.

E. **Near infrared spectroscopy**

1) Summary

Near-infrared spectroscopy uses near infrared which has a high permeability for living organisms. It was developed so that changes in hemoglobin concentration and blood flow, triggered by activity in the cerebral cortex, could be mapped on the brain's surface. For measurement, two wavelengths of near infrared (around 800 nm wavelength) are exposed to the surface of the head, and the scattered light emitted from inside the brain is then examined from a point that is a few centimeters away. Exposed light is absorbed by the blood in the living organism; the main absorbing component is hemoglobin in red blood cells. There are two types of hemoglobin: oxygenated hemoglobin and deoxygenated hemoglobin. Since each has a different absorption spectrum, changes in concentration of each type of hemoglobin as well as in blood flow can be measured using a method of spectral measurement that calibrates two wavelengths. For this procedure, the research subject wears a cap consisting of numerous optical fibers.

In near-infrared spectroscopy, the average value of localized neural activity is estimated by measuring the concentrations of oxygenated and deoxygenated hemoglobin in the blood, which reflect changes in blood flow and oxygen metabolism triggered by neural activity. Near infrared spectroscopy thus works by a similar principle to fMRI, yet each uses a different method for image reconstruction. MRI is based on three-dimensional image reconstruction using nuclear magnetic resonance of protons in living organisms, enabling the delineation of anatomical structures. fMRI utilizes the difference in magnetic property between oxygenated hemoglobin and deoxygenated hemoglobin. Change in brain activity causes localized changes in deoxygenated hemoglobin concentration which in turn fluctuate the MRI signal. By combining these time-oriented fluctuating signals with an anatomical structure, regional task-related activation can be elucidated. By contrast, unlike MRI, it is difficult to achieve image reconstruction with near infrared spectroscopy. This is because the light-scattering properties of a living organism are uneven. Therefore, near infrared spectroscopy gathers averaged signals that are generated in areas of a few centimeters in diameter which are formed between optical fibers that emit light and optical fibers that receive light. The most common method of image reconstruction is called the Back Projection method, which generates an image by interpolating the average value of each area. Yet in the past few years, another method has been proposed that statistically analyzes signals in each area and maps them onto a brain surface image. This image may be obtained by conducting an additional MRI scan or by employing a method that estimates parts of a standard brain from the location of the scalp. In particular, the latter method is often employed when testing infants and children. The spatial resolution of the image obtained is a few centimeters.

2) Effectiveness

Compared to MEG or fMRI, the greatest advantages of near-infrared spectroscopy include its less

restrictive experimental requirements and the lack of safety issues associated with the equipment. This method is considered lower risk because it does not require isolating the research subject in a sealed room or in a magnet, and it does not use substances such as liquid helium. Within the field of brain science, near infrared spectroscopy is characterized by the fact that it produces less noise than fMRI and that it enables natural brain function to be measured within an everyday environment. These characteristics enable measurement of brain function across a wide range of people, from infants to the elderly. Compared to EEG, near infrared spectroscopy has the advantage that it does not require paste or gel for impedance matching, and that in principle, it is easy to estimate the active parts in the cerebral cortex.

3) Ethical problems (Risks involved in testing)

Risks involved in using low-power lasers

Equipment has been approved by the Pharmaceutical and Medical Device Act as a general method of clinical testing, and there are no known safety issues. Near infrared spectroscopy equipment manufactured by Hitachi comprises of a class 1M low-laser product as specified in C-6802 under JIS specifications (equivalent to class 1M as specified in IEC60825-1 Edition 1.2). When the research facility in question has regulations on allowable laser exposure, equipment should be used in accordance with them. Notably, low-power lasers do not cause damage to skin or brain tissues. Some equipment, such as Hitachi's ETG series, have been approved for medical use as defined by the Pharmaceutical and Medical Device Act. In addition to public regulations, studies concerning the safety of near infrared spectroscopy have reported an estimated internal temperature by measuring the temperature inside a living organism and by simulating light diffusion.[1,2)]

Pain experienced by the research subject at the time of actual measurement

In addition to the "pain" caused by wearing a headgear with multiple fiber poles that connect to the optical fibers, the research subject needs to make an effort not to move his/her head as much as possible during testing, because recordings fluctuate if the pole is shifted from its original location. Remaining still can cause discomfort or pain when the test lasts for long periods.

4) Testing guidelines

1. Before the test, the experiment's general procedure should be explained to the test participant in detail, including the risks involved, and informed consent should be obtained. In research subject to the Guidelines for Medical and Biological Research 2021, involvement of NIRS per se is not considered invasive, but the level of invasiveness must be evaluated depending on the duration of restriction and the content of tasks given.
2. When the test involves patients, corresponding MEG guidelines should be adhered to.
3. Precautions during testing: While the length of the test is to be determined by the person in charge of the test or by the doctor in charge, as a general rule, each testing session should be limited to 15 minutes or less, and breaks should be offered to the research subject accordingly. During breaks, clinicians, experimenters and support staff should talk to the research subject, ask if there are any problems, and attend to those problems.
4. As a general rule, the entire testing session should be limited to an hour or less.

5) Explanatory documents for research subjects

As a general rule, follow the contents indicated in Section 6 of the current guidelines. Below, we provide examples of information that can be provided specifically for near-infrared spectroscopy and used in explanatory documents.

1. What is near-infrared spectroscopy?

Near infrared spectroscopy uses light from the near infrared part of the electromagnetic spectrum to record the changes in blood flow, volume, and oxygenation. Since blood provides nutrients and oxygen to the brain, this method can objectively determine when different areas of the brain are activated.

2. What are the reasons for using near-infrared spectroscopy?

By measuring and observing brain activity with the use of near infrared spectroscopy, brain function can be imaged. Although there are other methods of observing brain function, such as fMRI, MEG, EEG, and PET, near-infrared spectroscopy allows natural measurements to be taken in everyday environments and enables many studies that cannot be conducted with other methods. While methods exist to estimate brain function through subjective reports and behavioral performance in different tasks, these methods do not observe the brain directly and, therefore, do not provide strong scientific evidence for localization of brain function.

3. Are there any risks involved with near-infrared spectroscopy?

There is no danger involved. There is no need for the injection of any substances. We only ask that you do your best not to move, so that accurate test results can be obtained.

4. Types of near-infrared spectroscopy

Depending on the type of brain function examined in the test, the testing protocol may involve tasks with stimuli and/or participant responses. Sounds would be provided through earphones or speakers for experiments, including auditory stimuli; light, letters, or moving images for visual tasks; and a weak electric stimulation may be applied to the wrist or ankle for somatosensory (tactile) tasks. There is no need for concern since there are no safety issues associated with these tasks. (In explanatory documents for patients, add the sentence: “A doctor, technician, or nurse will be present at all times during the test.”)

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<Acknowledgement>Guidelines were created with the cooperation of Maki Atsushi (Hitachi Advanced Research Laboratory, Hitachi, Inc.)

F. **Neuropsychological studies**

It can be expected that, in the future, methods used in neuropsychological studies will be combined with non-invasive measurement methods, such as fMRI, PET, MEG, EEG, TMS, and near-infrared

spectroscopy, to research higher-order functions of the cerebrum. In anticipation of this, it is necessary to carefully consider the ethical aspects of neuropsychological research methods.

1) Summary

Neuropsychological studies have been conducted for some time. Their objective is to investigate patients who have spontaneously developed organic or functional disorders of the brain, such as diseases or injuries, by investigating their cognitive processing using questionnaires or by observing their reactions to various tasks. In addition to verbal and behavioral data, data of brain measurements and physiological indices are collected.

2) Effectiveness

Neuropsychological studies can effectively explore the internal processes (i.e. cognitive processing) of patients or research subjects with disorders, which enables inference regarding normal cognitive processing. However, impaired sites and functions cannot be controlled, and therefore variation among research subjects tends to be significant.

3) Ethical problems (Risks involved in testing)

Neuropsychological tests are associated with the risk of placing psychological stress on research subjects. Sufficient attention needs to be paid to this point.

4) Testing guidelines

In research subject to the Guidelines for Medical and Biological Research 2021, neuropsychological tests per se are not considered invasive, but the level of invasiveness must be evaluated in cases involving questions related to a subject’s mental trauma.

1. Because neuropsychological tests assess overt or latent disorders of cognitive function, they may reveal previously unidentified conditions in research subjects. This may damage their self-esteem and result in unnecessary stress. When the tests are included as part of treatment, it is crucial to perform them in a supportive environment. If the results are to be published in case reports, patient consent needs to be obtained. For tests conducted for investigational purposes, the importance and necessity of assessment and recording must be clearly explained using the explanatory documents approved by the facility's ethical review committee, and written consent from the research subjects must be obtained before the tests are performed. If the research subjects do not want to undergo a test, the test should not be performed; if it has already begun, it should be aborted immediately. Also, consideration must always be given to formulating the diagnosis and providing testing in a manner that benefits the research subjects. Given that research subjects are not healthy volunteers but patients, collecting more data than necessary must be avoided.

2. In neuropsychological studies, cognitive data of healthy participants are also often collected for comparison. In such cases, before data collection, it is necessary to provide a sufficient explanation of the importance and necessity of assessment and recording using the explanatory documents reviewed by the ethical review committee of the facility concerned, and to acquire participants’ written consent.

5) Explanatory documents for research participants
As a general rule, follow the contents indicated in Section 6 of current guidelines, except for the tests performed as a part of treatment.
<Acknowledgement>Guidelines were created with the cooperation of Masami Yamaguchi (Chuo University) and Akira Midorikawa (Chuo University).

G. **Brain Machine Interface (BMI) and neurofeedback**

1) Summary
A Brain Machine Interface (BMI) is a neural engineering technology that digitally connects the brain and a device outside the body to enable communication between them by measuring brain activity using a specific method and discriminating (decoding) motion intention or other information through computer analysis. In other words, the BMI allows direct information exchange between the brain and the external environment, bypassing the body. BMIs are classified according to the technique by which brain information is recorded: non-invasive BMI, which involves the collection of brain information by remote-sensing methods such as scalp electroencephalography and fMRI; and invasive BMI, which employs chronic recording probes surgically placed on the cerebrospinal surface, in the cerebrospinal tissue, or intravascularly for the collection of brain information. While a non-invasive BMI is sometimes called a Brain Computer Interface (BCI), there is no clear boundary between BCI and BMI. When research ethics in BMI research is concerned, it is desirable to follow each section of the present guidelines according to the method used to measure brain activity. Moreover, unique ethical issues have been acknowledged among investigators even regarding only non-invasive BMIs, and have mostly arisen due to the development of new technologies for decoding or modifying brain information

2) Effectiveness
From an informational perspective, the effectiveness of BMIs that directly and digitally connect brain and machines is roughly classified according to whether the BMI is used as a neural prosthesis or for neural modulation. A neural prosthesis is an BMI technology used for substituting functions of the sensory and/or motor systems lost by injury or other cause. A typical example of a neural prosthesis is a motor system prosthesis, such as a robotic prosthesis driven by brain-derived information. On the other hand, neural modulation by a BMI involves intervention in the activity of central nervous system by using brain activities as clues for the purpose of inhibiting abnormal neural activities or stimulating functionally impaired neural or compensatory circuits to enhance neurological function. A BMI-based technique to facilitate rehabilitation and closed-loop deep brain stimulation (DBS) to adjust trigger of DBS used for the treatment of Parkinson’s disease on the basis of neural activities may be regarded as examples of neural modulation by a BMI. Neurofeedback is an experiment system in which a signal that reflects a certain neural process is measured and decoded by real-time fMRI or other methods; this signal is then presented to a research subject who manipulates this signal by changing the state of his/her own brain. Neurofeedback is another example of neural modulation by BMI technology.

3) Ethical problems (Risks involved in testing)

At this point, safety risks associated with BMIs are speculated to be roughly equivalent to those associated with the measurement methods mainly involved. However, ethical problems unique to the principles of BMIs have begun to be pointed out. It would be extremely convenient if information could be easily exchanged between the brain and the outer environment by BMI technologies in the future. However, without efforts of risk management and communication in pace with technological advancement, excessive expectations or misconceptions regarding the application of BMI technologies may spread in society faster than our understanding of these technologies. BMIs are currently considered to still be in an investigative stage, and what we need is a calm understanding of the current situation: that direct exchange of information between the brain and the outer environment is possible but extremely limited. On the other hand, clinical research and clinical trials using DBS and BMI are ongoing worldwide, and AI supporting BMI technology is advancing rapidly. Consequently, a serious discussion of ethical problems in securing the privacy and autonomy of individuals in decision-making has begun.[1)] Active discussion based on a systematic review from ethical aspects[2)] is ongoing. Ethical issues to be considered in conducting BMI research include: (1) short- and long-term safety of research subjects; (2) humanity; (3) autonomy; (4) bias (stigma); (5) privacy/information security; (6) research consent; (7) responsibility and regulation; (8) justice; and (9) ability enhancement. Discussion of ethics, specifically concerning neurofeedback, is ongoing in consideration of the potential societal impact of treatment of psychiatric disorders[3)] and neuroenhancement.[4)]

4) Testing guidelines

The guidelines for each measurement method should be followed. Research on BMI/neurofeedback in human subjects for the purpose of developing treatment methods of psychiatric and neurological disorders largely differs from research on treatment methods involving application of energy from outside the body, such as in DBS to be described below. Nevertheless, all types of research should follow related guidelines, rules, and regulations, including the Guidelines for Medical and Biological Research 2021 and Clinical Trials Act. In research subject to the Guidelines for Medical and Biological Research 2021, the level of invasiveness must be evaluated based on the measurement method used, the duration of the restriction, and the content of the tasks assigned. In cases of other basic research on BMIs, the following points should be explained to research subjects and their informed consent should be obtained before the test.(1) the range of investigational use of measured signals, (2) the information security of measured signals and their analysis results, (3) the possible extent and duration of the effects of BMIs and neurofeedback on brain functions, and (4) device safety mechanisms in cases of control of external devices by BMI. If explaining these points is difficult because the investigator does not want research subjects to have preconceptions about the study, debriefing after the research is recommended. Invasive BMI research involving human subjects is a “specified clinical trial.” Even though being non-invasive, BMI research in nature, intervention research related to the development of medical devices may be handled as a “specified clinical trial.”

5) Explanatory documents for research participants

In principle, Section 6 of the current guidelines should be followed. Explanatory documents to be used in BMI research for the purpose of developing medical devices should conform to the requirements for those used in a “specified clinical trial.”

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H. **Research involving human genomes or gene analysis**

Genome analysis or genetic analysis is a method that identifies genetic factors (genome sequences) associated with a disorder or physiological trait. This method is currently established as extremely powerful through the development of various DNA markers, the deciphering of the human genome reference sequence in the Human Genome Project, and the HapMap Project. Moreover, it became technically possible to routinely decode an individual’s whole genome sequence. This method can be applied to investigate not only the deciphering of genetic causes and molecular mechanisms of disorders but also the genetic or molecular basis, of various physiological traits. Studies that combine this method with physiological analysis or imaging have been conducted frequently, contributing to deciphering of the brain nervous system.

Typical methods of genome or genetic analysis include linkage analysis of family specimens and association analysis, which compares a group with disorders or specific features against a control group without such disorders or features. While there are various DNA markers, a system of analysis is currently being established that uses a DNA chip equipped with single-nucleotide polymorphism (SNP) markers, which cover the entire genome. This makes it relatively easy to perform a genomic or genetic analysis from a technical standpoint.

In practice, studies that include analysis of the human genome or genetic analysis must be planned in accordance with the relevant guidelines and laws established by related ministries and agencies, including the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. The research plans must be reviewed and approved by the ethical review committee established at each research implementing entity.

I**. Deep brain stimulation (DBS)**

1) Summary

Deep brain stimulation (DBS) is a therapeutic technique that improves symptoms in neurological and psychiatric disorders by stereotactically inserting electrodes into deep brain structures such as the thalamus and basal ganglia and applying electrical stimulation to the target sites with an implanted nerve stimulator. Destruction of deep brain tissue had long been known to improve tremor and Parkinson's symptoms. However, before the practical application of MRI, determination of the loci to be destroyed was guided by plain radiography, cerebral ventriculography, and pneumoencephalography, and the precision of such imaging techniques was not always satisfactory. Around 1990, Benabid and colleagues at Grenoble, France reported the effectiveness of DBS in patients with Parkinson's disease and tremor [1,2]. Being covered by the National Health Insurance in Japan in 2000 and thereafter, DBS currently plays an important role in the treatment of conditions such as Parkinson's disease, dystonia and essential tremor.

No definite answer has been given to the question what impacts electrical stimulation by DBS has on the target nuclei and nerve fibers. However, DBS is generally considered to inhibit neural activity due to its effects similar to those of lesional procedures. In addition, the fact overactive nuclei are selected as targets for placement of stimulation electrodes supports the interpretation described above. On the other hand, some discuss the possibility that DBS stimulates inhibitory nerves to reduce overall neural activity. Also, a theory that DBS dissociates the inputs to neurons and outputs from neurons to inhibit abnormal nerve signal transmission [3].

2. Effectiveness (surgical indication)

Surgical indication for and effects of DBS are described in detail in "Treatment Guidelines for Stereotactic and functional Neurosurgery Fourth Edition" [4].

The treatment for Parkinson's disease, essential tremor, and dystonia starts with drug therapy. In some cases of essential tremor and dystonia refractory to drug therapy, DBS or a lesional procedure is considered. The site of electrode placement for essential tremor is the thalamic ventral intermediate (Vim) nucleus or posterior subthalamic area (PSA), while that for systemic dystonia with severe symptoms in the truck is the internal segment of the globus pallidus (GPi). In local dystonia such as writer's cramp, the thalamic ventro-oral (Vo) nucleus is selected as target. In these conditions, improvement of motor symptoms by DBS is expected. In Parkinson's disease, DBS is considered in cases with development of wearing off or prolongation of off time although drug therapy is effective or cases with dyskinesia as an adverse reaction of drug therapy. In such cases of Parkinson's disease, either the subthalamic nucleus (STN) or GPi is selected as target. Improvement of motor symptoms by DBS is expected also in Parkinson's disease, although with minor effects on non-motor symptoms. Since the end of 2023, DBS targeting bilateral anterior thalamic nuclei has been covered by the National Health Insurance for refractory focal epilepsy with difficulties in radical operations including focal resection.

First of all, the greatest feature of DBS lies in its capability of modulating stimuli from outside the body. In other words, this technique allows modulation of the stimulated area by modulating the stimulus intensity. Recently, a new stimulation electrode called "directional lead" has been made available. This stimulation electrode adopts an electrode configuration involving radially oriented 3 segments, in contrast to the conventional ring-shaped design. Separately controlled use of individual electrode segments realizes directional electrical stimulation, which is expected to enhance

therapeutic effects and reduce adverse reactions caused by stimulation. Besides new electrodes, software products visualizing the spatial relationship of the stimulated area to nuclei and nerve fibers are developed.

3) Ethical problems (Risks involved in testing)

The greatest adverse reactions of DBS are requirement of surgery to implant electrode(s) and a stimulator and almost permanent implantation of these devices in the body. Surgery for DBS generally involves installation of a stereotactic apparatus and subsequent placement of electrode(s) according to the route and site of placement as planned on preoperative MRI images. In addition, depending on each case, improvement of symptoms due to intraoperative stimulation is checked and the brain potential is measured with microelectrodes to confirm proper placement of the stimulation electrode. Thereafter, a stimulator is placed under the precordial skin. The first risk associated with DBS is intracranial hemorrhage related to electrode placement. Hemorrhage along the electrode and subdural/epidural hemorrhage as well as hemorrhage due to venous injuries are reported, while hemorrhage remains asymptomatic in many cases. Another risk associated with DBS is device-related infection. While this complication occurs during the perioperative period most frequently, it may occur even after a substantial time has passed. Removal of the device is required in most cases. Events requiring device repair due to defects, disconnections, and other causes are also common [5,6].

STN-DBS for Parkinson's disease may cause development of psychiatric symptoms and reduction of higher brain function. Psychiatric symptoms include impulse control disorder and depression [7]. Additional adverse events include dyskinesia, weakness, dyslalia, and sensory disturbance.

4) Testing guidelines

Improvements in implantable devices, including stimulation electrodes and implantable pulse generators (IPGs), are expected. Recent advancements include the introduction of a directional lead, described above as a stimulation electrode, and IPGs compatible with the combined application of multiple stimulation conditions. IPGs compatible with remote adjustment of stimulation conditions are also available [8]. Furthermore, an IPG capable of measuring and recording the potential generated by deep brain stimulation. This IPG is capable of driving a closed-loop system that automatically controls stimulation conditions, using β oscillations as an indicator [9]. Future development of such adaptive DBS systems, which capture parameters reflecting the physiological characteristics of disease symptoms and deliver stimulation under optimal stimulation conditions, is expected.

Improved device performance has enabled long-term recording and remote retrieval of local field potentials (LFPs) in patients [10]. Such devices are also capable of storing physiological data in patients and of remote retrieval of stored data [10]. In most cases, data thus obtained are used for improvement of the patient's disease. Nevertheless, these data are expected to contribute to neuroscience as well, because physiological brain signals generated by nuclei in the human deep brain are extremely difficult to obtain from individuals other than patients on DBS therapy. On the other hand, these data potentially contain personal information that could reflect thoughts and emotions of the patient. It is essential for such data to be handled in accordance with the Guidelines

for Medical and Biological Research 2021 and the Act on the Protection of Personal Information and then utilized for research.

Potential expansion of indications of DBS is also considered. In particular, effectiveness of DBS in severe obsessive-compulsive disorder and depression has been reported from outside Japan [11] [12], and DBS is expected as a therapy for these conditions. In contrast, there are many issues to be resolved before introduction of DBS into the treatment of these conditions in Japan, because DBS is potentially capable of controlling mental activities and emotions.

5) Explanatory documents for research participants

While DBS for the treatment is utilized in general clinical practice, measurement of EEG using electrodes for DBS is handled as a practice for investigational purposes. Since DBS is a non-invasive research method, research utilizing it is positioned as observational research. However, adjustment of drug dose and control of stimulation conditions in patients with Parkinson's disease for purposes other than clinical testing are considered as interventional research. The conduct of research mentioned above requires explanations to and consent of the patient in ways appropriate for the methods of individual research.

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J. Transcranial ultrasound stimulation (TUS)

1) Summary

Clinical use of transcranial ultrasound stimulation (TUS) targeting central nervous system dates back to 1954. In the United States, William & Francis Fry brothers started their research attempting to treat cranial nerve diseases by thermocoagulation of a particular part of the brain utilizing focused ultrasound [1]. Almost concurrently in Japan, Oka and colleagues reported clinical application of focused ultrasound starting from animal studies [2]. However, utilization of TUS for the central nervous system stagnated thereafter and did not lead to clinical application. Recently, an Israel-based company, InSightec, Ltd., developed a medical device that creates coagulation foci under real-time observation of the location and temperature rise of the target by using a phased array transducer guided by MRI (MR-guided focused ultrasound, MRgFUS). This was an example of successful social implementation of focused ultrasound technology applied to the central nervous system. This device demonstrated its effectiveness first in essential tremor [3], followed by expansion of indication to Parkinson’s disease and clinical trials in dystonia. Treatment of these conditions involves high-intensity focused ultrasound at a frequency of 600 kHz or higher (called HIFU). Meanwhile, research using low-intensity focused ultrasound (LIFU) is ongoing. Transcranial LIFU involving focused ultrasound at a frequency of approximately 500 kHz or lower is a technology not for thermal destruction of tissue but for temporary adjustment/stimulation of neural activity within a particular region of the brain [4]. Devices capable of accurately stimulating a particular region of the brain with the aid of a navigation system have been developed. In particular, such devices realize stimulation of deep brain regions (difficult to stimulate with magnetic stimulation devices) as well as adjustment of brain circuits. Clinical application to improvement of brain function is also in progress. Furthermore, ultrasound irradiation at a frequency of 230 kHz using the MRgFUS device described above with concomitant intravenous administration of microbubbles allows temporary

disruption of the blood-brain barrier. Clinical research utilizing this technique is in progress [5]. In addition to application to chemotherapy, various antibody treatments, and cell therapy for brain tumor, the technique is expected to have a potential to realize clearance of amyloid β accumulated in Alzheimer's disease.

2) Effectiveness (surgical indication)

MRgFUS targeting Vim has already been covered by insurance in Japan for essential tremor and tremor associated with Parkinson's disease. Besides these conditions, MRgFUS is also covered by insurance for the treatment of Parkinson's disease targeting GPi. LIFU is expected not only as a means to disrupt the blood-brain barrier (BBB) but also as a method for neuromodulation against diseases, although still in the research phase. Target diseases include depression, neuropathic pain, and dementia.

LIFU, capable of realizing minimally invasive deep brain stimulation, is drawing attention as a new tool for neuromodulation. Along with the development of devices, advances in research from animal studies to preclinical/clinical research are expected.

3) Ethical problems (Risks involved in testing)

MRgFUS has a similarity to conventional radiofrequency coagulation in creation of coagulation foci in deep brain tissue. Consequently, its local complications are similar to those of conventional coagulation. Representative complications unique to MRgFUS include intraoperative headache and nausea/vomiting. Although remaining to be identified, the cause of headache is presumed to be pain in skin or dura. Development of pain correlating with the amount of ultrasound energy may force to discontinue treatment [6]. Postoperative skin swelling in the head and face typically improves within approximately 1 week. Clinical application of LIFU is currently in the research phase, and problematic points associated with this technology are considered as remaining to be identified in the future.

4) Testing guidelines

In cases of treatment covered by insurance, procedures defined for the conduct of invasive procedures in general clinical practice should be followed, including determination of indication, comparison with other treatments, and explanation of safety and risks. In research aimed at further expanding the indication, the target disease is selected from conditions for which the effectiveness of radiofrequency coagulation has already been confirmed. Nevertheless, it might be appropriate to consider for going back to the launch of a non-clinical trial. For either LIFU or HIFA, measures in accordance with the Clinical Trials Act or the conduct of a clinical trial are eventually required.

Findings on the clinical application of BBB disruption using devices for MRgFUS have been reported outside Japan. In Japan, however, no microbubbles have been granted regulatory approval for use for this purpose. As a consequence, development of this system similarly requires measures in accordance with the Clinical Trials Act and other related rules and regulations or the conduct of a sponsor- or investigator-initiated clinical trial.

In cases using LIFU for the purpose of testing or improvement of neurological symptoms, the situations are similar. The fact that no LIFU device has been granted regulatory approval by the

PMDA in Japan must be recognized. Although LIFU is considered to involve relatively minimal invasiveness, its clinical use requires the conduct within the framework of clinical research regardless of the device to be used. This also applies to cases using LIFU for testing or investigational purposes, aiming at functional recovery through neuromodulation.

Precautions in conducting LIFU are extensively described in "Recommendations on Low-intensity Transcranial Focused Ultrasound Stimulation" (Jpn J Clin Neurophys 49(2):114-118, 2021). This article defines "low intensity" as "100 W/cm2 or lower." According to the safety standards for diagnostic ultrasound devices established by FDA, the desirable upper limit of spatial peak pulse average intensity (ISPPA) is 30 W/cm2 or lower, while the upper limit of spatial peak temporal average intensity (ISPTA) is considered as 3 W/cm2. Previous reports have stated that stimulation is achieved without pain at an ultrasound intensity within the range described above. While adverse events include unintended BBB hyperpermeability, microhemorrhage, and others, LIFU is a relatively safe method if used in accordance with the safety standards by FDA. Other adverse events assumed include low-temperature skin burns. Based on the facts described above, recommendations published by the Committee on Brain Stimulation, Japanese Society of Clinical Neurophysiology conclusively describe the following conditions for ultrasound stimulation: frequency, 0.2-0.7 MHz; intensity (ISPPA), 30 W/cm2 or lower; sonication duration, 1 second or shorter; daily number of sonication, 200. At least, the safety standard for diagnostic ultrasound by FDA, an ISPPA of 190 W/cm2 or lower should be strictly followed. Accumulation of evidence for LIFU is not yet sufficient at present, and appropriate guidelines for its use concerning optimal conditions for stimulation remain to be developed.

5) Explanatory documents for research participants

As a general rule, follow contents stated in Section 7 of current guidelines. For HIFU as well as BBB disruption by concomitant use of microbubbles, clinical research aiming at further expansion of indication is expected. For LIFU as well, research involving human subjects is considered to be conducted due to its minimal invasiveness, while using the same TUS, there is a wide variety of purposes, testing methods, or invasiveness thereof and it is difficult to create one template. It is therefore preferable that these documents be prepared by the investigator himself/herself according to their individual research.

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K. Intracranial electroencephalography

1) Summary

Electroencephalography using intracranial electrodes involves chronic placement of electrodes on the brain surface or in the brain parenchyma, literally located inside the skull, by neurosurgical procedures. Approximately 30% of patients with epilepsy are resistant to medical treatment with anti-seizure medications (drug-refractory). In patients with drug-resistant refractory focal epilepsy, a treatment option for radical cure (seizure freedom) is focal resection (epilepsy surgery), surgically resecting the epilepsy focus. Based on electrophysiological tests, such as video-EEG monitoring, and diagnostic imaging by MRI and FDG-PET, a working hypothesis is developed for the epileptic focus and the epileptic network in the brain. When (1) non-invasive tests fails to identify the epilepsy focus, (2) the epilepsy focus is presumed to be located in the vicinity of an important functional region of the brain, or (3) neuroimaging fails to visualize the epilepsy focus, the results of various non-invasive tests are integrated to construct a working hypothesis for the epilepsy focus/network, instead of conducting primary focal resection. If the clinical team considers the working hypothesis reasonable, electrodes are chronically placed within a clinically required region usually for 1 to 2 weeks. After electrode placement, the dose of anti-seizure medication is reduced, and seizures are recorded. Subsequently, the anti-seizure medication dose is returned to its original level, and functional brain mapping is performed using electrical stimulation. In this way, the epilepsy focus/network and functional region in the brain located in its vicinity are identified for subsequent focal resection. Previously, the mainstream of the procedure for intracranial electroencephalography was to limit electrode placement to the unilateral hemisphere based on the working hypothesis developed for the epilepsy focus/network and then, after craniotomy and dural incision, to place an array of subdural electrodes (SDE) (consisting of multiple electrodes in a grid-or strip-like arrangement at intervals of 5 to 10 mm) on the brain surface for recording neural activity (electrocorticograms) within a 2-dimensional plane. In recent years, in contrast, stereotactic electroencephalography (SEEG) has been disseminated. This technique involves multiple cylindrical depth electrodes, each with a diameter of approximately 1 mm (5 to 10 cylindrical electrodes are arranged within a single depth electrode), inserted from the cerebral surface into deep brain loci (hippocampus, medial surface of cerebral hemisphere, etc.) and realizes three-dimensional (stereotactic) measurement of EEG, including those generated from deep brain loci. SEEG does not require craniotomy and causes less physical stress on patients. While SEEG is capable of stereotactically recording EEG from deep brain loci such as the hippocampus, insular cortex, and the

medial surface of the cerebral hemisphere, as well as from bilateral hemispheres, if necessary, the results obtained are records from spatially dispersed loci [1].

Using the electrodes placed, SEEG records both physiological neural activity and pathological neural activity (interictal epileptic discharge and ictal changes in EEG) during the resting period and each sleep cycle. In addition, methods for investigating brain functions based on the records of neural activity during the execution of particular tasks for testing brain functions and functional modification caused by perturbation, such as high-frequency electrical stimulation, are established (functional brain mapping)[2]. Furthermore, although not referred to in this section and not yet approved in Japan under the Pharmaceuticals and Medical Devices Act, SEEG will be utilized in the future as a part of BMI using information of EEG recorded and for detecting changes in EEG leading to the onset of seizure and triggering electric stimulation in a closed-loop mode to interrupt seizure activity (responsive neurostimulation, NeuroPace, Inc., insurance coverage approved in the United States).

2) Effectiveness

Compared with scalp electroencephalography, associated with signal attenuation caused by the skull and volume conduction caused by spinal fluid, intracranial electroencephalography is capable of directly recording electrical activity from the cerebral cortex, the source of EEG signals. In addition, intracranial electroencephalography is less susceptible to artifacts (including movement, electromyogram signals, and perspiration) and yields a high signal-to-noise ratio. Consequently, this method is capable of recording and analyzing both low-frequency activity at frequencies below 1 Hz (infraslow) and high-frequency activity at hundreds and thousands of Hz as wideband EEG[3]. Based on comparison between electrocorticograms and single-unit recordings, activity at a frequency up to 60-200 Hz called either high gamma activity, high-frequency oscillation (HFO), or ripple has been suggested to be associated with firing activity of neurons [4]. Ongoing attempts to apply it clinically as an alternative to functional brain mapping using high-frequency electrical stimulation are currently underway. Of the low-frequency activity at frequencies under 1 Hz, activity called direct current (DC) potential (ictal DC sift) from a source currently unidentified is assumed to be associated with glial cells including astrocytes and recorded ictally at the epilepsy focus [5]. This activity is also used to identify epileptic foci in combination with high-frequency oscillations[6, 7]. Taking advantage of its spatial and temporal resolution, intracranial electroencephalography is applicable to network analysis, through correlation analysis of cortical rhythm between the sites of electrode placement. Although depending on the site of electrode placement, this method enables analysis of deep brain regions including the thalamus and hippocampus where non-invasive methods have difficulties in recording or intervention by stimulation.

While methodologies for providing high-frequency electrical stimulation through an electrode to the cerebral cortex have been established as described earlier, perturbation by short, single electrical stimulation and recording of the evoked response spreading to other brain regions mainly via white matter fibers (cortico-cortical evoked potential, CCEP) allow investigation of effective connectivity and cortical excitability [8]. CCEP is actually utilized for identification of the transmission pathway for ictal discharge and functional monitoring for preservation of particular white matter fibers (such

as arcuate fasciculus involved in language function) in neurosurgery [9]. Further application to neurological research related to functions other than language is expected in the future.

3) Ethical problems (Risks involved in testing)

1. General risks

Intracranial electroencephalography is a test conducted in patients with some brain diseases involving invasive procedure. Therefore, its conduct is subject to medical constraints in many aspects. Accordingly, sufficient consideration is needed for the fact that this test may cause serious complications in some cases. Placement of subdural electrodes often involves craniotomy with a wide opening of the skull and may cause development of infection pain, and hematoma as surgery-related complications [1]. Meanwhile, SEEG involves stereotactic insertion of electrodes through burr holes opened on the skull using a dedicated instrument. Consequently, the complications described above are less frequent in SEEG compared with those in subdural electrode placement and postoperative recovery of the patient is rapid. This often allows earlier conduct of a variety of tests during the postoperative period. In intracranial electrode placement for preoperative examination in preparation of focal resection, seizure recording and necessary clinical tests are conducted for 1 to 2 weeks after dose reduction of anti-seizure medication. The longer placement period may be associated with the higher risk of infection, particularly intracranial infection. The duration of intracranial electrode placement must be defined for clinical purposes and minimized. In addition, the extent of fatigue caused by tests conducted for investigational purposes needs to be such that does not cause any clinical issues.

2. Electrical stimulation

Brain function is estimated by providing high-frequency electrical stimulation (50-60Hz, usually 1-5 seconds) through an electrode to cortical tissue beneath it to temporarily disrupt physiological neural activity, and by analyzing the resulting functional modification. On the other hand, functional brain mapping involving high-frequency electrical stimulation may cause some epileptic discharge-like changes in EEG called “afterdischarge” or induce actual seizures. In particular, stimulation of epilepsy foci is associated with a high risk of inducing such events. Therefore, functional brain mapping in patients with epilepsy involving high-frequency electrical stimulation is conducted under the supervision of a physician or a clinical laboratory technologist monitoring changes in EEG and usually under administration of anti-seizure medication at a sufficient dose. For low-frequency electrical stimulation (≤ 1 Hz), the risk of inducing afterdischarge and seizure is minor [10]. Seizure induction may lead to interruption of the test and medical intervention such as additional administration of anti-seizure medication. Of note, exploration of epilepsy foci has been achieved by intentionally providing electrical stimulation to the epilepsy focus and brain region located in its vicinity to confirm seizure induction for reference of epilepsy focus identification (clinico-anatomical correlation) [11, 12].

The guidelines established by American Clinical Neurophysiology Society [13] recommend that the maximum safety threshold for electrical stimulation should be established by calculating the charge density: the value for subdural electrodes is 52-57 mC/cm^2/phase. However, no established standards are available for depth electrodes, and the stimulation threshold should be defined by taking the followings into consideration: leakage of electric current into the cerebrospinal fluid from

depth electrodes is smaller in amount, in contrast to subdural electrodes (simulation data suggest a leakage of up to approximately 87% for subdural electrodes[14]); and the standard for DBS established by the Food and Drug Administration (FDA) is 30 mC/cm^2/phase. When providing electrical stimulation, charge balance is important. Bipolar stimulation is associated with a smaller tendency to cause neuropathy compared with unipolar stimulation. For unipolar stimulation, it is desirable to periodically alternate the polarity of the electrodes.

Functional brain mapping involving high-frequency electrical stimulation at 50-60 Hz induces development of a variety of symptoms: positive symptoms (muscle contraction such as jerks, sensation of numbness, elemental sounds such as buzzer sound, paracusis of voice, visual symptoms such as flickering spots) in the primary sensorimotor area; and functional modification/suppression (motor arrest, verbal comprehension disorder/dyslalia, metamorphopsia) in the association area. These symptoms disappear as soon as stimulation ends. During a brain mapping test, potential symptoms should be explained to the patient, and care should be taken to ensure the test proceeds smoothly. In addition, attention should be paid to the possibility that electrodes placed on the surface of the skull base may induce pain via the trigeminal nerve due to electrical stimulation provided to the adjacent dura.

4) Testing guidelines

When the history of electroencephalography involving chronic placement of intracranial electrodes for preoperative evaluation of refractory focal epilepsy is reviewed, the first report of SEEG dates back to the early 1970s (Talairach and Bancaud et al., at Sainte-Anne Hospital, Paris)[15], while the first report of SDE to the early 1980s (Hans Lüders et al., at Cleveland Clinic, Cleveland)[16]. Currently established methods for the identification of epilepsy foci in focal epilepsy (identification of patterns of ictal changes in intracranial EEG) and functional brain mapping of the regions surrounding the foci (brain mapping technology using high-frequency electrical stimulation) were investigated and developed in the framework of clinical research, utilizing the state-of-the-art neurophysiological technologies available in each era, to be returned to future patients as clinical tests. Encouraged by the introduction of digital EEG at the beginning of the 21st century and advances in various methods for neurophysiological and mathematical analysis (including machine learning) achieved during the last 10 years, a variety of methods for electrical stimulation and EEG analysis have been proposed for clinical research.

From a neuroscience perspective, preoperative evaluation of refractory focal epilepsy, involving the chronic placement of intracranial electrodes, provides a valuable opportunity to investigate the physiological activity of the human brain directly at the brain surface and within the brain. While the electrode arrangement within each intracranial electrode and the duration of electrode placement are to be defined for clinical purposes, the latter can be used for neuroscience research after obtaining the patient's consent to participate as a clinical research subject. Targeting the brain of patients with refractory focal epilepsy harboring both normal and pathological regions, not only research on physiological (normal) brain functions but also research on the pathology of epilepsy and epilepsy-associated functional elasticity are ongoing all over the world. For example, the investigation of cortico-cortical evoked potential (CCEP) was promoted as a part of neuroscience research. While electrical stimulation used in CCEP is minimally invasive (approximately 1 Hz) compared with that

used in functional brain mapping (50 Hz), this method is positioned as a new intervention. Electrical signals are transmitted from the part of the cerebral cortex exposed to single electrical stimulation (site of stimulation) via intercortical connection, and CCEP is recorded at an adjacent or distant part of the cerebral cortex (site of response) as a stimulation-evoked potential. The transmission pathway for seizures from the epilepsy focus and the mode of connection between physiological functional areas of the brain are identified using the method for identifying effective connectivity between brain regions. While CCEP is translationally applied at present to clinical practice as an intraoperative functional monitoring test targeting arcuate fasciculus responsible for language function, research using CCEP is positioned as basic/clinical research in neuroscience and should be conducted as execution of a clinical research protocol involving the human brain. Developing a clinical research protocol that considers personal information is desirable not only for research involving prospective data collection but also for research involving the secondary use of existing patient data as part of a data science approach.

Such research involving practice beyond the scope of clinically necessary tests requires approval by ethical review committees at research implementing entities and facilities, including the hospital where the test is conducted. In research aimed at developing therapies or therapeutic technologies, the research procedures must be determined in accordance with the Clinical Trials Act and other related rules and regulations. From the viewpoint of neuromodulation including seizure inhibition, deep brain stimulation targeting anterior thalamic nuclei and subthalamic nuclei has come into the scope of clinical research. Placement of electrodes in these sites requires review by the certified review board (CRB).

Voluntary consent based on the patient's understanding of the research content is essential to research participation. Namely, research should be conducted only when consent is provided based on the patient's willingness to contribute to development of medicine/neuroscience through participation in the research[17]. Meanwhile, the patient is to undergo intracranial placement of electrodes for healthcare purposes, namely for surgical treatment of epilepsy. Due to conflict of interest and therapeutic misconception, his/her decision-making regarding the conduct of the test may not be fully voluntary [18]. The investigator needs to be fully aware of this. In this context, it is desirable to establish a system in which the team engaged in clinical decision-making and the team of investigators conducting the research are mutually independent. If this is difficult to realize, the team engaged in clinical decision-making should include members not involved in the research.

Research may be conducted after obtaining informed consent, provided an appropriate explanation is given that considers the above principles. It is desirable to establish a system in which an explanation is provided before electrode placement and an opportunity to withdraw consent is offered after placement.

Electrode placement should not be affected by the research protocol. The conduct of SEEG is based on the Guidelines for the Conduct of Stereotactic Electroencephalography (SEEG) (https://jes-jp.org/jes/senmon/VNS_about.html) developed on the initiative of the Japan Epilepsy Society. In conducting the research, the duration of intracranial electrode placement should be minimized to avoid any adverse clinical effects. Prior careful simulation in the planning phase is desired, considering opinions of the clinical team. Considering that clinical constraints inevitably limit the

duration of test, it is important to develop a testing protocol ensuring capture of scientifically significant findings within a limited time.

In research involving electrical stimulation, optimal values for parameters such as intensity and duration of stimulation are defined by consulting the latest literature for the sake of safety. Clinical conditions of the patient are confirmed prior to testing. Care should be taken to avoid exposing the patient to excessive physical and mental stress. During electrical stimulation testing, countermeasures such as intravenous antiseizure medication to stop seizure activity should be ready. The attendance of a primary physician or an alternative physician is required, so that measures can be taken if unforeseen situations arise.

5) Explanatory documents for research participants

As a general rule, follow the contents stated in Sections 6, 7, and 8 of the current guidelines. Given the characteristics of tests involving intracranial electrode placement, the information desirable to include in explanatory documents is provided below.

- Testing for investigational purposes is independent of testing for clinical purposes
- After providing consent to testing, the patient can withdraw the consent at any time depending on his/her conditions
- Benefit and risk of research conducted on the opportunity of a rare test called intracranial electrode placement

* Benefit for the patient is limited

- In case of tests involving electrical stimulation, specific risk and response

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5. **Methods for review of research proposals**

Approaches to ethics review differ among applicable laws, ordinances, and guidelines. In this section, the general responsibilities of ethical review committees stipulated in the Guidelines for Medical and Biological Research 2021 are discussed. These guidelines for medical and biological research can be applied to research involving human subjects other than "medical and biological research." Ethical review committees whose operations do not currently meet the requirements in these guidelines must develop rules that address and thoroughly consider these requirements for future operations.

The ethical review committee is an institution that utilizes a consensual decision-making system and is organized to undertake examinations and reviews of the ethical justification and scientific validity of conducting or continuing research, as well as other relevant matters. The principal investigator shall submit the matter to the ethical review committee for deliberation on the appropriateness of conducting the research. (Previously, the investigator submitted an application to the chief executive of the research implementing entity, and the chief executive of the research implementing entity asked for deliberations by the ethical review committee with respect to the appropriateness of conducting research or other matters.) After deliberations by the ethical review committee, the principal investigator shall submit the results of the deliberations, the documents submitted to the said ethical review committee, and any other documents requested by the chief executive of the research implementing entity, to the chief executive of the research implementing entity, in order to receive approval for conduct of the said research at the said research implementing entity. When the principal investigator requests approval for conduct of the research, the chief executive of the research implementing entity shall, while respecting the opinions of the ethical review committee, decide whether to approve or deny approval for conduct of the research and decide on other necessary measures concerning the research. When the principal investigator asks for deliberations with respect to the appropriateness of conducting research or other matters, the ethical review committee shall review the matters, neutrally and fairly, in accordance with these Guidelines, including information on any conflicts of interest of the research implementing entity and the investigator, etc. concerning the research from ethical and scientific viewpoints, and shall present its opinions in writing or by electromagnetic means. With respect to the research reviewed, the ethical review committee shall conduct necessary investigations from ethical and scientific viewpoints and shall provide the principal investigator with necessary opinions concerning the research, including revisions to the research protocol and termination of the said research.

A.Organizing ethical review committee

The organizer of the ethical review committee shall prescribe the organizational structure of the said committee and rules for operating the committee, as well as ensure that members of the ethical review committee and other individuals engaged in administrative work perform their duties in accordance with the said rules. Other responsibilities of the said ethical review committee include storage of records, disclosure of the status of the said committee's meetings and committee's reviews, and implementation of measures for the education and training of members.

It used to be mandatory to establish an ethical review committee at each research implementing entity. This was changed, and the requirement to found a committee at each institution was removed from national laws, ordinances, and guidelines. In the Guidelines for Medical and Biological Research 2021, the representative investigator shall, in principle, submit a matter to a single ethical review committee for deliberation to make a comprehensive review on the research protocol for multi-institutional joint research. Additionally, research implementing entity without its own ethical review committee is allowed to request that the committee at another institution perform research reviews. When the principal investigator requests review by the ethical review committee established outside his/her own research implementing entity, the said ethical review committee must conduct the review and express its opinions only after it fully understands the research implementation system at the research implementing entity that makes the request, which requires sharing of necessary information. The principal investigator who submits a matter on which the ethical review committee deliberates shall not be present when deliberation and adoption of opinions are carried out at a meeting of committee. When it is necessary to do so in order to understand details of the said deliberations by the ethical review committee, however, the said principal investigator may attend a meeting by obtaining the said committee's consent.

B. Composition and operation of the ethical review committee

The composition of the ethical review committee shall comply with all of the following requirements in order that the duties of the committee, such as reviewing research protocols, are executed appropriately. Those members as defined in each of the groups of (i) to (iii) below cannot concurrently hold the same status in other groups. The same requirements shall apply to the quorum of the committee's meetings.

(i) The committee shall have a member who is an expert in natural science, such as a medicine and medical care professional, etc.;

(ii) The committee shall have a member who is an expert in humanities and social sciences, such as a professional in ethics and law, etc.;

(iii) The committee shall have a member who can reflect the opinions of the general public, including viewpoints on research subjects;

(iv) The committee shall have at least two members who do not belong to the institution to which the organizer of the committee belongs;

(v) The committee shall have both male and female members; and,

(vi) The committee shall have five or more members.

It is desirable for research conducted by any members of the Japan Neuroscience Society to include individuals with knowledge regarding the content, methods, and devices of neurological research, who fulfill the requirements in (i), and to ensure diversity of expertise and gender to the greatest extent possible. The ethical review committee may invite nonmembers with expertise in specialist areas to provide assistance depending on matters subject to review and content of such. When reviewing the research protocol for which research subjects require special consideration and presenting its opinions on such research, the ethical review committee shall, as necessary, seek the opinions of experts on such research subjects. The investigator, etc. engaged in the research that is subject to deliberation shall not be present when deliberation and adoption of opinions are carried out at a meeting of the committee. When so requested by the said ethical review committee, however,

the investigator, etc. may attend a meeting to provide information on the said research. The ethical review committee shall endeavor to adopt its opinions unanimously.
To ensure that a high level of review is implemented, investigators are required to prepare and submit an appropriate research protocol before conducting the research. The Guidelines for Medical and Biological Research 2021 include the principles regarding which matters should be described in the research protocol to be reviewed by the ethical review committee. Please refer to these guidelines as necessary. For example, the principal investigator shall instruct and manage the investigators and other persons involved in conducting the said research so that the research is properly conducted in accordance with the research protocol and that the reliability of the results is ensured. When the principal investigator learns of the occurrence of a serious adverse event in the conduct of research involving invasiveness, he/she shall promptly take necessary measures. Accordingly, the research protocol is required to contain description in accordance with these principles.

6. **On informed consent**

A. Procedures for obtaining informed consent

When the investigator, etc. intends to conduct research, or when a person who only provides existing specimens and/or information intends to provide existing specimens and/or information, he/she shall, in principle, obtain informed consent in advance in accordance with the following procedures (1) through (5), respectively, as provided in the research protocol approved by the chief executive of the research implementing entity concerning the conduct of the said research. However, this shall not apply to cases where existing specimens and/or information are provided or received in accordance with the provisions of laws and regulations. In the Guidelines for Medical and Biological Research 2021, procedures of obtaining informed consent in the following five cases are discussed: (1) cases where research is to be conducted by acquiring new specimens and/or information; (2) cases where research is to be conducted utilizing existing specimens and/or information retained by the research implementing entity; (3) cases where existing specimens and/or information are to be provided to other research implementing entity(s); (4) cases where a person only provides existing specimens and/or information; and (5) cases where research is to be conducted based on existing specimens and/or information provided in accordance with the procedures in (3). The Guidelines for Medical and Biological Research 2021 specify principles regarding which matters should be explained to research subjects, etc. when obtaining informed consent. Please refer to these guidelines.
Furthermore, for the research conducted by the members of the Japan Neuroscience Society, explanatory documents to be used for obtaining informed consent should address the length of time that research participants will be involved in the research, photos and an summary of the devices to be used, levels of physical or mental discomfort, and an arrangement to reduce such discomfort. In fact, subsection (1) of the section “Procedures for obtaining informed consent” in the Guidelines for Medical and Biological Research 2021 describes procedures that vary depending on the status of invasiveness as well as the status of intervention. Consequently, objective review of these factors is important in formulating a research plan. The Guidelines for Medical and Biological Research 2021 newly specify the method for obtaining informed consent. Please refer to these guidelines.
While the format of informed consent documents may differ between research implementing entities or facilities, or by research methodology, it is generally advisable to use a written document and to

consider the points listed below as common elements, and to include them in the explanatory documents given to research subjects.

(i) Title of the research and the fact that approval of the chief executive of the research implementing entity has been given concerning its conduct;

(ii) Name of the research implementing entity and the principal investigator (including the names of collaborative research implementing entities and names of principal investigators at the collaborative research implementing entities in conducting a multi-institutional joint research);

(iii) Purpose and significance of the research;

(iv) Method and time period of the research (including purposes for utilizing and handling of specimens and/or information acquired from the research subjects);

(v) Reasons why asked to be enrolled in the research;

(vi) Burdens placed on the research subjects and predictable risks and benefits;

(vii) The fact that research subjects, etc. may withdraw their consent at any time, even after they have given consent, when the research is to be conducted or continued (when it may be difficult to take measures that follow withdrawal by the research subjects, etc., a statement to that effect and the reason for the difficulty);

(viii) The fact that the refusal or withdrawal of consent by the research subjects, etc. when the research is to be conducted or continued does not cause any disadvantage to such research subjects, etc.;

(ix) Means to make information on the research public;

(x) The fact that research subjects, etc. can request and obtain or read the research protocol and documents concerning method of the research, to the extent such does not interfere with the protection of personal or other related information of other research subjects, etc. or the originality of the said research, as well as the procedure to obtain or read such protocols and documents;

(xi) Handling of personal or other related information (including the processing method, if the information is processed, and a statement to the effect that anonymized or anonymously processed personal information is to be created, if such is the case);

(xii) Means for storing and disposing of specimens and/or information;

(xiii) Status of research-related conflicts of interest of the research implementing entity, such as research fund resources, as well as research-related conflicts of interest of the investigator, etc., such as his/her individual income;

(xiv) Handling of results, etc., obtained through research;

(xv) Response to consultation, etc. (including genetic counseling) made by the research subjects, etc., and other individuals concerned ;

(xvi) When the research involves any financial expenditure on or remuneration for the research subjects, etc., a statement to that effect and details of such;

(xvii) When the research involves medical technique beyond usual medical practice, description of alternative procedure(s) or course(s) of treatment;

(xviii) When the research involves medical technique beyond usual medical practice, a response related to the healthcare delivery to the research subjects after the research;

(xix) When the research involves invasiveness, whether or not compensation will be offered for research-related health damage and details of such compensation;

(xx) With respect to specimens and/or information acquired from the research subject, when any of those may be used or provided to other research implementing entity(s) for the research in the future that is not identified at the time of obtaining consent from the research subjects, etc., a statement to that effect and the contents of utilization assumed at the time of obtaining consent; and,
(xxi) When the research involves invasiveness (excluding minor invasiveness) and intervention, the fact that the monitor(s), the auditor(s), and the ethical review committee will be granted direct access to the specimens and/or information acquired from the research subjects, without violating the confidentiality of the research subjects, to the extent necessary.

Attention should be paid to the fact that, for the use, provision, and receipt of specimens and information, procedures differ in terms of objectives or level of anonymization, and preparation and storage of records are required.
Informed consent provided by a representative, etc. or acquisition of informed assent (i.e., expression of understanding and agreeing, with respect to whether the research shall be conducted or continued, of research subjects who are considered to be objectively unable to give informed consent upon receiving an explanation of the said research to be conducted or continued in easy-to-understand language according to their ability to understand) needs to be discussed by the applicable ethical review committee in the following cases: (a) when the research subject is a minor, (b) when the research subject is an adult but is objectively judged to be unable to give informed consent, and (c) when the research subject is deceased.
B. Withdrawal of consent
When a research subject, etc. withdraws all or part of his/her consent to begin or continue participating in the research, or rejects the conduct or continuation of all or part of the research based on certain notifications or disclosures regarding information on the research, the investigator must immediately take measures (discontinuation of experiments, discontinuation of use and disposal of already-obtained specimens and information, suspension of provision of specimens and information to another facility, etc.) according to the content of this withdrawal or rejection, and explain the measures to the research subjects, etc. However, these requirements are not applicable in cases where these measures are difficult to implement and the chief executive of the research implementing entity decides to exempt investigators from these measures based on the opinions of the ethical review committee. In this case, the investigator, etc., shall endeavor to provide an explanation to the research subject, etc., concerning the fact that measures in accordance with the said withdrawal or refusal will not be taken, along with the reasons, and to obtain the understanding of the research subjects, etc.
C. Necessity of post-hoc explanation in cases where not all information can be disclosed in advance
In principle, when not all the information regarding the research content can be disclosed to research subjects in advance for reasons related to research planning, the rationale and methods for post-hoc disclosure need to be explained to and approved by the ethical review committee or other parties. If there is approval to refrain from disclosing some information, investigators need to disclose the information afterwards, thoroughly explain the reason for no disclosure, and sincerely apologize to the research participants. Investigators also need to answer all questions posed by the research participants to avoid any misunderstanding.

D. For research subjects affiliated with the same implementing entity as the persons conducting the research

The above principles regarding informed consent must be followed even for research subjects affiliated with the same research implementing entity as the persons conducting the research.

7. **Protection of personal information of research subjects (including candidates)**

A. Definition of personal information

Personal information is defined as that which pertains to living individuals and which meets either of the following criteria.

(i) Individuals can be identified based on any combination of the items included in the information concerned (excluding the personal identification code and including items that can be cross-checked with other information and that become personally identifiable when cross-checked), such as those mentioned in the name, date of birth, or other descriptions, or recorded or expressed in sounds, gestures, or other forms.

(ii) The information concerned includes the personal identification code (the code is considered to be personal information in and of itself).

B. Responsibilities of investigators regarding personal information

With respect to the handling of personal information, anonymized personal information and anonymized personal information held by administrative organs, the investigator, etc. and the chief executive of the research implementing entity shall comply with the provisions of these Guidelines, in addition to the Act on the Protection of Personal Information, Act on the Protection of Personal Information Held by Administrative Organs, Act on the Protection of Personal Information Held by Incorporated Administrative Agencies, etc. and related ordinances.

When conducting research, those involved must not obtain personal information by deceit or other illicit means. In principle, they also must not deal with personal or other information obtained in association with the conduct of the research that lies beyond the scope of the consent provided by the research subjects in advance. Moreover, they must appropriately handle all personal and other information obtained in association with the conduct of the research that is retained at their research implementing entity (including cases where storage is outsourced), in order to prevent the leak, loss, or damage of the information or to manage its security in other ways. For this purpose, personal information of research subjects, including correspondence tables, needs to be anonymized and strictly managed.

If it is impossible to completely prevent the direct identification of research subjects or if research participants may possibly be identified, an explanation to that effect must be given to the research participants and their consent must be obtained in advance.

Please appropriately refer to the Act on the Protection of Personal Information, Act on the Protection of Personal Information Held by Incorporated Administrative Agencies, etc., and Act on the Protection of Personal Information Held by Administrative Organs. They differ from each other and are reflected in the guidelines for medical and health research as well as other ethical guidelines for research.

8. **Precautions when presenting research results at conferences and in academic journals**

When research results are published, research participants and their communities (such as regions and groups they belong to) must, in principle, remain unidentifiable. When using photos or videos of

research participants, it is necessary to make sufficient effort not to identify the participants. Moreover, to avoid disadvantaging research participants and their communities by causing misunderstandings of the research results, the expressions used in publications must be carefully selected.

In some cases, audio or visual records are used to accurately report behavioral or language characteristics. When there is a possibility that these records will be used in public, for example in a study group, and participants may be identified, an explanation to that effect must be given to the participants and their informed consent must be obtained in advance. In presenting the research results, it must be clearly stated that consent from the research participants was obtained.

Presentation of research results at academic conferences and in journals is discussed above. When results-related information is disseminated through non-specialized media, such as general newspapers, magazines, television, and radio, it is desirable to handle personal information in the same way as described above.