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Excitatory and Inhibitory Effects of Transcranial Magnetic Stimulation

ZHEN NI, ROBERT CHEN*

Division of Neurology, Department of Medicine, University of Toronto and Toronto Western Research Institute, Krembil Neuroscience Centre, University Health Network, Toronto, Ontario, Canada

This paper reviews the use of transcranial magnetic stimulation (TMS) in investigating intracortical circuits in the primary motor cortex (M1). TMS is a noninvasive and painless method of stimulating the human brain and has become a widely used technique in neurophysiology and neurology. When TMS is applied to the M1, it generates a motor evoked potential (MEP) in the target muscles. TMS also activates different intracortical circuits within the M1 and connections from other cortical areas to the M1. These intracortical circuits interact with each other. Abnormalities in these circuits are found in neurological and psychiatric disorders and studies of these circuits are useful in understanding the pathophysiology of these conditions.

K e y w o r d s: transcranial magnetic stimulation, primary motor cortex, motor evoked potential, intracortical circuit, inhibition and facilitation

1. Introduction

There is a long history of scientists using magnetic fields to study the human brain. French physicist and physician, Jaques-Arsène d'Arsonval, was a pioneer on the application of magnetic fields. In 1896, he successfully produced visual effects using a high magnetic field (1.8 Tesla). Moving through the magnetic field or changing the intensity of the magnetic field produced the sensation of flashes of light due to electrical current induced in the retina. Later studies confirmed that these visual sensations (phosphenes) can be evoked with different stimulus parameters [1]. In 1985, Barker et al. [2] used transcranial magnetic stimulation (TMS) to stimulate the human primary motor cortex (M1). Since then, TMS has become a widely used

* Correspondence to: Robert Chen, 7MC-411, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, M5T 2S8, Canada, e-mail: robert.chen@uhn.on.ca
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method in neurophysiology and neurology because it is noninvasive and painless. When TMS is applied to M1, it activates facilitatory interneurons, which in turn discharge corticospinal neurons and generates motor evoked potentials (MEP) in the target muscles. Besides this facilitatory effect, TMS can also activate the neural circuits within or outside M1. In this article, we will review recent studies of these inhibitory and facilitatory circuits within M1 and from other cortical areas to M1. These circuits are often investigated by paired-pulse TMS paradigms. Furthermore, these neural circuits interact with each other. We will also review studies of these interactions using triple-pulse TMS paradigms. In addition, we will discuss the findings in the patients with Parkinson's disease (PD), Alzheimer's disease (AD) and dystonia.

2. Intracortical Circuits within M1

Intracortical circuits can be investigated by a paired-pulse TMS paradigm with a conditioning stimulus (CS) followed by a test stimulus (TS) (Table 1) [3]. The MEP amplitudes generated by the CS followed by the TS are compared to the MEP amplitudes generated by TS alone. The paired-pulse induced MEP amplitudes vary with the CS intensity, the location of CS, the interstimulus interval (ISI) between CS and TS, the TS intensity and other factors such as voluntary contraction.

2.1. Short Interval Intracortical Inhibition and Facilitation

The first intracortical circuits identified by paired-pulse paradigm are those mediating short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). A preceding subthreshold CS inhibits the MEP induced by a suprathreshold TS at ISIs of 1–5 ms and this is named SICI. On the other hand, facilitation occurs at ISIs of 7–30 ms and is termed ICF (Fig. 1). This paradigm explores the intracortical inhibitory and facilitatory neural circuits in the M1 [4]. Although the subthreshold CS does not discharge the corticospinal neurons, it activates the inhibitory or facilitatory interneurons in M1. There are two phases of SICI, peaking at ISIs of ~1 ms and 2.5 ms respectively. SICI at 2.5 ms is likely mediated by gamma-aminobutyric acid type A ($GABA_A$) receptors because drugs that enhance $GABA_A$ increase SICI [5]. It has been proposed that SICI at 1 ms is due to the refractoriness of the cortical neurons [6]. However, SICI at 1 ms increases when the MEP size induced by TS is raised from 0.2 to 1 mV. It was argued that synaptic inhibition also contributes to SICI at 1 ms because stronger TS should activate more corticospinal neurons and overcome the refractory period, which should lead to less inhibition [7]. Additional evidence comes from the observation of SICI during the cortical silent period (SP). The SP is a period of suppression of voluntary EMG activity following a suprathreshold TMS (see below). It was

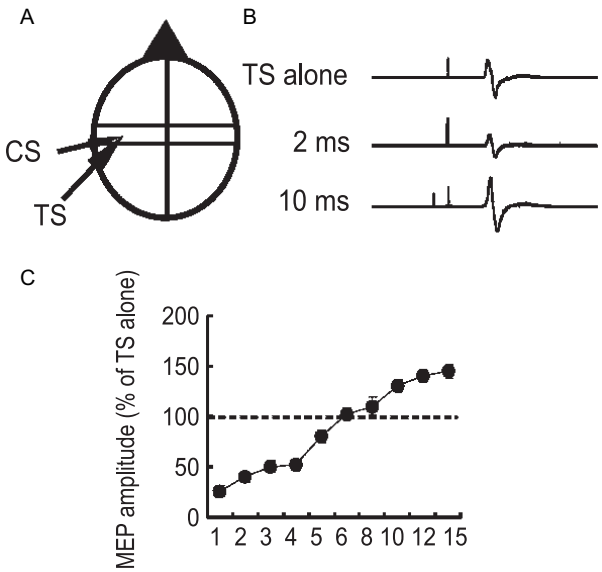

Fig. 1. Example of paired-pulse TMS paradigm investigating short interval intracortical inhibition and facilitation in the motor cortex. **(A)** The brain areas stimulated. Short interval intracortical inhibition (SICI) and facilitation (ICF) can be elicited by a subthreshold conditioning stimulus (CS) and a suprathreshold test stimulus (TS) delivered to the motor cortex. **(B)** Recordings from a representative subject. The top trace shows MEP produced by single pulse TMS (TS alone). The middle trace shows SICI elicited by paired-pulse (CS followed by TS) at interstimulus interval (ISI) of 2 ms. The bottom trace shows ICF elicited by paired-pulse at ISI of 10 ms. **(C)** Group data from 10 subjects for SICI/ICF at different ISIs. The dashed line indicates the MEP amplitude generated by TS alone (100%). Values below 100% represent inhibition and values above 100% represent facilitation. Modified from Ni & Chen (2009) [3]

reported that SICIs both at 1 ms or 2.5 ms decrease to a similar extent during the SP when refractory period should not be affected [8].

The mechanism mediating ICF remains unclear. Excitatory glutamatergic interneurons in M1 may be responsible for ICF [9]. However, subcortical and spinal activities may also influence ICF [10]. SICI is abnormal in several neurological disorders. In PD patients, reduction in SICI at ISIs of 1–5 ms with improvement after dopaminergic medication has been reported [11] but some studies found normal SICI [12]. In addition, reduced SICI was observed in dystonia and AD [13, 14]. ICF is normal in these patients.

2.2. Long Interval Intracortical Inhibition

With a suprathreshold CS applied 50–200 ms prior to the TS, the test MEP is inhibited. This type of inhibition is referred to as long interval intracortical inhibition (LICI) [15]. LICI at ISIs longer than about 50 ms is likely mediated within M1 rather than

at subcortical levels [16]. Pharmacological studies suggest that LICI is likely mediated by $GABA_B$ receptors [17]. $GABA_B$ – mediated intracortical circuit(s) can also be activated by a single pulse TMS. When a suprathreshold TMS pulse is applied to a contracting muscle, there is a period of suppression of the background EMG activity following the MEP, known as silent period (SP). Proprioceptive input induced by muscle twitch associated with the MEP plays no major role in generating the SP [18]. Although the early part of the SP is in part related to spinal inhibition, the later part is related to the interruption of voluntary drive at the cortical level. This was confirmed by testing the spinal motoneuron pools during the SP with H-reflex [19]. It is likely that the SP is mediated by $GABA_B$ as administration of $GABA_B$ receptor agonist baclofen [20] and GABA uptake blocker tiagabine [17] resulted in prolongation of the SP induced by TMS. The SP was found to be prolonged in some patients with stroke [21] and shortened in PD [22] and dystonia [23].

2.3. Short Interval Intracortical Facilitation

When a suprathreshold first stimulus is followed by a slightly subthreshold or threshold second stimulus at certain ISIs, the test MEP induced by the first stimulus is facilitated. This is referred to as short interval intracortical facilitation (SICF). Effective ISIs for SICF are 1.1–1.5 ms, 2.3–3.0 ms and 4.1–4.5 ms [24]. Because differences among these ISIs are similar to the intervals (~1.5 ms) of different indirect (I) waves recorded from implanted epidural electrodes, it is suggested that SICF is due to the interactions of I-waves generated by the two stimuli [24]. SICF originates in the cortical level because there is no facilitation if electrical stimulation, rather than TMS, is used to elicit the second stimulus and the facilitation is associated with increased amplitudes of the I waves generated by the first stimulus [24]. Application of $GABA_A$ agonists decreases SICF, suggesting that GABAergic activity may involve in SICF [25].

3. Intracortical Circuits from Other Cortical Areas to M1

Intracortical circuits from other cortical areas to M1 can also be investigated by a CS-TS TMS paradigm. Usually, two TMS coils are used. The CS is applied to different cortical areas depending on the intracortical circuits being investigated. TS is applied to M1 with a different coil. The MEP amplitude generated by CS followed by TS is compared to that generated by TS alone to test for inhibition or facilitation at the M1.

3.1. Short and Long Latency Interhemispheric Inhibition

Interhemispheric inhibition (IHI) refers to the neurophysiological mechanism in which one hemisphere inhibits the opposite hemisphere (Fig. 2A). With a paired-

pulse paradigm, it was found that a preceding CS applied to M1 inhibits the MEP generated by a TS applied over the contralateral M1 at ISI of ~10 ms (short latency IHI; SIHI) [26] and ~40 ms (long latency IHI; LIHI) [27, 28]. Studies in patients with cortical and subcortical infarction [29], and studies of the ipsilateral silent period in patients with agenesis of the corpus callosum [30] support the view that IHI

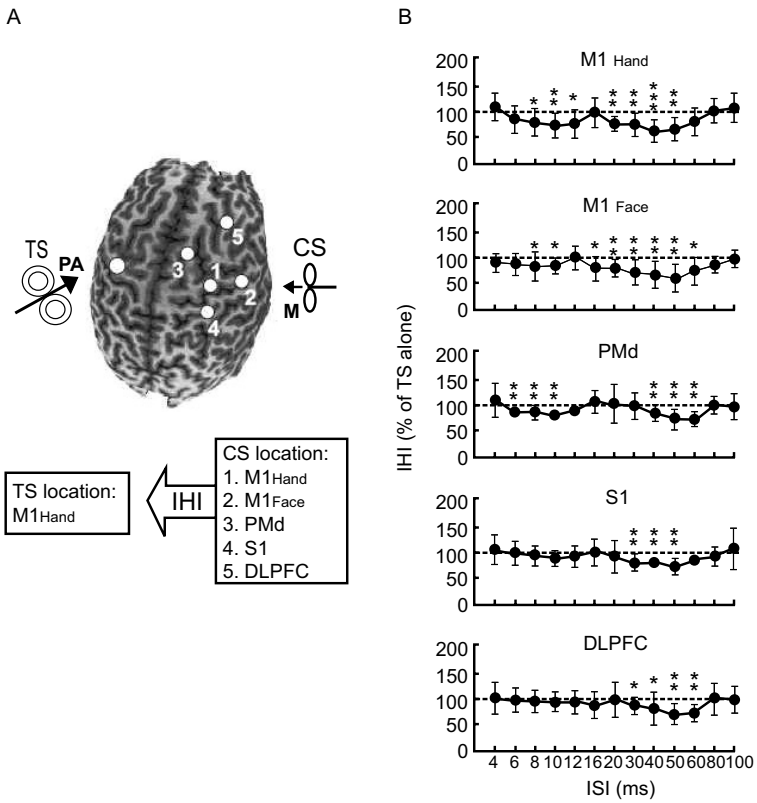

Fig. 2. Example of paired-pulse TMS paradigm for investigating intracortical inhibitory circuits projecting to motor cortex (interhemispheric inhibition). **(A)** Experimental setup. A conditioning stimulus was applied to one of the different sites in the right hemisphere shown as five white dots. They are the hand muscle representation in M1 ($M1_{Hand}$, 1), facial muscle representation in M1 ($M1_{Face}$, 2), dorsal premotor cortex (PMd, 3), somatosensory cortex (S1, 4) and dorsolateral prefrontal cortex (DLPFC, 5). The test stimulus (TS) was applied to the hand representation (shown in white dot) of the left M1. **(B)** The time courses of interhemispheric inhibition (IHI; group data from 12 subjects) from five different cortical areas to the contralateral M1. The abscissa indicates the interstimulus interval (ISI). The ordinate indicates the amplitude of conditioned MEP as a percentage of the MEP amplitude from TS alone. The dashed lines indicate the MEP amplitude generated by TS alone (100%). Values below 100% represent inhibition and values above 100% represent facilitation. There are two phases of IHI with maximum inhibition at ISIs of ~10 and ~50 ms for $M1_{Hand}$, $M1_{Face}$ and PMd. For S1 and DLPFC, the early phase of IHI is absent and only the late phase is evident. $*P<0.05$, $**P<0.01$, $***P<0.001$, compared to TS alone. Modified from Ni et al. (2009) [35]

is produced via a transcallosal pathway. Direct evidence that IHI involves cortical inhibition was obtained from the recordings of descending corticospinal volleys in patients with implanted epidural electrodes [31]. Pharmacological studies suggest that LIHI is mediated by post-synaptic $GABA_B$ receptors, while the transmitter system mediating SIHI remains unknown [32]. The transcallosal projection to M1 exhibits SICI and SICF similar to those of the corticospinal projection [33, 34]. A recent study showed that besides the interaction between homologous M1s, IHI, especially LIHI, is a property of other cortical areas projecting to M1. These cortical areas include the dorsolateral prefrontal cortex, dorsal premotor cortex (PMd) and somatosensory cortex (Fig. 2B) [35]. LIHI is decreased in PD patients with mirror movements, but is normal in other PD patients. SIHI is normal in PD [36].

3.2. Interhemispheric Facilitation

Interhemispheric facilitation (IHF) can be investigated by a similar CS-TS TMS paradigm but can only be observed with specific stimulus parameters. IHF between homologous M1s was found when small test MEPs were used under slight voluntary contraction in the target muscle. IHF only occurs with a TS delivered in the anterior-posterior current direction (opposite to the usual current direction) and with CS of relatively low intensity (5–10% above active motor threshold). The ISI required for facilitation is 4–5 ms. A similar effect is produced using an electrical CS, suggesting that corticospinal discharge rather than activation of interneurons may be responsible for IHF [37]. Further investigation demonstrated that IHF can be induced by CS over PMd with lower intensity (0.6 or 0.8 of motor threshold) at ISIs of 6 or 8 ms [38]. The magnitude of IHF is determined by the CS intensity, TS current direction and the status of target muscle (rest or active).

3.3. Short and Long Latency Afferent Inhibition

CS using electrical stimulation of the median nerve at the wrist inhibits the MEP induced by the subsequent cortical TS [39]. This inhibition peaks at two discrete ISIs. One phase peaking at ISI of ~20 ms is termed short latency afferent inhibition (SAI) [40], and another phase peaking at ISI of ~200 ms is termed long latency afferent inhibition (LAI) [41]. SAI likely represents cholinergic effects [42] but is also decreased by certain benzodiazepines that potentiate GABA transmission [43]. The neural transmitter mediating LAI is unknown. SAI was normal in PD patients off medication but was reduced with dopaminergic medication [44]. In addition, SAI is decreased in AD patients and this abnormality can be partly restored by the cholinesterase inhibitor rivastigmine [45]. LAI is reduced in PD patients independent of their medication status [44].

3.4. Cerebellar Inhibition

CS over the cerebellum delivered by a double-cone coil inhibits the MEP induced by TS over the contralateral M1 5–7 ms later; this is known as cerebellar inhibition (CBI) [46]. Because CBI can be elicited either by an electrical or a magnetic CS and is absent when an electrical TS is applied over M1, it was proposed that a cerebellothalamocortical pathway is involved in CBI [46]. Additionally, it was found that the suppressive effect of magnetic CS is absent in patients with degeneration of the cerebellar cortex, but is present in patients with lesions in the afferent pathways to the cerebellum [47]. Therefore, the CS may activate Purkinje cells in the cerebellar cortex and inhibit the contralateral M1 by a disynaptic pathway through the ventral thalamus [48]. CBI was found to be normal in essential tremor [49] but reduced in PD [50].

The methods used for investigating the intracortical circuits, as well as their underlying neural transmitters and the findings in diseases are summarized in Table 1.

Table 1. Summary of intracortical circuits

	SICI	ICF	LICI	SICF *	SIHI	LIHI	SAI	LAI	CBI
First stimulus	Sub TMS	Sub TMS	Supra TMS	Supra TMS	Supra TMS	Supra TMS	MNS	MNS	Supra TMS
Second stimulus	Supra TMS	Supra TMS	Supra TMS	Sub TMS	Supra TMS	Supra TMS	Supra TMS	Supra TMS	Supra TMS
ISI (ms)	1-6	8-30	50-200	~1.5, 3.0, 4.5	~10	~40	~20	~200	5-7
Transmitter	$GABA_A$	Glu	$GABA_B$	?($GABA_A$)	?	$GABA_B$	Ach	?	?
PD	↓ or ↔	↔	↑ or ↓	?	↔	↓(with MM)	↔(↓on med)	↓	↓
Dystonia	↓	↔	↑or ↓	?	↓	↓	↔	↓	?
AD	↓	↔	?	↔	?	?	↓	?	?

Abbreviation: SICI, short interval intracortical inhibition; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; SICF, short interval intracortical facilitation; SIHI, short interval interhemispheric inhibition; LIHI, long interval interhemispheric inhibition; SAI, short interval afferent inhibition; LAI, long interval afferent inhibition; CBI, cerebellar inhibition. ISI, interstimulus interval; Sub, subthreshold; Supra, suprathreshold. PD, Parkinson's disease; AD, Alzheimer's disease; MNS, median nerve stimulation; TMS, transcranial magnetic stimulation; MM, mirror movement. GABA, gamma aminobutyric acid; Glu, glutamate; Ach, acetylcholine. ↓, decrease; ↑, increase; ↔, no change; ?, not known.

* Note: For SICF the test MEP is generated by the first stimulus. For other intracortical circuits test MEP is generated by the second stimulus.

4. Interactions between Intracortical Inhibitory and Facilitatory Circuits

Intracortical circuits do not act in isolation but interact with each other. The interactions among intracortical circuits can be investigated by triple-pulse TMS paradigms, in which one TS pulse and two CS pulses are employed.

4.1. LICI (SP) Inhibits SICI

As noted above, LICI is mediated by $GABA_B$ receptors [5] and SICI is mediated by $GABA_A$ receptors [17]. Interaction between LICI and SICI can be investigated by a triple-pulse paradigm. SICI in the presence of LICI was found to be weaker (Fig. 3A). This finding suggests that LICI not only inhibits the corticospinal output through $GABA_B$ mediated postsynaptic inhibition, but also reduces SICI through $GABA_B$ mediated presynaptic inhibition of the $GABA_A$ system (Fig. 3B) [51]. A subsequent study showed that a similar mechanism operates during voluntary muscle contraction. It was found that during the SP (mediated by $GABA_B$ receptors), SICI is reduced [8]. The reduction of SICI conditioned by presynaptic $GABA_B$ activity may follow a different time course from that of postsynaptic inhibition. Corticospinal output was suppressed by LICI at both 100 and 150 ms after the preceding CS whereas the suppression of SICI only occurred at 100 ms but not at 150 ms [52]. ICF is increased during the SP although it remains unchanged at rest, and this may be explained by the effect of the voluntary drive. In PD patients, the reduction in SICI caused by LICI is much weaker than in the age-matched controls regardless of medication. This suggests that presynaptic $GABA_B$ mediated inhibition of $GABA_A$ activity is decreased in PD and may be a non-dopaminergic feature of the disease [12].

4.2. LAI Inhibits LICI

Sensory afferents may influence intracortical circuits in the M1. A triple-pulse paradigm was used to investigate the interaction between LAI and SICI or LICI. It was found that both LAI and LICI decrease when they are elicited together and that the reduction of inhibition is related to the strength of LAI but not to the strength of LICI, suggesting that LAI inhibits LICI. No interaction was found when LAI and SICI are applied together [53].

4.3. Interactions between IHI and Other Intracortical Circuits

IHI has been found to influence intracortical circuits. In the presence of SIHI, SICI decreased and the reduction is related to the degree of SIHI, suggesting that SIHI inhibits SICI. LICI also decreases in the presence of SIHI [54].

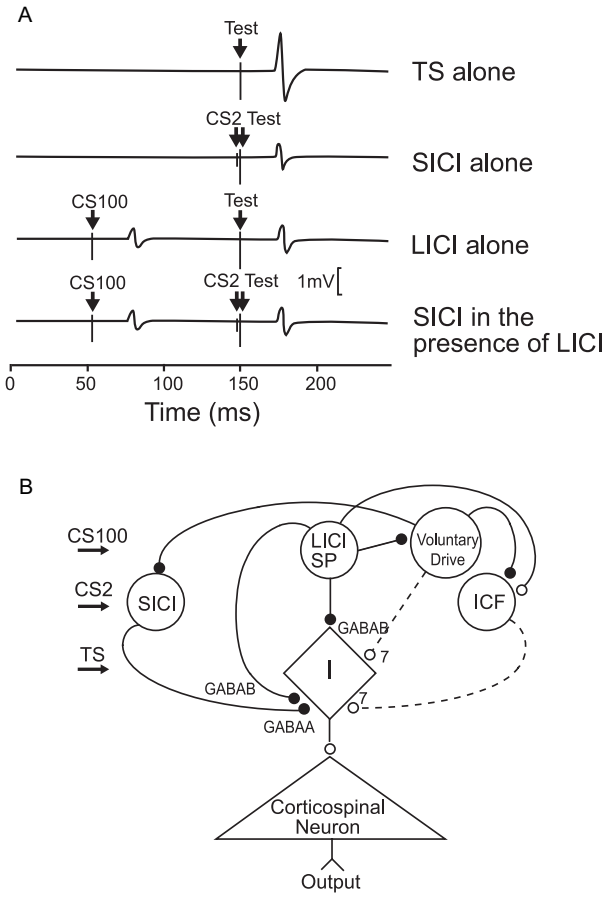

Fig. 3. Interactions between long interval intracortical inhibition and short interval intracortical inhibition. **(A)** Recordings from a representative subject showing the interactions between long interval intracortical inhibition (LICI) and short interval intracortical inhibition (SICI). The top trace shows the MEP produced by the test stimulus (TS) alone. The second row shows the SICI alone. CS2 refers to the conditioning stimulus (CS) delivered 2 ms preceding TS. The third row shows the LICI alone. CS100 refers to the CS delivered 100 ms preceding TS. The bottom trace shows the SICI in the presence of LICI. Note that the MEP amplitude is similar to the LICI alone (third row), suggesting that SICI is reduced in the presence of LICI. **(B)** Possible mechanism underlying the interaction between SICI and LICI (silent period, SP). The rhombus (labeled with I) at the center indicates a common interneuron that projects to the corticospinal neuron. The corticospinal neuron produces the output to spinal motoneurons. The common interneuron receives inputs from the SICI and LICI (SP) circuits. Voluntary drive is projected onto the common interneuron from other brain areas. The small filled circles show inhibitory effects, and small open circles show facilitatory effects. CS100 activates the LICI (SP) circuit. CS2 activates the SICI circuit. TS activates the common interneuron. SICI is mediated by $GABA_A$ receptor, whereas LICI (SP) neuron is mediated by $GABA_B$ receptor. The question marks indicate that the nature of the interactions is not clear. The LICI (SP) neuron inhibits SICI neurons through presynaptic $GABA_B$ mediated inhibition. In addition, the LICI (SP) neuron also facilitates the circuit meditating intracortical facilitation (ICF) in the presence of voluntary contraction. Modified from Sanger et al. (2001) [51] and Ni et al. (2007) [8]

While IHI influences intracortical circuits, intracortical circuits also modulate IHI either at the originating M1 or the target M1. In the target M1, LIHI is reduced in the presence of LAI and the reduction of inhibition correlated with the degree of LAI, suggesting that LAI inhibits LIHI. SIHI does not interact with LAI [28]. In the originating M1 for IHI, SICI and LICI reduce both SIHI and LIHI, suggesting that the transcallosal output from the originating M1 is susceptible to intracortical inhibition as the corticospinal output. ICF has no effect on either SIHI or LIHI [55].

4.4. Interaction between CBI and Intracortical Circuits

Cerebellar projections influence both inhibitory and facilitatory circuits in M1. It was found that CBI inhibits SICI and facilitates ICF. Reduced thalamocortical facilitation to the SICI circuit may explain decreased SICI in the presence of CBI. Increased ICF may be caused by reduction of SICI, which changes the balance of inhibition and facilitation in M1. On the other hand, CBI is inhibited by LICI. The TMS pulse that produces LICI may activate subcortical pathways targeting the cerebellar circuits, leading to the reduction of CBI [56].

5. Conclusions

Different intracortical circuits interact with each other in a complex manner. Future studies will explore other intracortical circuits and their interactions. The balance of inhibitory and facilitatory influences among these circuits determines the final output of the motor cortex. Studies of cortical inhibitory and facilitatory circuits will improve our knowledge of the pathophysiology of neurological and psychiatric disorders.

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