In this talk, I will present several past studies and a few new, on-going trials using NBS separately.

**Central motor conduction (CMCT) studies:**
The first clinical use of single-pulse TMS was CMCT. In addition to usual cortical and spinal stimulation, we added the framen magnum stimulation or pyramidal decussation stimulation, which enabled us to estimate the intracranial conduction time as well as CMCT. Moreover, we invented the conus medullaris stimulation which can detect the corticospinal (CST) conduction time from the cortex to the conus medullaris. Using these all methods together, we can analyze the conduction time in several parts of CST separately.

**Cerebellar inhibition (CBI):** We reported a conditioning stimulus over the cerebellum modulated the primary motor cortex (M1) excitability transiently. This effect was named CBI. CBI studies of patients with many kinds of ataxia suggested the following mechanisms for CBI. The cerebellar stimulation activates Purkinje cells which inhibit the deep cerebellar nuclei including dentate nucleus (DH). This inhibition of DN suppresses M1 through dentate-thalamus-cortical pathways. CBI was abnormally reduced in patient with essential tremor (ET). This supports the notion that cerebellar pathology is responsible for pathophysiology of ET.

**Neuroplasticity induction by quadripulse stimulation (QPS):** We invented a patterned repetitive transcranial magnetic stimulation (TMS) technique called QPS. It induces long-term potentiation (LTP) or long-term depression (LTD) effects depending on the interstimulus interval steadily. We applied this method for physiological analysis of a motor learning task. It showed that the pre-supplementary motor area (pre-SMA) plays
a critical role in the new sequence process whereas SMA proper plays a role in the speed-up process of well-learned tasks. These are compatible with previous findings in monkeys and humans.

**Gait induction by lumbar repetitive TMS:** We demonstrated that self-paced stimulation of the lumbar gait center induced a gait-like alternative movements in the legs. We applied this technique for paraplegic patients with a spinal cord injury. The combination of lumbar stimulation and rehabilitation enhanced the gait recovery as compared with the rehabilitation alone.

In the future, we may have some new methods of NBS, such as static magnetic stimulation (SMS) or transcranial focused ultrasound stimulation (tFUS), which should give us more progress in this field.
Through several waves of downhills and uphills in the past decades, Artificial Intelligence (AI) has now evolved into a must have new technology or tool in every domain. Furthermore, with the advent of powerful GPU, AI-related research or AI-based applications have sprouted in every corner of the world. Originated from pure internet connectivity the Internet of Things (IOT) has become a structure that can collect every piece of data from physical devices, daily activities, images or video into a data reservoir. As a result, tons of data are automatically generated into an enterprise database in a single day. This creates continuing demands on applying AI, IoT, and big data analytics to extract juicy contents from the huge databases. This talk will address from the AI and IOT (AIOT), and system engineering perspective for systems developed to resolve the sensing, networking and applications faced in healthcare. Case study of AIOT in exercise monitoring and control using camera and deep learning algorithms, monitoring and tracking of rehabilitation progress on Total Knee Arthroplasty Reconstruction (TKA), Parkinson’s Disease (PD) using IMU sensor devices, classification of fundus images from Retinopathy of Prematurity (ROP), etc. will be demonstrated in the talk.
Plenary lecture 2

Rare Sugars: our global challenge to create a healthy society by utilizing their health functions

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"Rare Sugars" are the name for monosaccharides and their derivatives that exist in a very small amount in the natural world. More than 50 kinds of monosaccharides belong to rare sugars, of which the total amount on the earth is less than 0.1%. Our team at Kagawa University has established a method for producing rare sugars and has been conducting functional research. D-allulose (also called D-psicose) is a C-3 epimer of D-fructose with almost zero calorie and tastes like sugar. It can contribute to the prevention and improvement of "metabolic syndrome" because D-allulose has been found to have several functions which show anti-hyperglycemic effect and reduce body fat. Human trials showed that D-allulose attenuates postprandial glucose levels in healthy subjects and in borderline diabetic subjects. The anti-hyperlipidemic effect of D-allulose, combined with its anti-inflammatory actions on adipocytes, is beneficial for the prevention of both obesity and atherosclerosis and is accompanied by improvements in insulin resistance and impaired glucose tolerance. It can be used as a food for specified health use or a food with functional claims. Another rare sugar, D-tagatose, a C-4 epimer of D-fructose, may be effective against caries and periodontal disease, and we have already started a human trial. D-allose, a C-3 epimer of D-glucose, has low calorie values and sugar-like taste. D-allose has an inhibitory effect to reduce production of radical oxygen species (ROS). In addition, it also showed a function of suppressing the growth of cancer cells.
Applications of D-allose can be pharmaceuticals, quasi-drugs, and medical foods. We are making a global challenge to control and overcome lifestyle-related diseases by utilizing health functions of rare sugars.
Brain phenotyping, in which brain MRI is used to capture anatomical features of the brain, is an established method for neuroscience research through which to examine the biological substrates of normal brain functions, development, and aging, as well as to investigate neuroanatomical alterations related to diseases in vivo. The enormous scientific impact of brain phenotyping, however, has not yet been translated to clinical environs because of insufficient reproducibility, despite its success in the research community. Clinical MRIs contain technological heterogeneity, including variations in scan protocol and hardware performance. Moreover, there is biological heterogeneity, which comprises variations of demographics, co-morbidity, and disease categories with different neuro-anatomical features, contrary to the homogeneous research population selected through strict inclusion and exclusion criteria. Such heterogeneity in clinical practice is one of the major causes of failure in clinical application of scientific discoveries. Toward our long-term goal of developing a methodological framework to improve clinical practice by introducing brain phenotyping for more effective use of clinical brain MRI, compared to current standard image reading, we are developing two types of resources: a high-throughput brain features-extraction pipeline, which is robust to the huge heterogeneity in brain MRIs of diseased brains; and a large clinical database, which consists of medical records acquired through clinical practice. These resources have been applied to quantify the various types of morphological and photometric abnormalities seen in pediatric and adult brain MRIs. There are two research directions. One is to extract mild pathological features that are difficult for human eyes to recognize. Another is to classify “visible” abnormalities based
on biological and clinical characteristics. A better understanding of the brain phenotypes that affect disease trajectory, dominant symptom, and treatment response is of central importance for precision medicine and will improve our ability to develop novel clues for therapeutic interventions.