Synaptic and Axonal Plasticity Induction in the Human Cerebral Cortex

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Abstract This chapter summarizes a newly developed method (quadripulse stimulation (QPS)) to induce neural plasticity in the human brain.

What Is QPS? One stimulation burst consisting of four monophasic pulses is given every 5 s for 30 min. In total, 360 bursts (1440 pulses) are given in one session. Short-interval QPS potentiates excitability and longer-interval QPS depresses the target area. QPS at intervals of 5 ms (QPS5) induces long-term potentiation (LTP) most efficiently and QPS50 induces long-term depression (LTD) most effectively in the human primary motor cortex (M1).

After QPS, no changes were found in the threshold, GABAergic function of M1, or acetylcholine function. In contrast, EPSP summation and sharpness of the IO curve are bidirectionally modulated by QPS. These findings indicate that excitatory synaptic efficacy is bidirectionally modulated by QPS. The effect is specific to the activated neurons. These all are consistent with synaptic LTP/LTD.

Dopamine enhanced both LTP of QPS5 and LTD of QPS50. It is again compatible with plasticity induction in animals. These are consistent with the concept that LTD was enhanced by the D1 agonist and LTD by the D1 and D2 agonists together, but the D1 agonist alone or the D2 agonist alone induced no changes in LTD.

In PD patients, even at an early stage, QPS induced neither LTP- nor LTD-like effects in the motor cortex. This lack of plasticity was normalized by L-Dopa intake in parallel with motor symptom improvements.

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Introduction

Neural plasticity is one main mechanism to support the flexibility of the human brain. It underlies several important human brain functions such as memory (hippocampus), motor learning (cerebellum), motor programming (basal ganglia), and so on. It has also some relation to reward learning, decision making, and addiction. It is well known that plasticity plays some roles also in the recovery of damaged function in some neurological disorders, such as cerebrovascular disease, Parkinson disease, dystonia, and so on. This chapter summarizes a newly developed stimulation method (quadripulse stimulation (QPS)) to induce neural plasticity in the human brain.

What Is QPS? [1]

There are several stimulation methods to induce plastic changes in the human brain. QPS must be the most powerful and reliable one for human plasticity induction. Figure 1 shows the protocol of QPS, and Fig. 2 demonstrates a set of four stimulators for QPS. After baseline (motor evoked potential) MEP recordings, one session
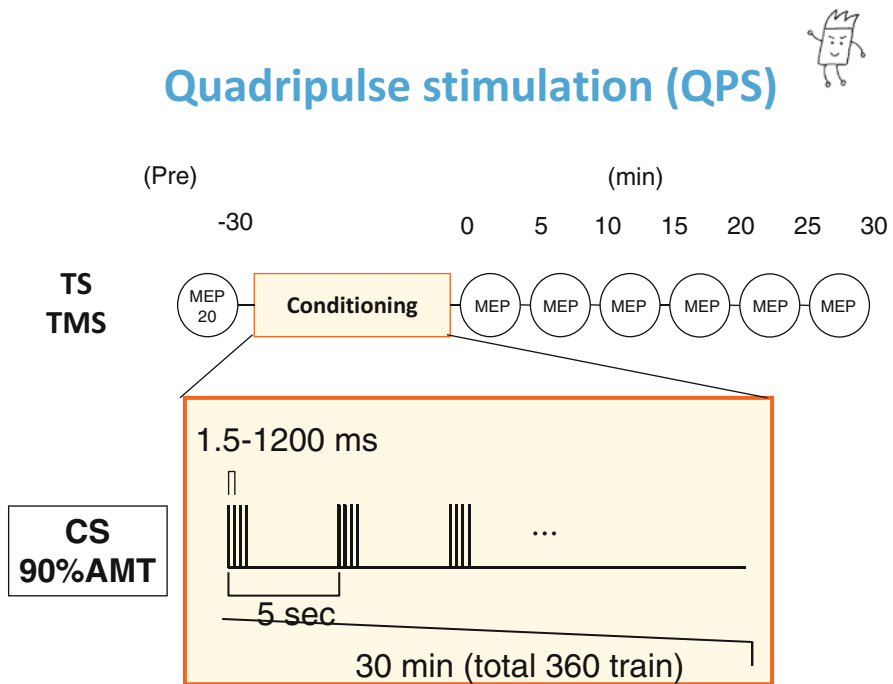

Fig. 1 QPS protocol

Fig. 2 Transcranial magnetic stimulator set up for QPS. Four monophasic magnetic stimulators are combined by a combine module

of QPS stimulation was performed and MEPs were followed by single-pulse transcranial magnetic stimulation (TMS) with the same intensity used in the baseline recordings (Fig. 1). In QPS, one stimulation burst consisting of four monophasic TMS pulses is given every 5 s for 30 min. In total, 360 bursts (1,440 pulses) are given in one session. The interval of TMS pulses was changed in different QPS conditioning sessions from 1.5 to 1250 ms. We evaluated the motor cortical excitability using the size of MEPs to TMS pulses at the same intensity.

Figure 3 shows typical MEPs before and after QPS5 (inter-pulse interval (IPI) 5 ms), QPS30, and QPS50. MEPs were enlarged after QPS5, whereas they were decreased in size after QPS30 and PQS50. After QPS, in total, the stimulated cortical area excitability is bidirectionally modulated depending on the interval of magnetic pulses in one burst. Short-interval QPS potentiates excitability, and longer-interval QPS depresses the target area. QPS at an interval of 5 ms (QPS5) induces long-term potentiation (LTP) most efficiently, and QPS50 induces long-term depression (LTD) most effectively in the human primary motor cortex (M1). Figure 4 shows the relation between the QPS effect and the IPI of TMS pulses, which fits well to the well-known Bienenstock–Cooper–Munro (BCM) curve. Their physiological characteristics, bidirectional modulation, dependence on the interval of pulses, and spatial specificity are all compatible with the plasticity reported previously. We conclude that QPS can induce neuronal plasticity in the human brain.

Plasticity in humans
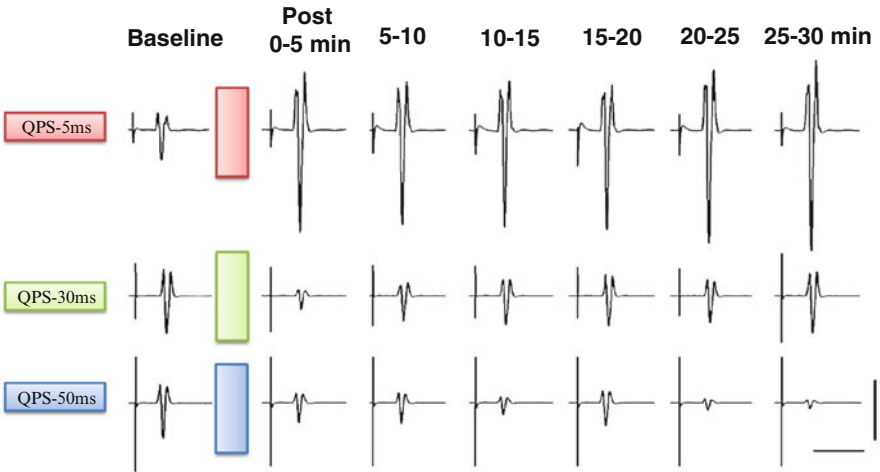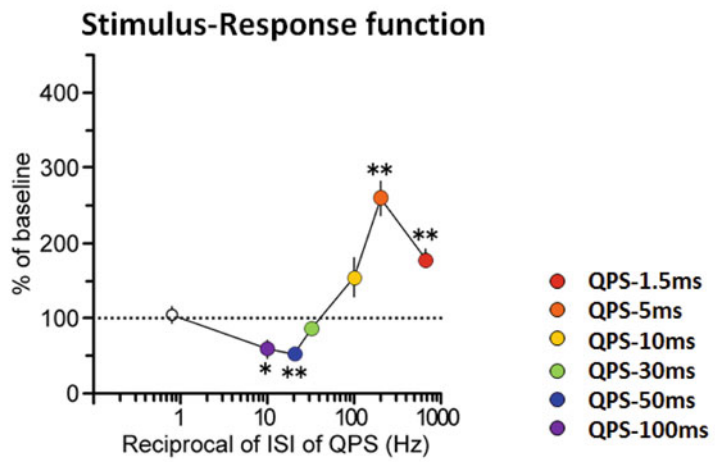# Quadripulse stimulation

Fig. 3 Typical motor evoked potentials (MEPs) in the QPS experiments. The *top row* are for QPS5, the *middle* for QPS30 and the *bottom* for QPS50. QPS5 prominently enhanced MEPs, and QPS30 or QPS50 depressed MEPs

Fig. 4 Correlation between the main effect and the reciprocal of the inter-pulse interval of QPS. This time course is almost the same the Bienenstock–Cooper–Munro (BCM) curve for synaptic plasticity

Mechanisms Underlying QPS [1]

To elucidate the mechanisms underlying QPS, we compared several physiological features between the baseline (before QPS) and after QPS. No changes were found in the threshold (Fig. 5a, d), GABAergic function of M1, or acetylcholine function. In contrast, both intracortical facilitation (ICF) and short-latency cortical facilitation (SICF) were bidirectionally modulated by QPS5 and QPS50 (Fig. 6a, b). Both of them may reflect glutamatergic EPSP summation. The sharpness of the IO curve was also bidirectionally modulated by QPS (Fig. 5c, f). The sharpness of the IO curve should also reflect the excitatory synaptic function of M1. These indicate that excitatory synaptic efficacy is bidirectionally modulated by QPS. Figure 5c, f show the special specificity of the QPS effect to the area conditioned by QPS. These are all consistent with the synaptic LTP/LTD (Fig. 7)

Nakatani-Enomoto et al. [2] supported the safety of QPS by recoding EEGs and measuring serum prolactin levels before and after QPS. Nakamura et al. [3] showed the independency of QPS effects on brain-derived nerve growth factor (BDNF)
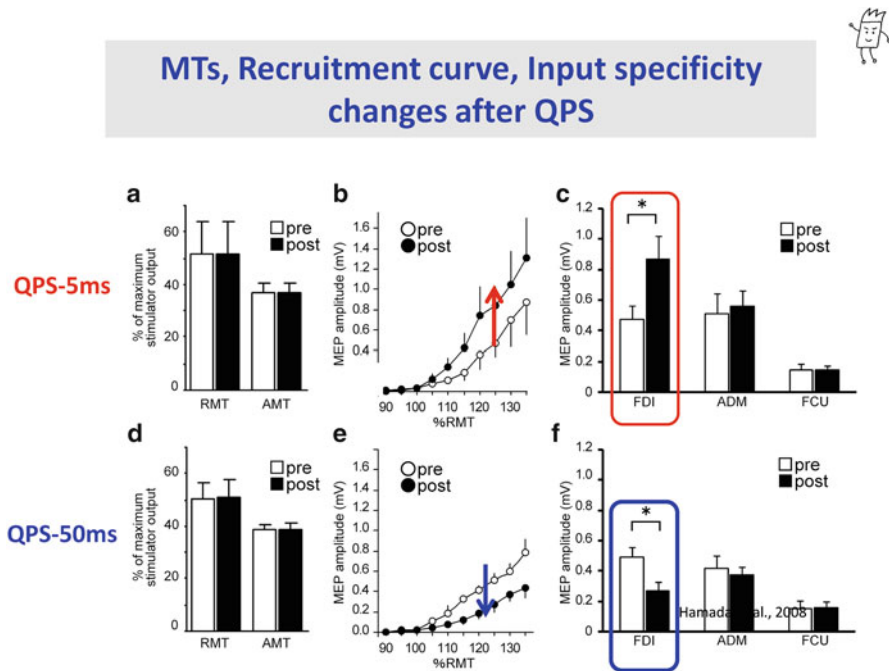

Fig. 5 Physiological characteristics before and after QPS. The threshold is shown in (**a**) and (**d**), the input-output curves in (**b**) and (**e**), and somatotopic specificity in (**c**) and (**f**). They revealed no changes in the threshold, bidirectional modulation of the IO curves, and somatotopic specificity to the target muscle. These are all consistent with bidirectional changes in the excitatory glutamatergic synapses
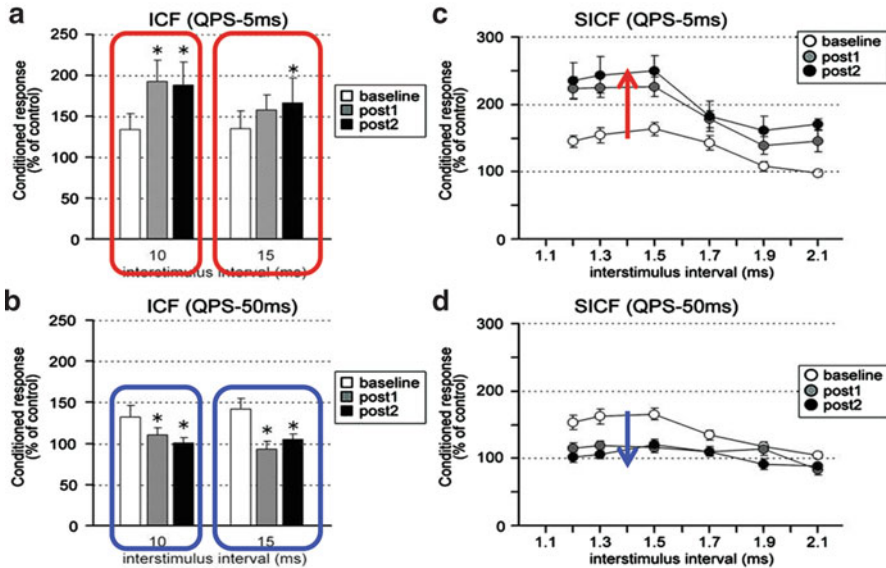
ICF (glutamate) and SICF (EPSP summation)

Fig. 6 Intracortical facilitation (ICF) and short-interval intracortical facilitation (SICF) before and after QPS. Both effects were bidirectionally modulated by QPS5 and QPS50. The results are all consistent with bidirectional modulation of glutamatergic synapses

Summary of Results

- **QPS at short intervals** ⟶ MEP↑, long duration (> 75 min)
- **QPS at long intervals** ⟶ MEP↓, long duration (>75 min)

- **MTs** ⟶ no change
- **MEPs at active** ⟶ QPS-short, ↑ ; QPS-long, ↓
- **Recruit curve** ⟶ bidirectional modulation
- **Input specificity** ⟶ FDI↑↓ , ADM no change
- **SICI** ⟶ no change
- **ICF, SICF** ⟶ bidirectional modulation
- **SAI, LAI** ⟶ no change

Fig. 7 Summary of physiological analyses of the mechanisms underlying QPS effects

polymorphism on which some plasticity induction methods depend. It is one superior point of QPS compared with other methods, especially when applying these methods to patients, because we do not need to consider BDNF polymorphism in judging the results in the patients.

Dopamine/Dopamine Agonists and Plasticity [5]

Dopamine/Dopamine Agonists in Normal Subjects [5]

It is well known that dopamine enhances both LTP and LTD, and the former is one of the D1 effects and the latter is a kind of D2 effect. To study the relation of dopamine or a dopamine agonist with QPS, we compared LTP/LTD effects between the conditions after placebo, L-Dopa, or pramipexole intake in normal volunteers. Figure 8 shows typical MEPs 30 min after QPS5 and QPS50 under the conditions
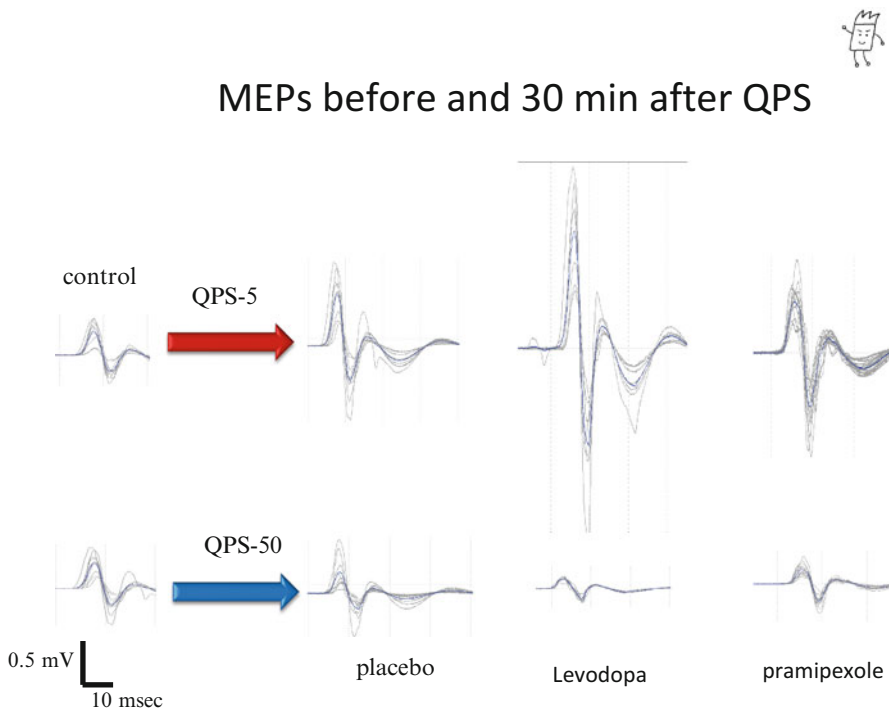

Fig. 8 L-Dopa or pramipexole influence on the QPS. The *left column* shows the baseline condition, the *other three rows* show MEPs 30 min after QPS5 or QPS50 after intake of placebo, L-Dopa, or pramipexole. L-Dopa enhanced both LTP- and LTD-like effects. In contrast, pramipexole did not affect QPS effects

of placebo, L-Dopa, or pramipexole intake. Under the placebo condition, QPS5 enlarged MEPs and QPS50 made them smaller, as shown above. Under the L-Dopa intake condition, both LTP-like and LTD-like effects were enhanced as compared with the placebo condition. In contrast, neither an LTP-like effect nor an LTD-like effect was modulated by pramipexole. This is again compatible with plasticity induction in animals. Pramipexole, almost purely a D2 agonist, may not enhance LTP because D1 activation strengthens LTP but D2 activation does not. It did not enhance the LTD-like effects, probably because both D1 and D2 coactivation is required for LTD [4].

Dopamine/Dopamine Agonists in PD

In PD patients, even at an early stage, QPS induced neither LTP nor LTD-like effects in the motor cortex. This lack of plasticity was normalized by L-Dopa intake in parallel with motor symptom improvements.

Meta-plasticity [6]

Flexibility plays critical roles in brain function, as shown above. However, flexibility or plasticity is sometimes harmful to the brain. Hyperpotentiation of the cerebral cortices may induce epilepsy, and excessive reward-seeking may produce an addiction to drugs or gambling. The brain, therefore, has several mechanisms to maintain the stable state to some extent. In other words, the brain is as flexible as possible, but within a certain safety range. To maintain this safety, the brain has meta-plasticity, which is called "plasticity of plasticity". The meta-plasticity function was studied with some priming stimulation over the primary motor cortex (M1), premotor cortex (PM), or supplementary motor cortex (SMA). Figure 9 shows the experimental protocol of the meta-plasticity experiment. Before the usual QPS experiments, we gave a priming stimulation for a short period (10 min), which had no influence on MEPs when given alone. Figure 10 shows the MEP time courses with and without priming stimulation (QPS5 for 10 min). In all QPS protocols, the QPS5 priming stimulation modulated the main QPS effects in the depressive direction. This is compatible with the meta-plasticity of animal experiments. It indicates that the human motor cortex has a safety-maintaining mechanism, just like animal M1.

Sensory Cortical Plasticity [7, 8]

The above studies were all done on M1. We studied the neural plasticity of the sensory cortex in humans, using sensory evoked potentials (SEPs). SEPs were bidirectionally modulated by QPS over M1. QPS5 over M1 potentiated SEPs and QPS50 depressed SEPs, but neither QPS5 nor QPS50 over the sensory cortex (S1) had any

M1 Priming effects on QPS-induced plasticity
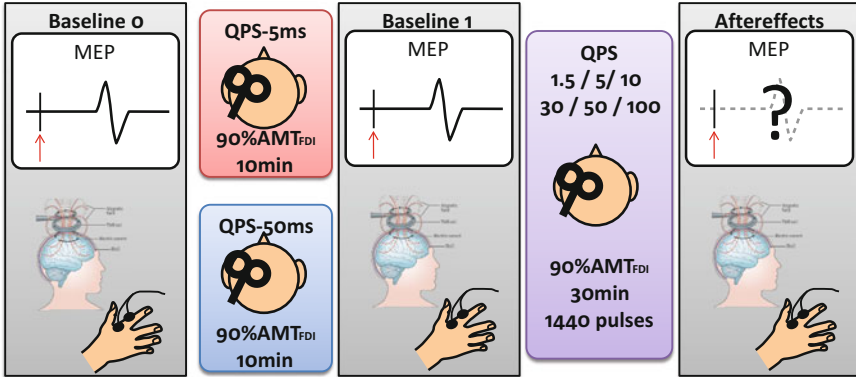

Fig. 9 Protocol for the meta-plasticity experiments
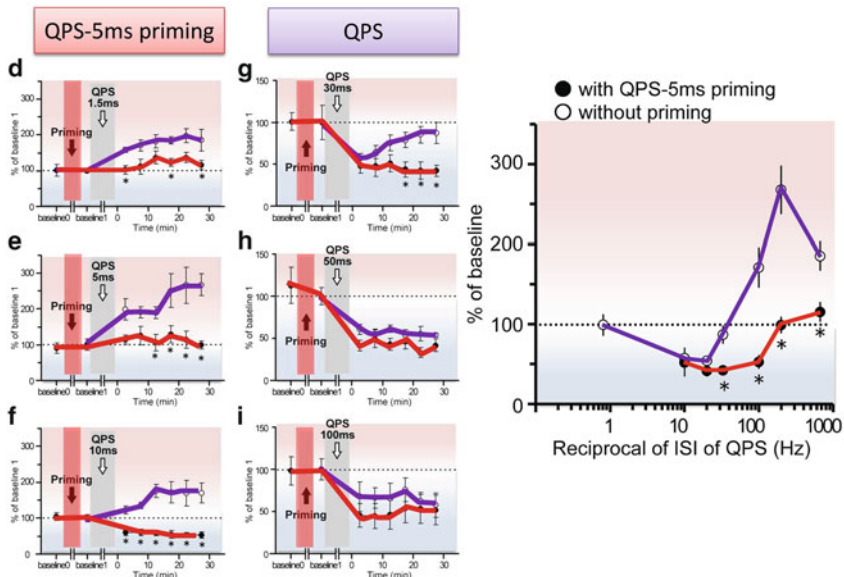

Fig. 10 Time courses of QPS 1.5, 5, 10, 30, 50, and 100 with and without QPS5 priming over M1. All time courses without priming (*purple*) were depressed by the QPS5 priming stimulation. The facilitatory priming stimulation depressed the main conditioning effects, which is compatible with the meta-plastic influence of the priming stimulation

influence on SEPs. This indicates that S1 is more influenced by motor cortical excitability changes than S1 excitability itself, through heterotopic synaptic plasticity. This finding may have some relation to sensory gating of motor performance. This directionality of sensory cortical plasticity was broken in myoclonus epilepsy patients. Any QPS protocols induced LTP-like effects in patients with cortical myoclonus but did not induce LTD. The safety-maintaining mechanisms may be broken in these epileptic disorders.

Axonal Plasticity in the Human Motor Cortex

All of the above works studied synaptic plasticity in the human brain, which is produced by synaptic efficacy changes without any axonal excitability changes (threshold for axonal membrane or the resting membrane potential). In some situations, axonal excitability changes are also induced in association with synaptic plasticity in animal experiments. We studied whether axonal plasticity is also induced in the human motor cortex after QPS over M1 using high-voltage electric stimulation (transcranial electrical stimulation (TES)) of M1. TES activates corticospinal tract axons directly, whereas TMS activates them through at least one synapse in M1 (Fig. 11). We compared the QPS effects on MEPs to TMS and those on MEPs to TES. QPS5 over M1 induced axonal depression in association with synaptic
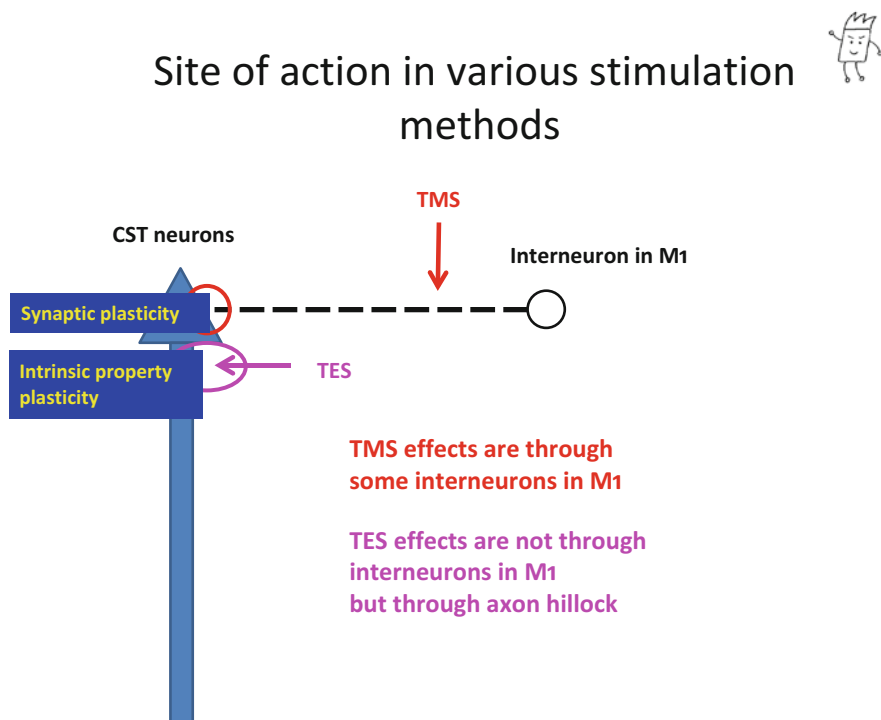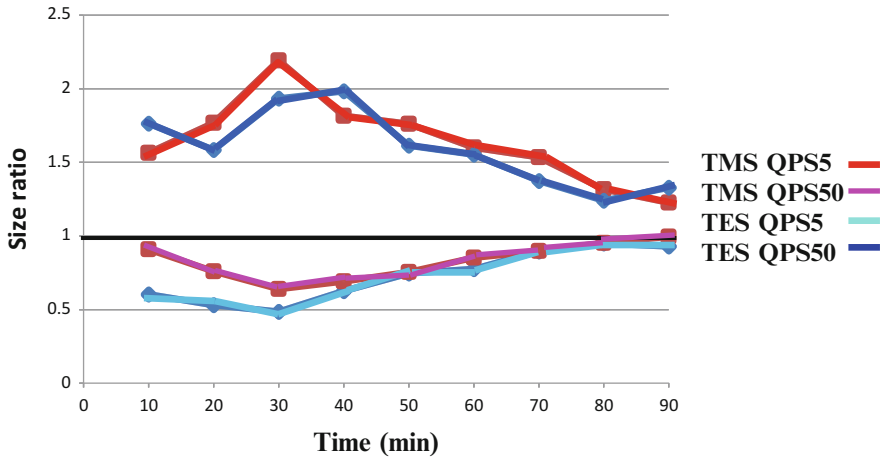

Fig. 11 Supposed activation sites in TMS and TES

Fig. 12 Time courses of MEPs to TMS and TES. QPS5 potentiated MEPs to TMS and depressed those to TES. Conversely, QPS50 depressed MEPs to TMS and potentiated those to TES

potentiation, and QPS50 induced axonal potentiation and synaptic depression (Fig. 12). This is the first report of axonal plasticity in the human brain.

Future Projects for QPS

We would like to finally use QPS for treatment of neurological and psychiatric disorders. Several projects are now ongoing, such as in Parkinson disease, depression, and cerebrovascular diseases. To show clinical efficacy of these methods as treatment, we need to take care of several points: what sham stimulation to use, axonal plasticity effects in addition to synaptic plasticity effects. We are also considering the effects on some distant areas after QPS in treatment applications [9]. I believe QPS will be used as some sort of treatment in the near future.

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