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PROMOTING PLASTICITY IN THE SOMATOSENSORY CORTEX TO ALTER MOTOR PHYSIOLOGY

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Abstract
Somatosensory pathways and cortices contribute to the control of human movement. In humans, non-invasive transcranial magnetic stimulation techniques to promote plasticity within somatosensory pathways and cortices have revealed potent effects on the neurophysiology within motor cortices. In this mini-review, we present evidence to indicate that somatosensory cortex is positioned to influence motor cortical circuits and as such, is an ideal target for plasticity approaches that aim to alter motor physiology and behavior in clinical populations.

Keywords
• Neural plasticity • Sensorimotor control • Transcranial magnetic stimulation (TMS)
• Clinical applications • Theta-burst stimulation (TBS) • Repetitive TMS (rTMS)

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1. Introduction

Challenges in the neural control of human movement are generally attributed to alterations in motor pathways and cortices. It is natural, therefore that clinical neurosciences have focused on motor pathways and/or motor cortices for the purpose of promoting neural plasticity and ultimately improving human movement. Commonly overshadowed is the role of somatosensory pathways and cortices in the neural control of human movement. Abnormalities in somatosensory processing contribute to impairments in motor control [1,2] and therapeutic approaches targeting somatosensory processing provide temporary improvements in motor function [3-5]. To date, clinical neuroscience research efforts directed at promoting plasticity in somatosensory paths and cortices are relatively sparse, yet this approach presents an opportunity to yield novel rehabilitation strategies that have the potential to improve human movement.

The ultimate goal of research in our laboratory is to translate fundamental science into clinically effective therapies aimed at improving motor control of the upper limb. We have capitalized on the use of plasticity-inducing transcranial magnetic stimulation (TMS) protocols to promote plasticity in somatosensory processing and have investigated their effects on neural output from motor cortices. This review begins with evidence demonstrating the influence of somatosensory cortex on motor cortical physiology and movement. Demonstrations of somatosensory cortical plasticity are discussed next. In the aforementioned sections we cite key findings from animal models that have established fundamental knowledge of the system and refer the reader to more extensive reviews on these topics. Last, we consider the clinical applications for promoting plasticity in the somatosensory cortices. The goal of this mini-review is to provide convincing evidence that somatosensory cortex influences motor physiology and behavior in an effort to capture new research interests that may capitalize on the propensity for plasticity in this area.

2. Somatosensory cortex influences motor cortical physiology and movement

2.1 Evidence from animal species

In non-human primates, the somatosensory cortex that is located in the postcentral gyrus is comprised of subareas 3a, 3b, 1 and 2 and each area contains distinct somatotopic maps of the body surface [1]. The term "SI" is typically used to describe area 3b only [2] so we refer to the collective subareas as "somatosensory cortex". Somatic input to area 3a is derived predominantly from muscle spindle receptors [3], while cutaneous inputs are primarily received by areas 3b [4] and 1 [5,6]. Area 2 receives input from both muscle [7] and cutaneous [8] sources. In monkeys, dense corticocortical connections exist between adjacent somatosensory and primary motor cortex (M1) [9,10]. All somatosensory subareas share anatomical connectivity with adjacent M1, with the exception of area 3b [11-14]. Somatosensory cortex also sends projections to interneurons in the dorsal and intermediate zone, and spinal motorneurons in the ventral horn [15].

The functional significance of the somatosensory-motor cortical interaction has been studied at great lengths in animal models and has led to different interpretations about the role of somatic cortex in motor control. Tetanic stimulation of cat somatosensory cortex leads to long-term potentiation (LTP) in M1 and is interpreted as a pathway important for motor skill learning [16,17]. Similarly, lesions in monkey somatosensory cortex impairs the acquisition of new motor skills but does not affect the performance of existing motor skills [18]. In monkeys at rest, cooling

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somatosensory cortex leads to an increase in the tonic firing rate of M1 neurons, an effect that is absent during movement. Further, following cortical cooling, forelimb movements are clumsy and ataxic providing evidence for a direct role for somatosensory cortex in the control of movement [19]. Microstimulation of somatosensory neurons demonstrate greater inhibitory versus facilitatory effects on muscle activity suggesting that somatosensory cortex has an inhibitory influence on motor physiology, and potentially a minimal role in the direct control of muscles [20]. However, somatosensory cortex is necessary for coordinated finger movement as demonstrated following injections of GABA agonist muscimol into somatic cortex [21].

2.2 Evidence from humans

2.2.1 Influence of somatosensory cortex on motor cortical physiology

Similar to monkey species, human primary somatosensory cortex (which we refer to as SI) appears to have at least four subareas that demonstrate evidence of somatotopic ordering for digits of the hand [22]. Investigations of the influence of SI on M1 physiology have benefited from advances in TMS plasticity-promoting protocols used to temporarily modify neural activity in SI and measure neural effects from M1.

Continuous theta-burst stimulation (cTBS) induces long-term depression (LTD)-like effects in targeted cortex [23], and in human applications involves a triplet of TMS pulses at 50 Hz [24] or 30 Hz [25] delivered at 5 Hz theta frequency. The motor evoked potential (MEP) evoked by a single suprathreshold TMS pulse is an index of M1 corticospinal excitability reflecting neural activity of corticospinal and spinal motorneurons, and is one measure typically obtained before and following plasticity-promoting protocols. Our lab has repeatedly demonstrated that cTBS at 30 Hz over SI leads to increased M1 corticospinal output as measured by greater MEP amplitude (i.e. LTP-like effects) for up to one hour following stimulation [26,27]. In contrast, cTBS over M1 leads to suppression of corticospinal output (i.e. LTD-like effects) that persists for about 30 minutes [26,27]. It is notable that cTBS over SI delivered at 50 Hz does not always lead to LTP-like effects [28,29] and the direction of induced current appears to be an important consideration [30]. Short-latency afferent inhibition (SAI) is a sensorimotor circuit whereby the amplitude of the MEP is suppressed by an afferent volley elicited by peripheral nerve stimulation ~20 ms in advance of the TMS pulse [31]. SAI is reduced prior to and during movement [32] with effects that depend on the specific digit being moved [33]. cTBS over SI leads to a reduction in the SAI circuit for ~45-60 minutes following stimulation, while cTBS over M1 does not alter the magnitude of SAI [27].

The mechanism by which altering excitability in SI modulates M1 physiology remains unknown. In monkeys, tetanic stimulation of somatosensory cortex evokes LTP in M1 laminae II/III [34]. In humans, excitatory neurons in the aforementioned laminae are considered responsible for generating the TMS evoked MEP [35]. Therefore, one possible mechanism by which SI alters M1 physiology in our studies involves SI induced LTP in laminae II/III M1 neurons.

Importantly, we have also demonstrated a lack of somatosensory influences via cTBS on M1 intracortical circuits of inhibition (short-interval intracortical inhibition) and facilitation (intracortical facilitation) [26,36]. Collectively, these data indicate that altering the excitability within SI induces LTP-like effects in selected cortical circuits and therefore offers an opportunity to promote circuit-specific plasticity in M1 (see Figure 1).

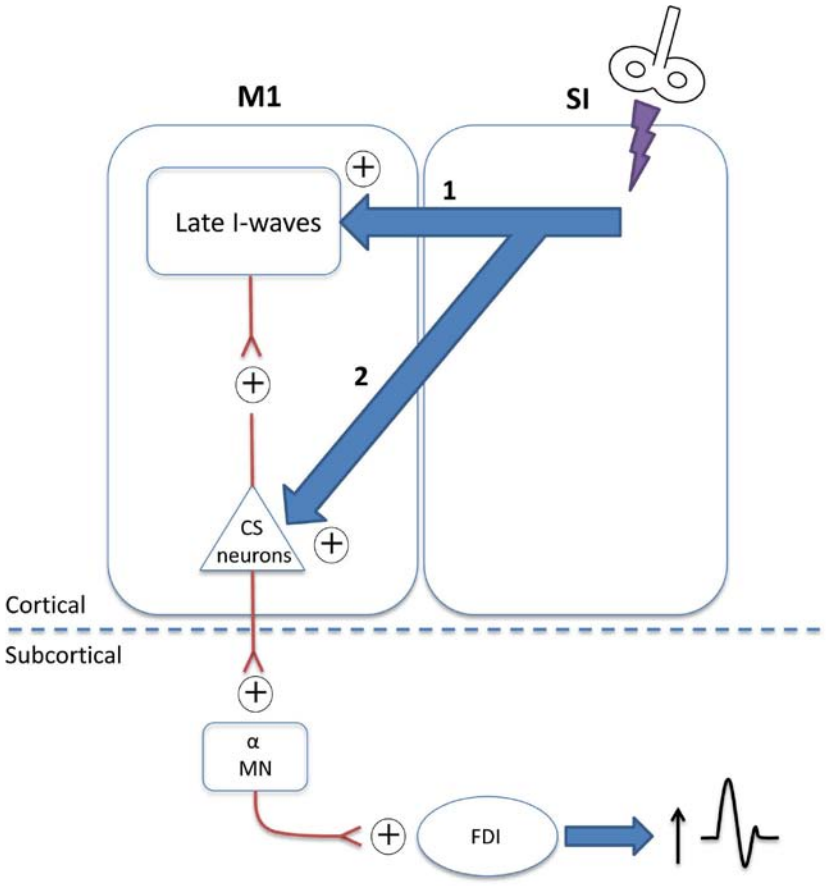

Figure 1. Putative mechanisms following continuous Theta Burst Stimulation (cTBS) over SI. Pathway 1 shows facilitation of late I-waves resulting in a reduction of short-latency afferent inhibition (SAI). Both pathways 1 and 2 result in a net facilitation of corticospinal (CS) neurons and the α-motorneuron (MN) pool causing increased excitability and a subsequent increase in Motor Evoked Potential (MEP) amplitude. M1 = primary motor cortex, SI = primary somatosensory cortex, FDI = First Dorsal Interosseus muscle.

2.2.2 Influence of somatosensory cortex on motor behavior

Multiple studies have investigated the relationship between M1 and SI using a variety of imaging techniques. Individuals with cerebrovascular lesions affecting SI are significantly less accurate performing finger movements compared to uninjured controls [37]. Functional magnetic resonance imaging (fMRI) studies, including those of healthy and clinical populations, demonstrate that M1 and SI share similar patterns of activation in real and imagined movements [38,39]. Somatosensory evoked potential (SEP) components N20 and P22 are larger when evoked from the Braille reading finger compared to the homologous digit on the opposite hand [40]. Further, activity within SI is strongly modulated by the occurrence of passive hand movement [41], illusory palmar flexion [42], and haptic exploration [43] suggesting a significant role of SI during movement.

The influence of SI on motor behavior has been investigated with various TMS plasticity-inducing protocols. Participants were tested across multiple days in their ability to accurately track a dot target on a computer monitor by simultaneously moving their wrist to control a digital representation of their position. Following practice, low-frequency repetitive TMS (rTMS) was applied over SI in the experimental group. Although both control and experimental groups showed improvements in the task after practice, the experimental group performed significantly worse [44]. In contrast, intermittent theta-burst stimulation (iTBS), thought to promote LTP-like effects when delivered over M1 [24] did not alter motor performance during maximal grip force or in tapping or aiming tasks, when applied over SI [45]. A likely explanation for the difference between outcomes in the above studies is the nature of the LTD versus LTP- inducing protocols. However, as suggested by the authors [44], differences in experimental setup, including the complexity of the motor tasks and whether or not vision was present to supplement somatosensory information, may also contribute to the observed difference between outcomes [44].

Recently, cTBS has been applied as a technique to disrupt individual areas of the brain during, rather than after the period of task practice. cTBS over M1 and other motor brain regions resulted in subjects being able to accurately complete some but not all of the tasks within the individual arm ability training task training program. However, when cTBS was applied over SI, subjects showed significant difficulties in tasks involving dexterity, tracking and aiming, suggesting a vital role for SI in motor behavior [46].

2.2.3 Evidence from movement disorders

Emerging evidence from clinical disorders affecting movement indicate that abnormalities in somatosensory processing may contribute to impairments in motor control. Focal hand dystonia (FHD), a movement disorder affecting volitional control of the hand, demonstrates impairments in somatosensory percepts. Temporal discrimination thresholds occur in 40 - 69 ms in healthy controls and require 100 - 155 ms in FHD [47-49]. Similarly, spatial processing of tactile information is abnormal such that gap detection and point localization thresholds are higher [47] and patients show compromised ability to determine the orientation of fine spatial gratings [48]. Aberrations in somatotopy also exist in FHD indicating reduced inter-digit spacing and abnormalities in the topographic ordering [50-52]. In addition to FHD, alterations in touch perception in Parkinson's disease [53,54], abnormal sensory gating in Tourette's [55], and reduced SAI sensorimotor circuitry in restless legs syndrome [56] all provide evidence for a role for somatosensory processing in the control of movement. We refer the reader to excellent in-depth reviews detailing somatosensory abnormalities in movement disorders [57,58]. Collectively, there are compelling examples of aberrations in the somatosensory system in disorders affecting movement, which suggest that such sensory abnormalities may directly contribute to motor symptoms.

3. Somatosensory cortex as target for inducing plasticity

3.1 SI plasticity in animal models

There is substantial evidence from animal models to indicate a propensity for plasticity in somatosensory cortex and we select only a few examples from this rich literature (for excellent reviews, see [59-61]). Decades of primate research have demonstrated alterations in somatotopic representations that follow experience or practiced behavior [62,63], cognitive factors of learning and attention [64-67], and lesions or manipulations of the peripheral or central nervous system [6,68,69]. Rapid cortical plasticity is observed in rat and monkey species following direct microstimulation of somatosensory cortex, which leads to immediate increases in the cortical representation of the respective skin site [70]. Further, immediately following amputation, somatosensory cortical neurons are responsive to adjoining body parts [71-73]. Reversible sensory deactivation with a peripheral lidocaine block in rats leads to rapid unmasking of responses at subcortical and cortical levels [74]. Peripheral stimulation leads to increases in receptive field sizes within one hour of stimulation [75].

It is notable that fundamental differences in plasticity may exist between somatosensory cortex and M1. In rats, both loci demonstrate short-term depression, short-term facilitation and LTD. However, LTP was shown to be easily and reliably evoked in somatosensory cortex and not M1, irrespective of the theta-burst frequency tested [76], suggesting a fundamental difference in the propensity for LTP between these loci. Excellent reviews on the neural basis of LTP and LTD in animal models are available [77-79].

3.2 SI plasticity in humans

At the level of the synapse, LTP and LTD result from the pattern of postsynaptic Ca^{2+} influx with the former achieved by high transient influx and the latter by lower, consistent currents [80]. Homosynaptic plasticity refers to changes in synaptic efficiency that are consequence of a neuron's own activity. Heterosynaptic plasticity refers to changes in efficiency as a consequence of another pathway. Animal models of homosynaptic and heterosynaptic LTP and LTD induction have instructed TMS-based approaches for inducing plasticity-like effects in humans (see Figure 2 for examples).

Several rTMS protocols have been developed to promote homosynaptic plasticity within targeted cortex. Rapid changes in touch perception and physiology occur following homosynaptic rTMS protocols over SI. Low-frequency, sub-threshold rTMS over SI increases tactile thresholds, causing a decrease in the ability to detect cutaneous stimuli [81]. A similar increase in tactile threshold is observed at similar frequencies using supra-threshold rTMS intensities [44,82]. In contrast, high-frequency rTMS (5 Hz) over SI decreases tactile discrimination thresholds [83] and also results in temporary changes in the somatotopic organization of SI [84,85]. iTBS over SI results in both an improvement in 2-point discrimination [45] and temporal discrimination. In contrast, cTBS over SI results in the opposite effect, showing a worsening in temporal discrimination [86]. Thus, after iTBS, subjects were more able to discriminate between two closely timed cutaneous stimuli and with cTBS subjects were less able to discriminate between the same stimuli [86]. iTBS over SI also increases the amplitude of the N20-P25 somatosensory evoked potentials (SEP) indicating physiological changes following stimulation [87].

Spike timing dependent plasticity is supported by increases or decreases in synaptic efficiency that relies on the temporal sequence of pre- and postsynaptic inputs to a neuron. Paired Associative Stimulation (PAS) is a form of TMS heterosynaptic plasticity founded in the principles of spike timing dependent plasticity [80]. In PAS, electrical stimulation of a nerve is paired repeatedly with single TMS pulses typically over the cortex [88]. If the two inputs are delivered such that the afferent impulse from electrical stimulation reaches the cortical neurons with their simultaneous activation by the TMS pulse (~20 ms for TMS targeting SI), increases in the corticospinal output are observed and LTP-like effects are thought to mediate the change [88,89]. The assumption underlying PAS effects is that nerve stimulation and the TMS pulse both evoke inputs onto a common neuronal population that ultimately demonstrates short-term associative synaptic plasticity due to the repeat pairing of separate inputs. PAS targeting SI yields increases in the P25 component of the SEP [90,91], suggesting

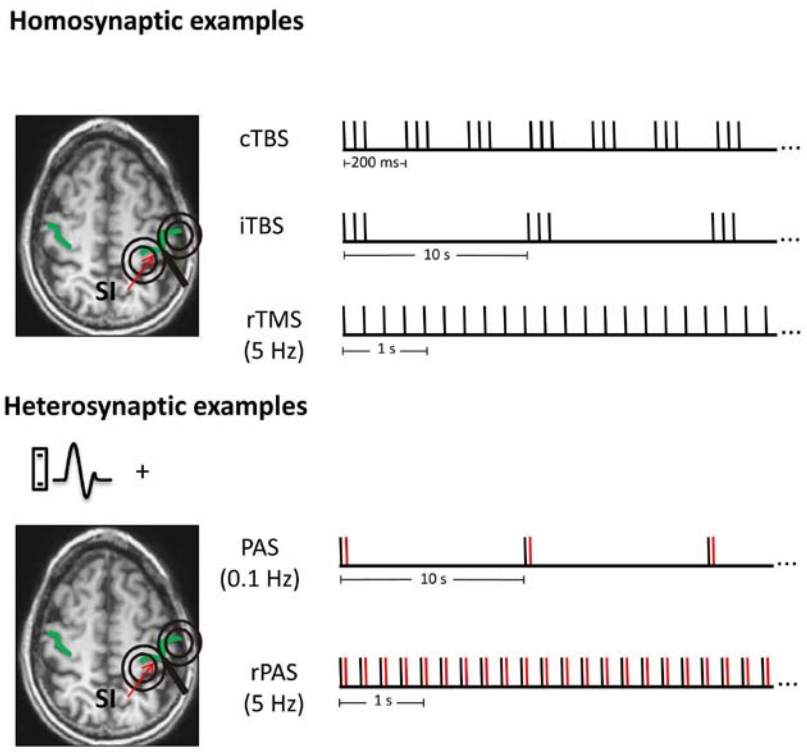

Figure 2. Schematic of Transcranial Magnetic Stimulation (TMS) protocols used in studies to promote plasticity in primary somatosensory cortex (SI). Left, homosynaptic protocols utilize TMS only to produce long-term potentiation (LTP)-like effects in SI and heterosynaptic protocols combine both TMS and peripheral nerve stimulation at varying inter-stimulus intervals. Green outline indicates the central sulcus on example anatomy. Right, black lines represent TMS stimulator pulses and red lines represent nerve stimuli. cTBS = continuous Theta-Burst Stimulation, iTBS = intermittent Theta-Burst Stimulation, rTMS = repetitive Transcranial Magnetic Stimulation, PAS = Paired Associative Stimulation, rPAS = repetitive Paired Associative Stimulation.

synaptic plasticity in layers II/III within SI [92,93]. Depression of the P25 component, however, was seen at an interstimulus interval of 20 ms, relative to the N20 component of each individual, suggesting that PAS yields bidirectional excitability, dependent on the timing of inputs [83].

4. Clinical applications for promoting plasticity in SI

Below we discuss evidence of plasticity-inducing TMS approaches targeting somatosensory processing in two clinical populations where somatosensory processing has been emphasized.

4.1 Stroke

SI has been shown to be a target for inducing plasticity to improve motor control following stroke. In rats with M1 infarcts, plasticity induced by prosthetics implanted in SI promote functional connectivity with residually functioning motor areas and improve motor skill recovery [94]. Much human research has been performed in the area of stroke rehabilitation showing that relatively non-invasive protocols can have marked changes in motor control. Based on research showing that applying a peripheral nerve stimulus to the skin results in increased activation of SI in healthy participants [95-99], the same technique has been used in stroke survivors. In addition to increasing excitability, conditioning with a peripheral stimulus prior to learning various motor tasks results in a heightened ability to complete these tasks [100].

Applying cTBS either over M1 or SI contralateral to the site of the lesion results in improved ability of post-stroke individuals to complete a targeting task. Participants moved

a computer mouse cursor to align with on-screen targets after cTBS was applied to either M1 or to SI. Stimulation over M1 resulted in an improvement in the early stages of the movement, and stimulation over SI resulted in a decreased time needed to complete the overall movement [101]. It is notable that only after the SI cTBS intervention did participants show significant improvement in completing basic tasks such as picking up a paperclip or folding a towel [101]. In a more recent study, 5 Hz rTMS applied over SI ipsilateral to the lesion led to improvements in motor learning and tactile discrimination [102].

4.2 Dystonia

Studies in dystonia have shown significant success in utilizing TMS plasticity protocols in order to reduce symptoms. Early research showed improvements in handwriting and writing pressure after low-frequency rTMS was applied to M1 [103] and premotor cortex [104], suggesting that multiple regions of the brain contribute to this form of dystonia.

Based on considerable evidence showing changes in the activation and organization of SI in individuals with dystonia [50,105-108], some research focus has shifted from M1 to SI as a potential target for therapeutic approaches. Low-frequency rTMS over SI applied for 30 minutes over 5-days in individuals with writer's dystonia resulted in significant improvement in writing as rated by both independent blinded raters and the participants themselves. Positive changes persisted during the 5-day testing period and for 3 weeks after the procedure [109]. When asked to perform an active movement of the fingers in the dystonic right hand, concurrent fMRI showed that rTMS over left SI results in increased activation of SI as well as surrounding cortical areas [109].

In another study, experimenters looked at performance on a purely sensory task following the application of high-frequency rTMS [110]. Those with writer's dystonia showed no change in performance on a frequency discrimination task, while controls showed improvement. fMRI analysis highlighted differences in activation patterns in the basal ganglia between dystonia patients, who showed no increased activation, and controls who exhibited significant activation of this region. It was proposed that the basal ganglia are indirectly activated by the directly stimulated SI, and in those with dystonia, these indirect connections are altered resulting in limited or no activation [110].

TBS has recently been applied to SI in controls and FHD, showing that iTBS and cTBS improved and reduced temporal discrimination performance in both groups, respectively, and to a similar extent. However, the ability to write was not improved in FHD [86]. This finding is significant as it suggests that the circuitry involved in this type of sensory discrimination task has a similar response to TBS plasticity protocols in both FHD and healthy populations.

5. Future considerations for studies aiming to promote plasticity in human SI

The ethics surrounding attempts to promote plasticity in the healthy, uninjured individual remain controversial. Approaches using TMS to promote plasticity in uninjured controls typically involve a single session of stimulation, since there is no apparent desire to induce more permanent plasticity in such individuals. However, the results of a single session of a TMS plasticity protocol applied in controls are often used to devise clinical trials in which multiple sessions are delivered in a clinical population for the direct purpose of promoting plasticity. In such attempts, there are unresolved issues that surround the anticipated metaplastic effects (i.e. beneficial versus maladaptive plasticity) and whether plasticity effects are greater or less than that which could be obtained from an uninjured, control group. However, recent TMS studies in uninjured controls are focused on quantifying metaplasticity effects following the delivery of two or more TMS plasticity-promoting protocols [111,112]. Further, TMS plasticity approaches have effects at remote loci, which need to be considered when interpreting effects [113]. Such studies will be instrumental for predicting plasticity effects, deleterious or not. Future clinical studies may consider measuring outcomes upon the addition of each subsequent TMS session, which may indicate the precise number of repeat sessions required to generate the desired effects.

6. Conclusion

In this mini-review we have presented animal and human evidence in favor of a powerful somatosensory cortical influence on motor cortical physiology and behavior. Somatosensory cortex exhibits a propensity for plasticity with injury or experience that can occur on rapid timescales. As such, SI in humans is an excellent candidate for promoting plasticity for the purpose of altering human movement. We have considered only clinical applications of FHD and stroke yet other populations including spinal cord injury, autism, Parkinson's and others may benefit from plasticity promoted in somatosensory cortex.

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