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Short-interval intracortical inhibition and manual dexterity in healthy aging

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ABSTRACT

Short-interval intracortical inhibition (SICI) acting on the first dorsal interosseus was measured using paired-pulse transcranial magnetic stimulation (interstimulus interval = 2 ms) in samples of young and healthy older subjects and correlated with manual dexterity measured with the Purdue Pegboard test and two isometric force-matching tasks. There was an age-related decrease in SICI and an age-related decline in all dexterity measures. The level of SICI was not correlated with any of the dexterity measures, but the appearance of atypical facilitation (rather than inhibition) in some subjects was associated with impaired pegboard performance but not force-matching performance. We conclude that SICI at rest is reduced with healthy aging but this loss of SICI does not directly contribute to the loss of dexterity; a shift in the balance of facilitatory and inhibitory processes in motor cortex to facilitation might interfere with sequenced hand movements.

1. Introduction

The decline of motor function, including manual dexterity, with healthy aging has been well documented (see the review by Ward, 2006). While this decline is due in part to peripheral changes, such as sarcopenia and nerve conduction, interest has recently focused on functional changes in the cerebral cortex that might contribute (Hortobágyi and DeVita, 2006). More specifically, since fine motor control requires suppressing activation of muscles that are antagonistic or irrelevant to the movement, attention has been drawn to age-related changes of inhibitory processes in motor cortex that might diminish motor performance.

It is well established that coactivation of agonist and antagonist muscles, including intrinsic hand muscles, increases with aging (Burnett et al., 2000; Klass et al., 2007). While the increase in coactivation with aging has been thought of as a strategy to increase joint stiffness and thereby limit movement variability, it might also hamper dexterous hand movements. Increased coactivation with aging has been linked to an age-related loss of cortical reciprocal inhibition, shown by the loss of the inhibitory effect of electrical stimulation of afferents from a forearm flexor on the size of the motor evoked potential (MEP) elicited in a forearm extensor by transcranial magnetic stimulation (TMS) of motor cortex (Hortobágyi et al., 2006). TMS has also been used to investigate age-related changes in short-interval intracortical inhibition (SICI), an intracortical inhibitory process evident in the inhibitory effect of a conditioning TMS pulse (which is below the threshold intensity required to elicit an MEP) on the amplitude of the MEP elicited by a suprathreshold TMS pulse delivered from 1 to 6 ms after the conditioning pulse (Kujirai et al., 1993). SICI appears to play a role in manual dexterity through selective suppression of unwanted muscle activation (Stinear and Byblow, 2003), in a process of surround inhibition (Sohn and Hallett, 2004). The evidence on age-related changes in SICI is mixed: studies to date have reported less SICI at rest in an old than a young group (Peinemann et al., 2001), no difference in SICI between old and young groups (Oliviero et al., 2006), and more SICI in an old than a young group (Kossev et al., 2002; Smith et al., 2009; McGinley et al., 2010). No reported studies have investigated if SICI and manual dexterity are associated in a group including young and normally aging individuals. We therefore measured SICI in young and old subjects with larger samples than has been typical of previous research and examined the association of these measures with measures of manual dexterity from two different tasks.

2. Methods

2.1. Subjects

Data are reported for forty-nine healthy volunteers who participated in the study. There were 25 younger subjects (13 females) whose ages ranged from 18 to 29 years (median = 20 years) and 24 older subjects (13 females) whose ages ranged from 59 to 88 years (median = 68 years). The younger subjects were university students and the older subjects were recruited from the local community.

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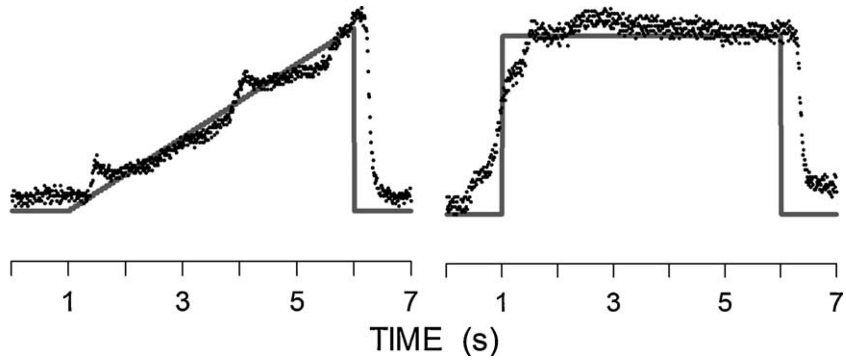

Fig. 1. Illustrative trials with a ramp target (left panel) and a square-wave target (right panel). The targets are shown as solid lines and the pinch forces as a series of points.

All subjects were self-reported right-handers and reported no motor or neurological impairment. To control for cognitive impairments that have been found to affect fine motor skill (Scherder et al., 2008) only those who scored within the normal range on the Montreal Cognitive Assessment (≥26) participated (Nasreddine et al., 2005). The procedures were approved by the University's Human Research Ethics Committee and all subjects gave informed written consent before participating.

2.2. Behavioral methods

Manual dexterity was assessed with the Purdue Pegboard test and a task that required control of pinch force to match the amplitude of a target which appeared as a level change on a visual trace that moved from left to right across a computer screen with constant velocity. Administration of the Purdue Pegboard task followed the standardized testing procedure. The peg-moving subtest required subjects to retrieve small pegs from a well with one hand and to insert them, one at a time, into a vertical array of holes in the pegboard beginning at the top hole and working down. The assembly subtest required subjects to retrieve four items in turn with alternate hands (a peg, a washer, a collar, and a second washer) and to assemble them by inserting the peg in a hole, and by placing the remaining three items (the washer, the collar, and the second washer) on the peg in turn. Subjects were instructed to complete each test as quickly as possible. The measures taken were the number of pegs moved and placed by each hand in a 30-s period and the number of four-item objects assembled with both hands in a 60-s period. For the force-matching task, subjects sat in front of a computer screen with their dominant right arm supported comfortably while gripping a vertical rod fitted with two force transducers on opposed flat surfaces with a pinch grip of their thumb and index finger. On each trial, subjects controlled their pinch force to match a visual trace that moved across the screen with successive points plotted at 100 Hz. Each trace consisted of three segments, an initial 1-s segment in which the trace was steady at a baseline level, a 5-s target segment in which the trace either increased linearly to the target level (the ramp target) or jumped immediately to the target level (the square-wave target), and a final 1-s segment in which the trace returned abruptly to the baseline level. A second trace that showed the instantaneous pinch force (sampled at 100 Hz) was visible throughout the trial in the same coordinate space as the target trace. The target force level for both the ramp and square-wave targets was set at 40% of each subject's maximum pinch force which was determined immediately before testing began. Five trials were done for each target type with a 10-s inter-trial interval. Illustrative traces are shown in Fig. 1. Accuracy was quantified as the root-mean-square (RMS) error during the 5-s ramp and 5-s square-wave target segments of each trace. Precision was quantified for the ramp targets as the mean absolute residual error around the best-fitting straight line of the forces produced during the 5-s target segment. Because the forces applied during square-wave trials typically overshot the target before stabilizing, precision in these trials was quantified as the mean absolute residual error around best fitting straight line of the forces during the last 2 s of each 5-s target segment.

2.3. Electrophysiological methods

Subjects were seated in a height-adjustable chair with their right forearms supported comfortably on a cushion on a table in front of them. The importance of keeping the arm relaxed throughout the brief testing session was emphasized. Electromyographic (EMG) activity was recorded from the relaxed first dorsal interosseus (FDI) muscle of the right hand using surface Ag–AgCl electrodes in a standard belly-tendon configuration with a ground electrode placed laterally over the wrist. The EMG signal was amplified (1000×), band pass filtered at 10–1000 Hz, and digitized with 14-bit resolution at 4000 Hz.

TMS pulses were delivered by a MagStim 200^2 BiStim system through a figure-of-eight coil with a 9-cm diameter. The coil handle was oriented at 45° to the mid-sagittal line to induce current in a posterior to anterior direction, approximately perpendicular to the central sulcus. TMS pulses were delivered over the left hemisphere at the motor 'hot spot' for the right FDI muscle, defined as the scalp site at which the mean amplitude of the motor-evoked potentials (MEP) evoked by five successive single pulses was largest. SICI was measured with a conditioning-test pulse procedure with an interstimulus interval (ISI) of 2 ms. The intensity of the test TMS pulse was set for each subject using a computer-controlled adaptive procedure to elicit an MEP amplitude of about 1 mV in the relaxed FDI muscle (Sinclair et al., 2006). The intensity of the conditioning pulse was set at 70% of the test pulse intensity. The mean conditioning and test TMS intensities (expressed as percentages of stimulator output) were 43.3% and 61.9% respectively for the young group and 45.5% and 65.0% respectively for the old group; test stimulus intensity was not significantly different between the two age groups (Mann–Whitney $U = 123.5$, $p = .88$). Twelve single pulses and 12 paired pulses were delivered in random order, with the interval between successive pulses selected randomly from the set 6, 8, 10, and 12 s. The stimulation phase was completed in less than 4 min. MEPs were scored as both peak-to-peak amplitude and total area; because these measures were very highly correlated in all subjects (mean $r = .98$, calculated using Fisher's r-to-z transformation) only the former measure is reported here. SICI was quantified as the ratio of the median MEP amplitude from the paired-pulse trials to the median MEP amplitude from the test-pulse trials; ratios less than one indicate the presence of SICI. The ratios were log transformed prior to statistical analysis, and back transformed means and standard errors are reported.

Table 1
The mean number of pegs moved by each hand and the mean number of objects assembled in the subtests of the Purdue Pegboard task by the younger and older groups. Standard deviations are in parentheses.

	Peg moving subtest		Assembly subtest (both hands)
	Left hand	Right hand	
Young	14 (2)	16 (1)	41 (4)
Old	12 (2)	12 (2)	28 (5)

3. Results

3.1. Behavioral results

Mean performance of each age group on the subtests of the Purdue Pegboard task is presented in Table 1. An age-related decline in performance was evident in all subtests. The old group moved fewer pegs than the young group with both the left and right hand. There were statistically significant main effects of Age ($F(1, 47) = 32.49$, $p < .001$, $\eta_p^2 = .41$) and Hand ($F(1, 47) = 12.27$, $p = .001$, $\eta_p^2 = .21$) and the interaction of Age and Hand ($F(1, 47) = 12.27$, $p = .001$, $\eta_p^2 = .21$), which was due to the presence of a right-hand advantage in the young group ($t(24) = 5.20$, $p < .001$) and its absence the old group, where the means were identical. The old group on average assembled fewer objects than the young group in the object assembly subtest ($t(47) = 10.96$, $p < .001$).

Similarly, age-related declines were evident in both the accuracy and the precision of the force-matching task with the ramp and square-wave targets. Fig. 2 shows accuracy (as the mean RMS error around the target) for both age groups for each trial with each target. The mean error was greater for the old than the young group for both the ramp target and the square-wave target ($F(1, 47) = 7.52$, $p = .009$, $\eta_p^2 = .14$ and $F(1, 47) = 14.54$, $p < .001$, $\eta_p^2 = .24$ for the two targets respectively). Accuracy increased with practice, shown by a statistically significant effect of Trial with both the ramp ($F(4, 188) = 4.28$, $p = .002$, $\eta_p^2 = .08$) and square-wave ($F(4, 188) = 3.10$, $p = .017$, $\eta_p^2 = .06$) targets. The interaction of Trial and Age was statistically significant for the ramp ($F(4, 188) = 14.18$, $p < .001$, $\eta_p^2 = .23$) but not the square-wave target ($F(4, 188) = 0.54$), reflecting the mean performance improvement by the old group between the first and second trial with the ramp target. Fig. 3 shows the precision of the pinch forces (as the mean of the residuals around the best-fitting straight line through the pinch forces during the 5-s ramp target and during the last 2 s of the square-wave target) for both age groups for each trial with each target. These sustained force levels were more precise in the young than the old group with the ramp target ($F(1, 47) = 152.35$, $p < .001$, $\eta_p^2 = .76$); the age difference was much smaller with the square-wave target and just failed to reach statistical significance ($F(1, 47) = 3.20$, $p = .08$, $\eta_p^2 = .06$). Neither the effect of Trial ($F(4, 188) = 1.42$, $p = .23$) nor the interaction of Age and Trial ($F(4, 188) = 1.54$, $p = .19$) was statistically significant with the ramp target; the effect of Trial was statistically significant with the square-wave target ($F(4, 188) = 5.03$, $p = .001$, $\eta_p^2 = .10$) but not the interaction of Age and Trial ($F(4, 188) = 0.55$).

3.2. Electrophysiological results

Illustrative test and conditioned MEPs from a young and an old subject are shown in Fig. 4. The measure of SICI (the ratio of the conditioned to test MEP amplitudes) taken at rest from each subject in the young and old age groups are shown in the frequency distributions in Fig. 5. Two features are of interest. First, the mean SICI score of the young group (0.30; SE = −.05, +.07) was smaller than that of the old group (0.61, SE = ±.11); this difference was statistically significant (assuming unequal variances, $t(38) = 2.60$, two-tailed $p = .02$). Second, the distribution of SICI scores of the old group was more dispersed than that of the young group (SD = 0.65 and 0.41 respectively). Inspection of Fig. 5 shows one young subject and four old subjects with SICI scores much greater than one, indicative of facilitation rather than inhibition; the ratios of these subjects ranged from 1.86 to 2.25. The greater proportion of subjects showing facilitation in the old than the young group was not statistically significant (Fisher's Exact Test, one-tailed $p = .19$); however, a power analysis showed that sample sizes of more than 100 would be required to detect a difference of this size with power = .80 (Faul et al., 2007). The stimulus intensities used in these five subjects who showed facilitation were very similar to those of the other subjects; the median test stimulus intensity (expressed as a percentage of stimulator output) was 60.0% for those showing facilitation and 62.5% for the remainder. One other young subject and three other old subjects showed ratios slightly greater than one. The mean MEP ratios of the two groups still differed after the five subjects who showed facilitation were excluded. In the reduced samples, the mean SICI score of the young group was 0.28 (SE = ±.05) and that of the old group was 0.47 (SE = −.07, +.08). This difference is a medium-sized effect (Cohen's $d = 0.62$) and was statistically significant ($t(42) = 2.07$, two-tailed $p = .04$). The age-related shift in the MEP ratios is evident in an increase in mode from 0.1 in the young group to 0.5 in the old group (Fig. 5). These values also indicate that the stimulus parameters used, including conditioning stimulus intensity, were suitable for eliciting SICI.

Fig. 6 shows the amplitude of individual test (single-pulse) and conditioned (paired-pulse) MEPs for two older subjects. The subject

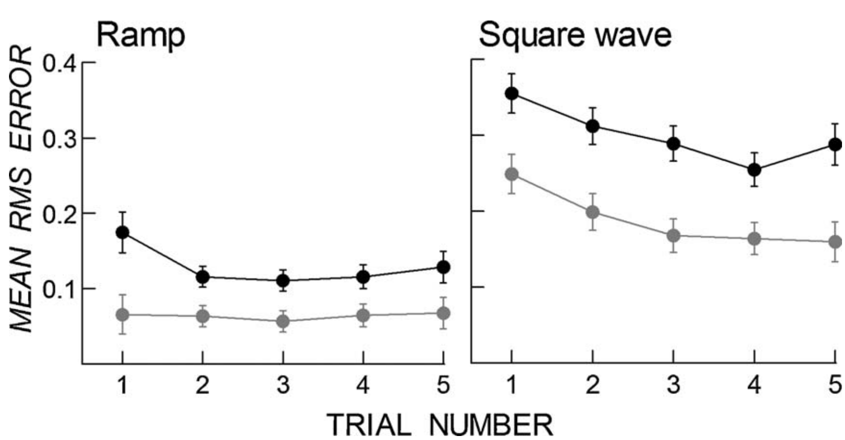

Fig. 2. Mean accuracy (expressed as the RMS error) for each trial for the ramp target (left panel) and the square-wave target (right panel) for the young sample (grey symbols) and the old sample (black symbols).

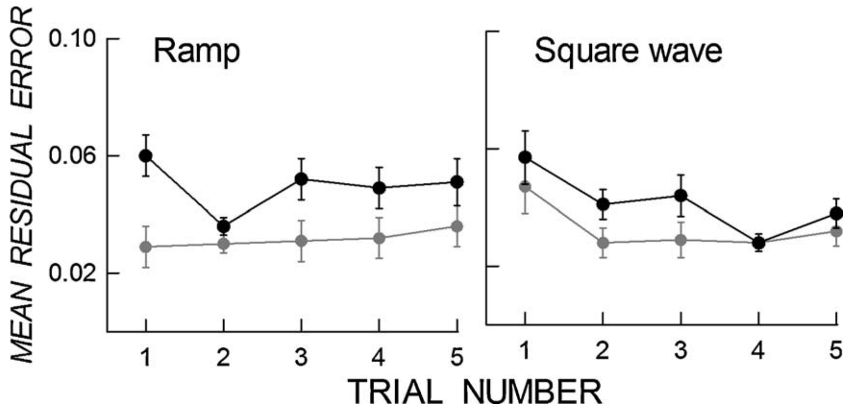

Fig. 3. Mean precision (expressed as the mean residual error around the best-fitting straight line) for each trial for the ramp target (left panel) and the square-wave target (right panel) for the young sample (grey symbols) and the old sample (black symbols).

whose MEPs are shown in the left panel displayed SICI comparable to a typical younger subject, with distinct (although overlapping) distributions of test and conditioned MEP amplitudes. The subject whose MEPs are shown in the right panel showed diminished SICI, which was the result of a uniform increase in the amplitude of the conditioned MEPs, rather than a patchy loss present on some but not other conditioned MEPs. This pattern was typical of those who showed an apparent loss of SICI.

3.3. Correlation of behavioral and electrophysiological measures

Scatter diagrams showing the relationship between the MEP ratio scores and performance on the Purdue Pegboard tasks and the force-matching tasks are shown in Figs. 7 and 8 respectively. The ratio scores were correlated negatively and moderately with performance on the pegboard tasks but not with the measures of either accuracy or precision on the force-matching tasks, despite the presence of substantial age-related performance differences on all measures. The correlation coefficients (with 95% confidence limits in parentheses) for the Purdue Pegboard tasks were −.42 (−.64, −.16), −.41 (−.62, −.15), and −.37 (−.60, −.10) for the pegs moved with the left hand, pegs moved with the right hand, and objects assembled respectively. Controlling for the effects of age with partial correlation reduced the correlation coefficients between the ratio scores and performance on the pegboard tasks to −.31 (−.54,

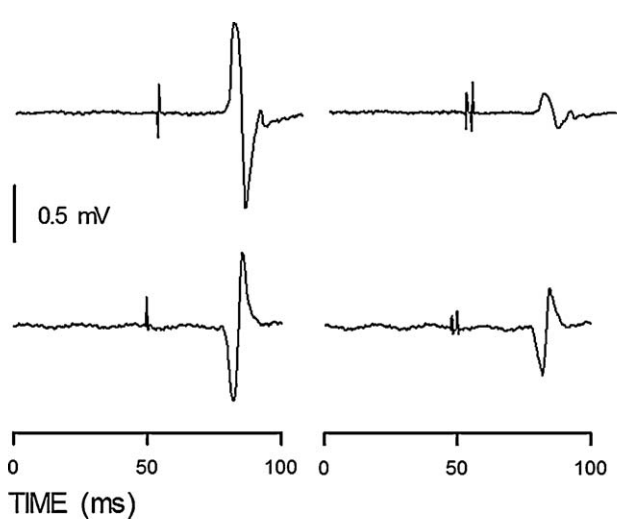

Fig. 4. Illustrative MEPS from a young (upper panels) and an old subject (lower panels). The two left-hand panels show test MEPs in the single-pulse condition and the two right-hand panels show conditioned MEPs in the paired-pulse condition. Stimulus artifacts are evident as vertical marks about 25 ms before the onset of the MEP in each case. The smaller conditioned than test MEPs show the presence of SICI in each subject.

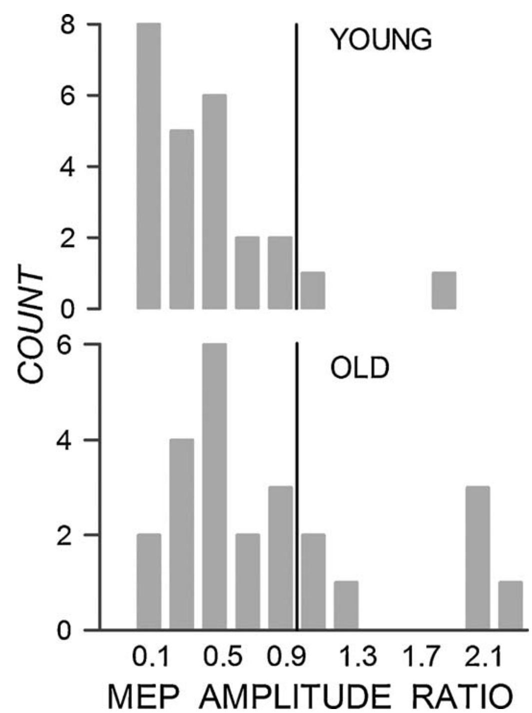

Fig. 5. Frequency distributions of the conditioned-to-test MEP amplitude ratios for the young sample (upper panel) and the old sample (lower panel).

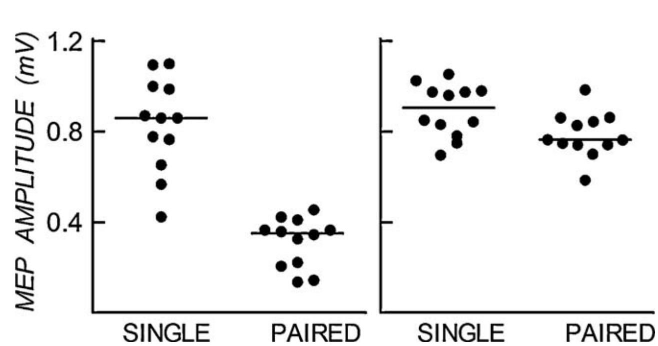

Fig. 6. Column scatter graphs showing the distribution of individual single- and paired-pulse MEP amplitudes for two subjects from the old sample (left and right panels respectively).

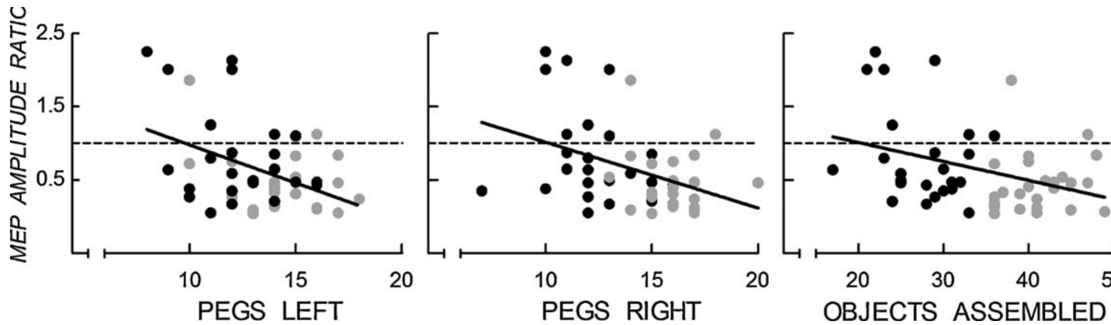

Fig. 7. Scatter diagrams showing the relationship between the measure of SICI (the ratio of conditioned-to-test MEP amplitude) and the three subtasks of the Purdue Pegboard task (left panel: the number of pegs moved with the left hand; middle panel: the number of pegs moved with the right hand; right panel: the number of objects assembled). Data points for young subjects are represented by grey symbols and those for old subjects are represented by black symbols. The best-fitting straight line for the entire data set is shown in each panel.

−.03), −.23 (−.48, .06), and −.12 (−.39, .17) respectively. Only the correlation between ratio scores and the number of pegs moved with the left hand remained statistically significant, presumably a result of the weaker association of age and this measure of performance of the non-dominant hand ($r = -.48$) than for pegs moved with the right hand and object assembly ($r = -.75$ and −.87 respectively). For average measures of all trials of the force-matching tasks, the correlation coefficients were −.07 (−.29, .29) and .15 (−.14, .42) for the accuracy measure for the ramp and square targets respectively, and .08 (−.21, .36) and −.15 (−.42, .14) for the precision measure for the ramp and square targets respectively. Correlation coefficients calculated separately for each of the five trials of the force-matching tasks were very similar to those for the average performance: for the accuracy measure. the range of coefficients was −.004 to −.14 for the ramp target and .13 to .19 for the square-wave target; for the precision measure, the range of coefficients was −.03 to .14 for the ramp target and −.15 to .00 for the square-wave target. Inspection of the scatter diagrams shows that the correlation of the MEP ratio scores and performance on the pegboard tasks depended on those subjects who showed atypical facilitation (i.e., the one young and four old subjects with MEP ratio scores of 1.86 and above). With these subjects removed from the analyses, the correlation coefficients were −.08 (−.38, .23), −.22 (−.49, .08), and −.16 (−.44, .14) for the pegs moved with the left hand, pegs moved with the right hand, and objects assembled respectively.

4. Discussion

The behavioral results were in accord with expectations: the expected right-hand superiority was evident on the Purdue Pegboard test in the young but not the old sample (Francis and Spirduso, 2000), and age-related decrements in performance were evident on all behavioral measures. The performance measures, therefore, were sensitive to the effects of aging. The electrophysiological results showed two changes in the paired-pulse TMS measurements associated with aging. First, the MEP ratio scores (the measure of SICI) were more variable in the old than the young sample, and second, the distribution of MEP ratio scores was shifted

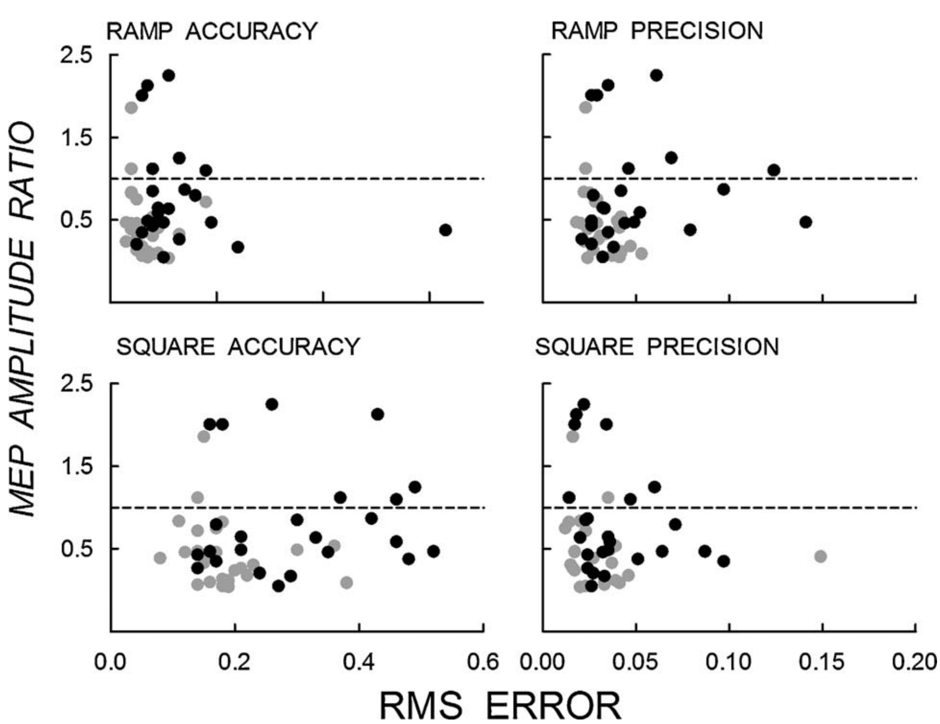

Fig. 8. Scatter diagrams showing the relationship between the measure of SICI (the ratio of conditioned-to-test MEP amplitude) and the accuracy and precision of the force-matching task for the ramp target (upper left and right panels respectively) and the accuracy and precision of the force-matching task for the square-wave target (lower left and right panels respectively). Data points for young subjects are represented by grey symbols and those for old subjects are represented by black symbols.

to higher values in the old than the young sample, indicating a small net loss of SICI with aging.

The greater variability of the ratio scores in the old sample is consistent with the data reported by Peinemann et al. (2001), whose Fig. 2 shows a greater spread of a composite measure of SICI (pooled over ISIs of 1, 3, and 5 ms) in the old than the young sample. Greater between-subject variability of cognitive, motor, and neurophysiological measures is characteristic of groups of elderly subjects (Vaillancourt and Newell, 2003; Hedden and Gabrieli, 2004). It is likely that the large variability in the MEP ratios in the elderly has contributed to the conflicting findings reported in the literature; sampling error, especially with the smaller samples typical of previous research, will inevitably limit the reproducibility of group results. The second of the age-related changes, the shift from smaller to larger MEP ratio scores in the old sample, is also consistent with the data reported by Peinemann et al. (2001). The measure of SICI, the ratio of conditioned to test MEP amplitudes, is a composite measure that reflects both inhibitory and facilitatory processes activated by the conditioning stimulus (Peurala et al., 2008). Two intracortical facilitatory processes have been identified with paired-pulse TMS: short-interval intracortical facilitation (SICF), which is evident in three successive peaks at ISIs of about 1.5, 2.5, and 4.5 ms (Tokimura et al., 1996; Ziemann et al., 1998), and intracortical facilitation (ICF), which is evident at ISIs of about 10–25 ms (Kujirai et al., 1993). Either or both of these facilitatory processes could be active to some extent when SICI is assessed with a 2-ms ISI, despite most subjects showing a net inhibition of the test MEP amplitude. The separate contributions of facilitation and inhibition can be assessed with SICI recruitment curves, which show the change in conditioned-to-test MEP ratios as a function of conditioning stimulus intensity. These curves are typically U-shaped, with the initial descending limb showing an increase in net inhibition with increasing conditioning stimulus intensity, and the later ascending limb showing a decrease in net inhibition with further increases in conditioning stimulus intensity. The ascending limb is thought to indicate an increasing contribution of facilitatory processes at the higher conditioning stimulus intensities (Peurala et al., 2008). SICI recruitment curves from samples of younger and older subjects show similar descending limbs, indicating a similar growth of inhibition with stimulus intensity in both groups, and systematically larger ratios in the ascending limb in the older sample, indicating a greater contribution of facilitation in the older than the younger group (Smith et al., 2009). The present results strengthen the evidence for an age-related shift in the balance of intracortical inhibitory and facilitatory processes in favor of facilitation, with a resultant net loss of SICI in older subjects.

The presence of atypical facilitation in some subjects is consistent with previous reports of individual data; atypical facilitation was present in 10% of the subjects in the current study, a figure in close agreement with previous observations of 13% of 53 subjects tested (Wassermann, 2002) and 11% of 84 cases (14 subjects each tested on 6 different occasions; Orth et al., 2003). It therefore appears that atypical facilitation is a real phenomenon, and not a procedural artifact or the result of measurement error. One limitation of the current study is that the conditioning stimulus intensity was set with reference to the intensity required to elicit an MEP of ~1 mV(specifically, at 70% of this level for each subject) and not with reference to motor threshold. It is possible, therefore, that the intensity of the conditioning stimulus might have been above motor threshold in some cases, leading to a net facilitation rather than a net inhibition. Although we cannot rule out this possibility, the similar incidence of facilitation in this study and the two previous studies which set conditioning stimulus intensity below motor threshold, and the high levels of SICI shown in the young group, suggest strongly that the present results are not an artifact of the stimulus parameters used in the present study. The presence of facilitation in the present study was related to performance on the Purdue Pegboard, but not to performance on the force-matching tasks. The relationship of the MEP ratio scores to the Purdue Pegboard measures was discontinuous: those subjects who showed atypical facilitation – most commonly, but not exclusively, the elderly – showed poorer performance on all measures of the pegboard task. The absence of correlation when the analysis was restricted to those subjects with MEP ratios less than or near one show that the level of SICI does not facilitate performance on the pegboard task in those subjects who showed a net inhibition. Rather, the correlational analysis indicates that a large shift in the balance of intracortical inhibition and facilitation toward facilitation, such that the ratios of conditioned to test MEP amplitude were much greater than one, was associated with below-average pegboard performance. This relationship between facilitation and pegboard performance strengthens the conclusion that atypical facilitation is a physiological process with a functional consequence, and not an artifact or an aberrant characteristic of some subjects without functional significance. The appearance of this relationship with the measures from the Purdue Pegboard test, but not from the isometric force-matching measures (which also showed an age-related decline), suggests that the presence of overt facilitation interferes with the effective and efficient sequencing of movements required by the Purdue Pegboard tasks. Performance on the isometric force-matching tasks, which required controlled force application and not sequenced individuated movements of different effectors, was not related to either the level of SICI or the presence of overt facilitation. Sequenced and individuated motor behavior is optimized by inhibition of antagonist and irrelevant muscle activity during movement. The central inhibitory control of antagonist activity, termed cortical reciprocal inhibition, is lost in the elderly (Hortobágyi et al., 2006), presumably leading to the greater coactivation of agonist and antagonist muscles with age (Hortobágyi and DeVita, 2006). Central inhibitory control of the activity of neighboring irrelevant muscles, which has been termed surround inhibition, has been shown to occur at the onset of an index finger movement (Sohn and Hallett, 2004), and is thought to act in part through SICI (Beck et al., 2008, 2009). Cortical reciprocal inhibition and SICI might work together to facilitate sequential individuated hand movements, and a general diminution of cortical inhibitory processes, leading to a preponderance of facilitation, might increase coactivation of antagonist and irrelevant muscles, and so interfere with sequential movements while leaving controlled force production unimpaired. Furthermore, it is known that all muscles acting on the thumb and index finger are coactivated during a maintained precision grip (Smith, 1981; Maier and Hepp-Reymond, 1995), and thus it is likely that coactivation of antagonist muscles during the force-matching tasks made them insensitive to the presence of atypical facilitation.

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