Surround inhibition depends on the force exerted and is abnormal in focal hand dystonia

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Surround inhibition depends on the force exerted and is abnormal in focal hand dystonia (FHD). To further characterize SI with respect to different force levels, single- and paired-pulse transcranial magnetic stimulation was applied at rest and during index finger movement to evoke potentials in the nonsynergistic, abductor pollicis muscle. In Experiment 1, in 19 healthy volunteers, SI was tested using single-pulse transcranial magnetic stimulation. Motor-evoked potentials at rest were compared with those during contraction using four different force levels [5, 10, 20, and 40% of maximum force (Fmax)]. In Experiments 2 and 3, SI and short intracortical inhibition (SICI) were tested, respectively, in 16 patients with FHD and 20 age-matched controls for the 10% and 20% Fmax levels. SI was most pronounced for 10% Fmax and abolished for the 40% Fmax level in controls, whereas FHD patients had no SI at all. In contrast, a loss of SICI was observed in FHD patients, which was more pronounced for 10% Fmax than for 20% Fmax. Our results suggest that SI is involved in the generation of fine finger movements with low-force levels. The greater loss of SICI for the 10% Fmax level in patients with FHD than for the 20% Fmax level indicates that this inhibitory mechanism is more abnormal at lower levels of force.

transcranial magnetic stimulation; short intracortical inhibition; fine finger movement; movement selection

The coordination of finger movement plays an important role in many daily tasks involving precision grip and fine motor skills. A basic question in the neurophysiology of motor control is how the brain shapes the complex control of the human hand in its various spatiotemporal commands needed to modulate speed, amplitude, and direction. The primary motor cortex (M1) and the corticospinal tract are crucial for the control of skilled finger movements, and lesions in these sites lead to a loss of individuated motor behavior (26, 28, 37). The anatomical organization of M1 and the corticospinal tract, which involves elements of divergence (30) and convergence (36) on several levels, may facilitate the generation of complex activation patterns.

Individuals performing a task using one finger selectively involuntarily move other fingers as well. This phenomenon is called enslaving and is due to biomechanical (22, 34) and neural constraints (30, 36). In the human hand, enslaving is most pronounced for the fourth finger, whereas the index finger and thumb have the greatest degree of independence (15, 39). The amount of enslaving increases in all fingers with increasing force levels exerted and is most pronounced in adjacent fingers (38).

For tasks like writing or playing the piano, a high level of precision, but also a great degree of independence between single fingers, is needed. Surround inhibition (SI) is a general neural principle to enhance contrast between neuronal activities and to select neuronal responses. It was first described in the retina, where cells are excited by light that falls in the center of their receptive field, whereas light in the peripheral areas of the receptive field has an inhibitory effect on the same cell (1). SI can also be observed in other sensory systems (4, 45). In the motor system, there is evidence that SI could aid the selective execution of desired movements in humans (2, 16, 17, 31, 41).

With the use of transcranial magnetic stimulation (TMS), a technique that allows the assessment of cortical inhibitory circuits noninvasively, synergistic muscles show increased motor-evoked potentials (MEP) during motor activation, while neighboring muscles are inhibited (41). In healthy subjects, SI is present during movement initiation but not during the maintenance of a contraction (2), suggesting it may be relevant for fine tuning and temporal shaping of complex task-dependent activity. However, it is not clear how SI is generated in healthy people.

One possible circuit involved in the formation of SI is the effect of the local inhibitory interneurons in M1 (2, 43). With the use of a paired-pulse TMS paradigm, short intracortical inhibition (SICI) can be assessed, which is thought to reflect the inhibitory effect of the horizontal interneurons in M1 (18, 25). Although SICI is reduced in activated and synergistic muscles just before and during activation (35, 42), some previous reports suggest that SICI contributes to the genesis of SI (40, 43). From a clinical perspective, the two most common types of idiopathic focal hand dystonia (FHD) are writer’s cramp and musician’s cramp. In both types of FHD, the first and most prominent feature is an impairment of high-precision movement at low-force exertion. Although dystonia is generally regarded as a motor execution abnormality due to a dysfunction in the cortico-striato-thalamo-cortical motor loop (3), the exact nature of the dysfunction is unknown. Typical clinical features of FHD are task- and context-specific abnormal posturing due to sustained muscle contractions interfering with the performance of skilled motor tasks (8). On the motor cortical level, increased excitability (21) and deficient modu-
RODUCTION of intracortical inhibitory circuits have been described in active, as well as in adjacent, relaxed muscles (2, 16, 40, 44). Because patients with FHD show deficient SI (2, 43), they may be a good model to study the underlying mechanisms of SI.

The physiology of force generation, especially for precision grip, has been studied extensively in animal models and in humans. In primates, there is a linear relationship between the force produced and the firing rate recorded from approximately one-third of the cortical motoneurons, whereas other cortical motoneurons show negative correlations (19, 29). In healthy humans, it is known that M1 excitability of synergistic muscles increases in accordance with the precision level required by the task (5, 14, 27). Furthermore, functional magnetic resonance imaging studies revealed that the motor network, including primary sensory motor cortex, dorsal premotor cortex, ventral premotor cortex, and bilateral supplementary motor areas, is more activated during a gentle (lower force) than a higher force precision grip (24). Therefore, the force level may influence how different brain areas modulate and possibly exert inhibition onto M1 and how this modulation may be impaired in motor disorders such as dystonia.

The aim of the present study was to identify whether SI is involved in force regulation during dynamic motor activation. The contribution of SICI to SI was assessed by comparing patients with FHD, where SICI is known to be reduced with age-matched healthy controls. First, we hypothesized that SI would be more pronounced for lower force levels, supporting the idea that this mechanism was especially relevant for skilled motor behavior. Second, we expected that the reduction of SICI in FHD patients would also be more pronounced for low-force levels, indicating that a loss of SICI was in fact part of the pathophysiology of FHD.

METHODS

Subjects. In Experiment 1, 19 healthy volunteers (age 25–69 years, mean 49 ± 3 years; 12 men) participated. In Experiments 2 and 3, 16 FHD patients (age 43–72 years, mean 54 ± 2 years; 13 men) and 20 age-matched healthy volunteers (age 37–72 years, mean 54 ± 2 years; 12 men) were tested. Fifteen healthy volunteers participated in all experiments.

All participants gave their informed consent to the experiments, which were approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke. All subjects were right-handed according to the Edinburgh Inventory (33). Participants had never been treated with neuroleptic drugs and had no history of other neuropsychiatric disorders, neurosurgery, or metal or electronic implants. Most of the patients had been treated with local muscle relaxants, and patients with a history of other neuropsychiatric disorders, neurosurgery, or metal or electronic implants were excluded. Most of the patients had been treated with local neuroleptic drugs and had no history of other neuropsychiatric disorders, neurosurgery, or metal or electronic implants. Most of the patients had been treated with local neuroleptic drugs and had no history of other neuropsychiatric disorders, neurosurgery, or metal or electronic implants.

Recording. Subjects were seated in a chair with their right arm resting on a side table, which was individually adjusted. Disposable surface silver-silver chloride EMG electrodes were placed on the right abductor pollicis brevis muscle (APB) and first dorsal interosseus muscle (FDI) in a bipolar montage. Impedance was reduced below 5 kΩ. The EMG signal was amplified using a conventional EMG machine (Nihon Kohden, Tokyo, Japan), band-pass filtered (20–2,000 Hz), digitized at a frequency of 4 kHz, and fed into a computer for off-line analysis.

Motor task. With their right hand lying flat on a table besides them, subjects pushed down on a small force transducer (Strain Measurement Devices, Meriden, CT; model S215 load cell) using the tip of their index finger in response to an acoustic signal. This leads to a flexion in the metacarpophalangeal joint of the index finger. FDI actively participates in the movement as a synergist to stabilize this joint. The acoustic signal stayed on for 2 s, and subjects maintained a given force level [5, 10, 20, or 40% of their maximum force (Fmax)] for this duration. Their force was continuously displayed online on an oscilloscope in front of them. Subjects practiced the task at the beginning of the experiment to attain a consistent motor performance (see Fig. 1). Latencies for stimulation were determined using an average of 10–15 trials in the beginning of the experiments, when subjects had attained consistent motor performance. This task has previously been established to infer SI (2).

TMS. For TMS, two high-power Magstim 200² machines (Magstim, Whitland, Dyfed, UK), via an integrated bistim module, were connected to a “Second Generation” figure-eight coil (Remote 3190-00) with an outer loop diameter of 80 mm. The coil was placed over the ’motor hot spot’ for eliciting MEPs in APB. This position was marked on the scalp to ensure proper coil placement throughout the experiment. Coil orientation was tangential to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. The resting motor threshold (MT) was determined to the nearest 1% of maximal stimulator output. MT was defined as the minimal stimulus intensity required to evoke MEPs of at least 50 μV in 5 of 10 consecutive trials. MEP size was determined by averaging peak-to-peak amplitudes. Trials with a preceding EMG of more than 0.02 mV in APB in the 50 ms before stimulation were rejected. Background EMG was calculated by assessing the root mean square over 50 ms before the onset of the MEP.

Experiment 1. Single-pulse TMS was applied at an intensity of 140% MT in 19 healthy subjects. Force levels of 5, 10, 20, and 40% of Fmax of the index finger flexion were required from the subjects in a randomized order, as described above. The four different force levels were tested in separate experiments in a randomized order. In each test, 12–15 stimuli at rest (i.e., 100 ms before the onset of the acoustic signal) and during the phasic phase (i.e., during the first peak of EMG in FDI) were applied in a randomized order with a third condition (in which no TMS was given). Twenty healthy subjects and 16 patients with FHD were tested. Considering the results of the preliminary tests demonstrated in Experiment 1, which showed that there was most significant SI for the 10% Fmax level, we chose to compare the 10% Fmax and the 20% Fmax levels. This selection was

Table 1. Patient demographics

<table>
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<tr>
<th>Sex</th>
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<th>Type</th>
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<th>Duration, years</th>
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<tr>
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<tr>
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M, men; W, women; WC, writer’s cramp; MC, musician’s cramp.
made to keep low the number of trials to avoid fatigue and to reduce the risk of inducing a dystonic posture in the patient group. Two separate tests were performed, in which TMS stimuli were given at rest and in the phasic phase intermixed with trials without stimulation. Similar to Experiment 1, the amount of SI is expressed as the ratio between MEP size during the phasic phase and at rest: SI = (MEP\text{phasic}/MEP\text{rest}) × 100%.

Experiment 3. For SICI, an interstimulus interval of 2.5 ms was used, which has been shown to be the most effective (43). Rest and the phasic phase were tested in separate tests for both force levels, resulting in four different tests. In the beginning of each experiment, test pulse intensity was adjusted to induce an MEP of 1 mV. First, SICI was tested at rest, adjusting the intensity of the conditioning stimulus to reduce the test pulse response to 60% (equal to 600 μV). This adjustment was performed to avoid saturation or floor effects (13). This conditioning intensity was then used for both force levels (10% and 20% F\text{max}) during the phasic phase (43).

We screened for coactiviation in the beginning of the whole series of experiments, when the subjects practiced the task, and minimized EMG in APB by careful instruction to the subjects regarding optimizing the position and the support of the hand on the platform. Still, during the time course of the experiments, three FHD patients and five control subjects showed coactiviation in APB. In each separate test, which consisted of 12–15 trials per condition, the maximum of rejected trials due to coactiviation was two in all subjects. On the other hand, we rejected on average three MEPs in each test due to anticipation or delayed reaction, which was assessed by EMG and the force produced. The lowest number of trials averaged in one condition for one subject was nine. The number of rejected trials was different between individual subjects but not between FHD patients and controls.

Statistics. In Experiment 1, the primary outcome measure was SI. MEPs were not always distributed normally. Therefore, to test for significant SI (different from 100% rest MEP), the Wilcoxon signed ranks test was used to compare MEP at rest with MEP during contraction for the force levels 5, 10, 20, and 40% of F\text{max}. After SI had thus been shown to be significant, further assessments of SI were done by calculating ratios of active MEP over rest MEP for each individual force level. Conover’s free distribution method, a nonparametric ANOVA based on ranks (10) was used to compare the different force levels as the within-subject factor in a repeated measurement design (force levels 5, 10, 20, and 40% of F\text{max}). Mean differences were calculated between the force levels and confidence intervals given after Bonferroni correction for repeated comparisons.

In Experiments 2 and 3, the primary outcome measures were SI and SICI, respectively. Due to nonnormal distribution of single-pulse MEP and conditioned MEP, nonparametric testing was applied as described for Experiment 1. The Wilcoxon signed ranks test was used to test for significant SI and SICI (different from 100% rest and test MEP in SI and SICI, respectively) for the force levels 10% and 20% of F\text{max} in FHD and controls. Conover’s free distribution method was used to calculate a two-way nonparametric ANOVA based on ranks (12) for the between-subject factor “group” (2 levels: FHD and controls) and the within-subject factor “force” (2 levels: 10% and 20% of F\text{max}).

In all experiments, the same tests were applied to evaluate background EMG, reaction time, force level, test MEP size, and MT. Results are presented as means and SE. P values <0.05 were considered significant. For analysis, SPSS 14.0 was used.

RESULTS

The mean F\text{max} determined for the index finger flexion was 0.95 ± 0.1 lb. (ranging from 0.5 to 1.6 lb.), and there was no difference between FHD patients and controls (P = 0.87). No differences between FHD patients and controls were found for movement accuracy or reaction time (mean latency FHD = 191 ± 12 ms, mean latency controls = 198 ± 14 ms). The error rate for motor performance was below 3% in all subjects.

Experiment 1. There was a significant main effect on SI (ratios of active MEP over rest MEP) of force level (F2,16 = 12.6; P < 0.001). The Wilcoxon test showed that there was significant reduction of MEP amplitude (SI below 100%) for 5% F\text{max} (P = 0.032; SI = 88.6 ± 4.2%), 10% F\text{max} (P < 0.001; SI = 76.9 ± 4.4%), and 20% F\text{max} (P = 0.036; SI = 87.9 ± 5.2%), whereas no significant SI was observed for the 40% F\text{max} level (P = 0.5; SI = 98.2 ± 7.4%, see Fig. 2). Pair-wise comparison of means revealed that SI was most pronounced at 10% F\text{max} with mean differences compared with 5% F\text{max} of −11.7% (95% CI ± −3.3, −20.2; P = 0.035) and compared with 40% F\text{max} of −21.3% (95% CI ± −5.2, −37.4; P = 0.002), whereas the mean difference compared with 20% F\text{max} was not significant (−11%; 95% CI ± 0.2, −22.2; P = 0.13).

![Fig. 2. Experiment 1, surround inhibition (SI). SI results are shown as means and SE for 19 healthy subjects. For the 5% maximum force (F_{max}), 10% F_{max}, and 20% F_{max} force levels, there was significant inhibition, although this did not occur for 40% F_{max}.](http://jap.physiology.org/)
The mean for MT was 48.4 ± 2% of maximum stimulator output. The MEP size at rest, tested separately for each force level, was not different between the four force levels (P = 0.8; 5%: 1.81 ± 0.1 mV; 10%: 1.81 ± 0.1 mV; 20%: 1.89 ± 0.2 mV; 40%: 1.96; ± 0.2 mV). For EMG in APB, there was no significant main effect of force level (P = 0.7), underlining that APB was not coactivated in the task. In contrast, there was a significant main effect for force level for EMG in FDI (P = 0.02), which increased with increasing force levels (P = 0.002).

Experiment 2. There was a significant main effect for group (F[1,33] = 11.4; P = 0.002) but not for force level (F[1,33] = 0.015; P = 0.9). The group-by-force level interaction showed a trend to be significant (F[2,66] = 3.4; P = 0.07), indicating that there may be a difference in the modulation of SI between the two groups. Wilcoxon signed rank test showed that there was significant SI (below 100%) for 10% Fmax (P = 0.001; SI = 65.8 ± 6.3%) and 20% Fmax (P < 0.001; SI = 72.6 ± 6.5%) in the healthy control group but not in the FHD patients (10% Fmax: P = 0.9, SI = 105.9 ± 8.7%; 20% Fmax: P = 0.07, SI = 91.9 ± 7.5%, see Fig. 3). This observation was supported by comparing the two force levels group-wise using the Mann-Whitney test, which revealed a significant inhibition for the 10% Fmax level (P = 0.001) between groups but not for the 20% Fmax level (P = 0.062). This result is in line with Experiment 1, in that healthy subjects showed most pronounced SI for the lower force level, whereas FHD patients did not show SI at all (2).

MT was not different between groups (P = 0.27; FHD: 44.7 ± 2.4%, controls 47.5 ± 2.4%). APB background EMG was not different between rest and phasic phase, nor between the two force levels (all P > 0.1).

Experiment 3. SICI was calculated as a percentage of the conditioned MEP size divided by the test MEP size. The conditioning pulse was adjusted to attain a reduction of MEP size to 60% of the test MEP size in the rest condition. In fact, the mean of the induced SICI was slightly higher for the two force levels (all P > 0.1). SICI was not different between groups nor between force levels (all P > 0.1). MEP test size was not different between conditions (all P < 0.1). SICI at rest was in the range of 3.8% (FHD: 3.8% ± 0.1 mV; at 10% Fmax: control 1.1 ± 0.1 mV, FHD 0.9 ± 0.1 mV; at 20% Fmax: control 1.2 ± 0.1 mV, FHD 1.3 ± 0.1 mV).

DISCUSSION

There are two main results from these experiments comparing TMS parameters at different force levels in patients with FHD and healthy controls. First, the single-pulse TMS experiments showed that there was significant decrease of MEP size in the inactive, “surrounding” muscle (APB) at lower force levels, which was most pronounced at the 10% Fmax level and was abolished at 40% Fmax. This finding will be discussed in terms of possible underlying mechanisms, one of which is the modulation of SI likely being a relevant mechanism contributing to the generation and control of motor performance when applying lower force levels. Second, there was a significant loss of SICI for the 10% Fmax level in the FHD group, which was restored for the 20% Fmax level, whereas controls did not modulate SICI. Both findings are in line with previous reports (2, 43) but extend these studies in showing that the amount of SI and the related modulation of SICI were strongly related to the amount of force exerted.
Modulation of SI. Previous reports have supported the view that SI occurs in a relaxed, nonsynergistic muscle during movement initiation in a neighboring muscle (43). A similar decrease in MEP size is not observable during the maintenance of this contraction (2). Although MEP size increases in the active muscle with increasing force or task precision (5, 14), little is known about a nonsynergistic, neighboring muscle, when the amount of force is varied. In line with previous reports (2, 40, 41, 43), the term SI is used for this selective reduction in MEP size in the surrounding muscle, which reflects the summation effect of inhibitory and excitatory influences on its M1 representation. There is evidence that increased intracortical inhibition may contribute (43), although a reduction of excitatory influences cannot be excluded with the present experiments. The results of this study show that, in the absence of background EMG in APB, the inhibition of this surrounding muscle was present at low-force levels and then diminished with increasing force. The findings may suggest that SI is relevant for skilled finger movements that generate lower force levels, which would fit well with the clinical observations in FHD patients, in whom SI is known to be impaired (2, 40, 42), as are skilled finger movements, such as writing and playing the piano.

In the present results, there was a difference in SI in controls between Experiment 1 (76.9 ± 4.4%) and Experiment 2 (63.7 ± 5.4%) for the 10% Fmax condition, which may be explained by the fact that not all controls participated in both experiments (for Experiment 1, n = 19; for Experiment 2, n = 20; 15 subjects participated in both experiments). For Experiment 1, controls were younger on average than the subjects tested in Experiment 2.

Furthermore, in the present study, the 5% Fmax level induced less inhibition than the 10% Fmax level in healthy controls. Because the test conditions, such as gain on the oscilloscope, sound, and force transducer were exactly the same and the motor performance was not worse for this specific force level, it may be possible that the very small amount of force (on average 0.04 lb.) may be so low that cortical activation may not need to be limited by the active, energy-demanding generation of surrounding inhibition.

Functional implications of SI. The present results showed a peak increase of the inhibition for the 10% Fmax level, which was not observed for the 40% Fmax level, and showed that there were no differences in motor performance between the force levels. There is a variety of reasons why this may be the case. First, we had subjects practice the task in the beginning of each session to attain a consistent motor performance; perhaps there were differences in task difficulty in the beginning, which were then masked. Subjects did not report any systematic differences with the tasks; some had more trouble with the lower force levels and others with the higher ones. Second, it may be due to the task itself. The motor task used was very simple, standardized, and unidirectional and was not aimed to test skilled motor performance. In future studies, especially with an interventional design, a more detailed behavioral assessment (e.g., using a more complex motor sequence or a more demanding motor task) may provide further insights and reflect behavioral changes.

Potential mechanisms involved in the generation of SI. It is not clear at this point how SI is generated in healthy subjects. As mentioned before, FHD is a good model to better assess this mechanism (40, 43), since FHD patients show a lack of SI. The fact that this loss of SI is accompanied by a reduction of SICI that occurs selectively in the same phase of the movement may suggest that SICI is involved (2). However, the interaction of different cortical circuits during movement generation may be influenced by different factors. One of the factors seems to be the amount of force, as well as the changes in the patterns of cortical activity needed to generate that force (24). During a gentle (lower force) precision grip, the motor network, including primary sensory motor cortex, dorsal premotor cortex, ventral premotor cortex, and bilateral supplementary motor areas, showed higher levels of activation than at the same grip with higher force (26). This may imply that secondary motor areas, e.g., those involved in shaping a particular grip to be in accordance with the requirements of the task, play a more important role in low-force precision tasks. Further studies will be needed to better understand the contribution of these circuits to the generation of SI.

GRANTS

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REFERENCES

SURROUND INHIBITION DEPENDS ON THE FORCE LEVEL