

Age-related changes in short-interval intracortical facilitation and dexterity.

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ABSTRACT

Functional changes in the primary motor cortex might contribute to the age-related decline in fine motor control. We measured short-interval intracortical facilitation (SICF) in an intrinsic hand muscle with paired-pulse transcranial magnetic stimulation at interstimulus intervals (ISIs) of 1.5, 2.5, and 4.5 ms in young and old subjects and examined its association with dexterity. We found age-related effects in SICF, with greater facilitation in old than young subjects at the 1.5-ms ISI and greater facilitation in young than old subjects at the 2.5-ms ISI. SICF at the 2.5-ms ISI was positively correlated with performance on a task that required coordinated and dextrous use of both hands, suggesting that this measure indicates a capacity for executing demanding manual tasks.

INTRODUCTION

The decline in motor control with age, which results in part from age-related changes in cortical control of voluntary movement [1], is particularly pronounced for fine hand movements [2,3]. Inhibitory and facilitatory processes in motor cortex that modulate the excitability of the output cells of primary motor cortex and hence shape voluntary movement have been identified with transcranial magnetic stimulation (TMS) [4]. These processes have been explored with paired-pulse TMS protocols, which typically show the effect of a conditioning stimulus (S1) on the amplitude of the motor evoked potential (MEP) evoked by a following test stimulus (S2). Augmentation of the conditioned MEP amplitude in an S1-S2 sequence above that elicited by the test stimulus alone reveals a predominant activation of facilitatory processes by the conditioning stimulus, whereas suppression of the conditioned MEP amplitude below that elicited by S2 alone reveals a predominant activation of inhibitory processes by the conditioning stimulus. In a variant of this procedure, in which a suprathreshold S1 precedes an S2 which is near motor threshold, the amplitude of the paired-pulse MEP is greater than that evoked by the suprathreshold S1 alone [5,6]. This facilitation (short-interval intracortical facilitation, SICF) is a cortical phenomenon [6-8], and results from interactions of S1- and S2-evoked activity within the network of excitatory interneurons that drive the corticospinal neurons. Varying the S1-S2 interstimulus interval (ISI) shows sharply tuned peaks in SICF with a period of ~1.5 ms, following the intrinsic periodicity of the excitatory interneuronal network.

The level of SICF measured at an ISI of 2.5 ms ($SICF_{2.5}$) in the cortical representations of two intrinsic hand muscles during preparation of a manual grasp has been shown to be sensitive to the particular grasp being prepared. During preparation to grasp a bar, SICF was

greater in the first dorsal interosseus (FDI) than the abductor digiti minimi (ADM), anticipating the relative engagement of these muscles in the grasp response itself. In contrast, during preparation to grasp a large disc, SICF was greater in ADM than FDI, again anticipating the relative engagement of the muscles in the response being prepared [9]. Furthermore, the difference between $SICF_{2.5}$ measured in the two muscles predicted the subsequent difference in the level of activation of the two muscles, both when grasping the handle and when grasping the disc [9]. $SICF_{2.5}$ therefore offers a sensitive measure of the excitability of excitatory processes in motor cortex that precede and produce dextrous environmentally guided hand movements. Changes in M1 with increasing age might lead to changes in SICF, and these changes might in turn be associated with the age-related decline in manual dexterity. The aims of this study were first, to measure age-related changes in SICF, and second, to explore the relationship between SICF and manual dexterity. We measured SICF in FDI at three ISIs (1.5, 2.5, and 4.5 ms) and manual dexterity (with the Purdue Pegboard test) in samples of young and old subjects.

METHODS

Data are reported for fifty-four healthy subjects, 27 younger subjects (19 females; median age = 18 years; range 17–37 years) and 27 older subjects (15 females; median age = 69 years; range = 60–89 years). All subjects were right handed with Laterality Quotients ≥ 80 on the Edinburgh Handedness Inventory [10]. Because mild cognitive impairment is associated with a loss of fine motor control [11] we tested only subjects who scored within the normal range (≥ 26) on the Montreal Cognitive Assessment [12]. The younger subjects were recruited from undergraduate students and the older subjects were recruited from the local community. The procedures were approved by the local Human Research Ethics Committee and all subjects gave written informed consent.

The testing procedure took about one hour, in which manual dexterity was measured and SICF measured with TMS. Manual dexterity was measured with the four sub-tests of the Purdue Pegboard test which were administered following the standardized testing procedure. The peg-moving sub-tests required subjects to retrieve small pegs from a well 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. These sub-tests were done with the left hand alone, the right hand alone, and with both hands simultaneously. The assembly sub-test 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. The measures taken were the number of pegs moved and placed in a 30-s period and the number of four-item objects assembled with both hands in a 60-s period.

For the TMS procedure, participants were seated in a comfortable reclining chair with the right forearm supported by a cushion with the elbow in semiflexion and the wrist in semipronation. Subjects had no behavioral task to perform and remained relaxed throughout the procedure. Surface electromyogram (EMG) recordings were made from the FDI muscle of the right hand with Ag-AgCl electrodes in a tendon-belly configuration and a ground electrode at the wrist. The raw EMG signal was amplified (1000x) and bandpass filtered (10–1000 Hz) and then digitized with 14-bit resolution at a sampling rate of 4 kHz. Peak-to-peak MEP amplitudes were measured in a 40-ms time window beginning 10 ms after the TMS pulse(s). Single- and paired-pulse stimuli were delivered by two MagStim 200² stimulators connected through a BiStim module to a figure-of-eight coil which was positioned flat on the head over the left motor cortex with the coil handle pointing backwards and rotated ~45

degrees away from the midline to induce a posterior-anterior current flow in the brain. The optimal coil placement for activation of the right FDI muscle was determined as the site over left motor cortex where slightly suprathreshold stimulation consistently produced the largest MEPs. A tripod was used to secure the coil in this position for the duration of testing. The resting motor threshold (RMT) intensity was then determined as the minimum stimulus intensity required to elicit at least five MEPs of 50 μ V or greater in ten successive stimulations and the stimulus intensity required to evoke an MEP with a mean peak-to-peak amplitude of about 1 mV when given alone was found. Mean RMT (in percent of maximum stimulator output) was 49.3 (SD=7.1) for the young group and 49.1 (SD=11.4) for the old group. The mean stimulus intensity required to evoke a 1-mV MEP was 55.0 (SD=8.2) for the young group and 54.6 (SD=13.4) for the old group. Following the established protocol [3] the intensity of S1 was set to evoke an MEP of \sim 1 mV when given alone and the intensity of S2 was set to 90% of RMT. Four stimulus conditions were given: a control condition (S1 alone) and three paired-pulse conditions (S1 followed by S2) at ISIs of 1.5, 2.5, and 4.5 ms. A session consisted of 20 randomized blocks of the four stimulus conditions, for a total of 80 trials. Inter-trial intervals were selected at random from 7, 8, 9, and 10 s. SICF is expressed as the ratio of the mean MEP amplitude evoked by the paired-pulse condition to that evoked by the single pulse alone (S1). The ratios were log transformed before analysis to normalize the distributions, and back-transformed means and standard errors are reported.

RESULTS

Table 1 shows the mean performance of both age groups for each sub-test of the Purdue Pegboard. The older group performed more poorly than the younger group on all sub-tests. On the unimanual peg-moving sub-test there were significant effects of Age ($F_{1,52}=59.25$, $p<.01$, $\eta_p^2=.53$) and Hand ($F_{1,52}=7.78$, $p<.01$, $\eta_p^2=.13$) and a significant Age by Hand

interaction ($F_{1, 52}=12.67, p<.01, \eta_p^2=.20$), which resulted from the presence of a right-hand advantage in the young but not the old group. Older participants inserted significantly fewer pegs with both hands than their younger counterparts ($t_{52}=6.58, p<.01$, Cohen's $d=1.5$) and also assembled significantly fewer objects than the younger participants on the assembly sub-test ($t_{52}=8.15, p<.01$, Cohen's $d=2.17$).

Table 1 about here

Figure 1 shows the mean amplitude ratio scores for both groups at each ISI. The lower limit of the 95% confidence interval of each mean was greater than one, indicating that facilitation was present in all conditions. Both age groups showed a systematic decline in SICF with increasing ISI, reflected in a significant main effect of ISI ($F_{2,104}= 64.99, p<.01, \eta_p^2=.56$). The main effect of Age was not significant ($F<1$), but there was a significant Age by ISI interaction ($F_{2,104}=9.58, p<.01, \eta_p^2=.16$). Analysis of the interaction with Fisher's LSD showed that $SICF_{1.5}$ was greater in the older than the younger group ($t_{104}=3.03, p<.01$) whereas $SICF_{2.5}$ was greater in the younger than the older group ($t_{104}=3.03, p<.01$). There was no significant difference in the levels of $SICF_{4.5}$ between the two groups.

Figure 1 about here

The relationship between the level of SICF at each ISI and performance on the Purdue Pegboard sub-tests was explored with a correlational analysis (see Table 2). There were weak negative correlations between $SICF_{1.5}$ and performance on the four sub-tests. In contrast, $SICF_{2.5}$ was positively correlated with performance on all four sub-tests; the correlations were weak for the two sub-tests which measured the number of pegs moved with the left hand and the right hand, and moderate (and statistically significant) for the sub-tests which measured the number of pegs moved with both hands simultaneously and the number of objects assembled by both hands. However, after controlling for the effect of age with partial correlation, the correlation between $SICF_{2.5}$ and object assembly remained significant ($r=.27$,

95% confidence interval .07, .50) whereas that with the number of pegs moved with both hands did not ($r = .16$, 95% confidence interval $-.10, .42$). The correlations between SICF_{4.5} and performance on all sub-tests were all near zero.

Figure 2 and Table 2 about here

DISCUSSION

There are three main findings: first, as expected, there was a general age-related decline in manual dexterity with an accompanying loss of asymmetry in the old group; second, there were age-related changes in SICF, with greater SICF_{1.5} in the old than the young group and greater SICF_{2.5} in the young than the old group; and third, there were moderate positive associations between SICF_{2.5} and performance on the Purdue Pegboard sub-tests that required both hands.

SICF was present at all ISIs, and was greatest at 1.5 ms and least at 4.5 ms, consistent with previous reports [5,6]. The first and later SICF peaks are affected differently by manipulation of TMS stimulus parameters, indicating different underlying physiological processes [13]. SICF_{1.5} is thought to result from S2-evoked excitation of the initial axonal segments of excitatory interneurons that were subliminally excited by S1, whereas SICF_{2.5} and later peaks are thought to result from summation of excitatory synaptic activity [14]. The differential sensitivity of SICF_{1.5} and SICF_{2.5} to the effects of healthy aging is the first demonstration that the different physiological processes underlying facilitation at these intervals are differentially sensitive to a biological variable.

Although uniformly negative, the correlations between SICF_{1.5} and the dexterity measures were weak and not significantly different from zero. Thus this probe of motor cortical excitability, despite being sensitive to aging, probably does not contribute to the age-related

loss of dexterity. The correlations between SICF_{2.5} and the number of pegs moved with the left and right hands separately were both positive, but again weak and not significantly different from zero. However, the correlations between SICF_{2.5} and the sub-tests that required use of both hands (peg moving with alternating hands and object assembly) were positive and moderate. Higher levels of SICF_{2.5} were associated with more pegs inserted with both hands and with more objects assembled using both hands, suggesting that the excitability of the underlying processes measured with the muscle at rest contributes to the effectiveness with which tasks that engage both hands are performed. The pattern of correlations observed between SICF_{2.5} and the four sub-tests can be interpreted in terms of the motor demands of the tasks. The two unimanual peg-moving tasks require successive grasps of a peg, transport, and placement in the target hole under visual guidance. Peg moving with both hands has the same demands with an additional demand that the movements of the hands are coupled spatially and temporally. Object assembly, in turn, has similar demands to peg moving with both hands, with an additional demand that different movements of the hands are coordinated and with a greater reliance on fingertip dexterity. The correlation of SICF_{2.5} with the last sub-test might reflect its greater motor demands. A greater excitatory capacity of the motor cortex, indicated by greater SICF_{2.5}, might support performance of the most demanding sub-test. The other sub-tests are less demanding, and so not as sensitive to the excitatory potential of the interneuronal circuits driving the output cells of the motor cortex.

Aging impairs precisely controlled hand movements [2,3] and coordinated bimanual movements [15]. The generally lower levels of SICF_{2.5} in the old than the young subjects might contribute to the age-related performance decline on coordinated bimanual movements that require precise fingertip control. The current study investigated SICF only in the dominant left motor cortex and it is not known if the age-related changes reported here are

also present in the non-dominant motor cortex. Nevertheless, the left motor cortex in right-handers is known to be dominant in preparation of movements for execution by both hands and in the execution of bimanual movements [16] and thus it is likely that the present findings are important for the control of hand movements generally.

CONCLUSIONS

The present study is the first to examine changes in SICF with aging, and the relationship between these changes and manual dexterity. Healthy aging differentially affects SICF_{1,5} and SICF_{2,5}, showing that the neurophysiological processes that produce facilitation at each ISI differ. The association of higher levels of SICF_{2,5} with better performance on dexterity tasks that required coordinated fingertip control of both hands shows a functional correlate of this cortical measure and suggests that it indicates cortical capacity to control demanding motor performance.

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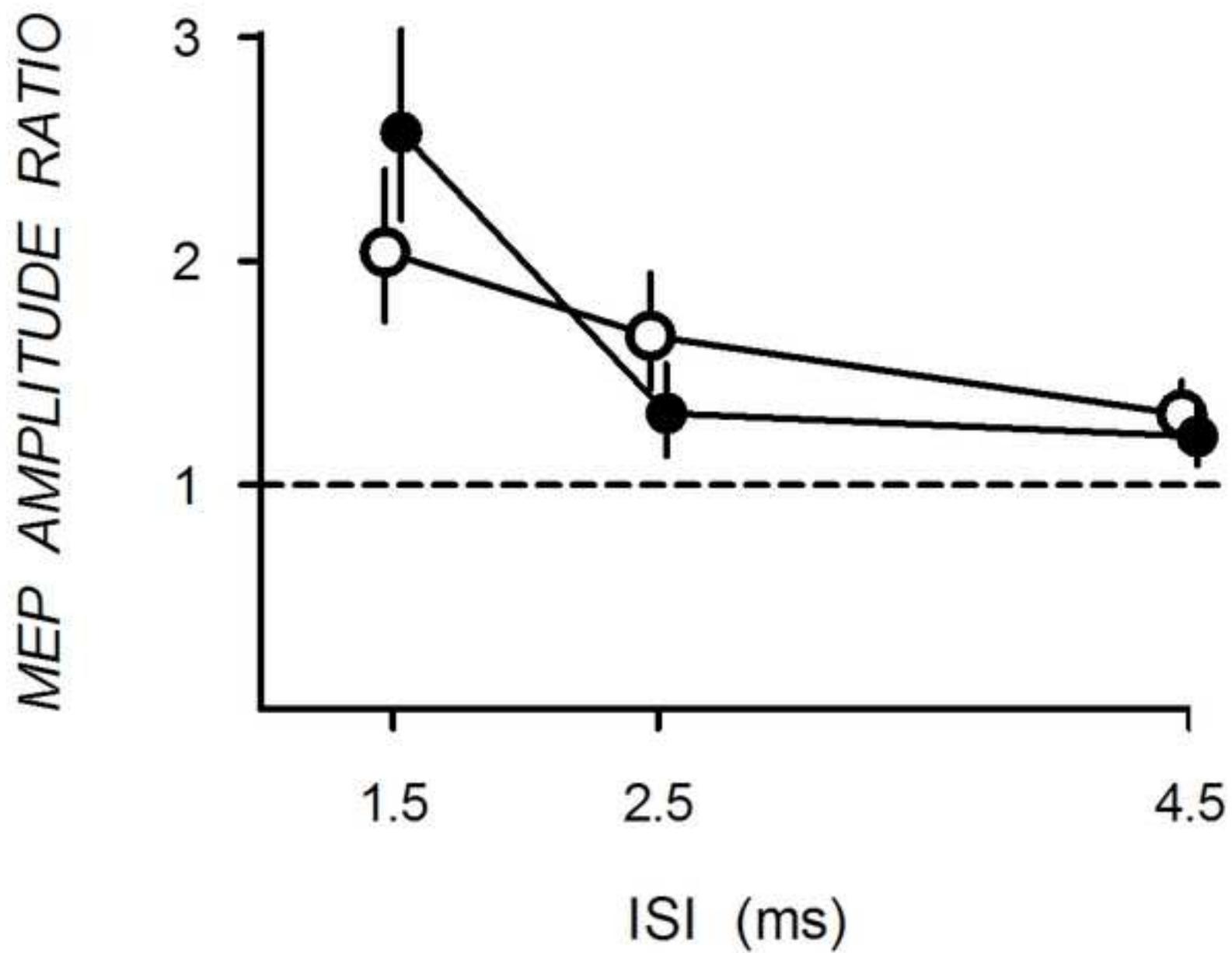
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FIGURE CAPTIONS

Figure 1. Mean MEP amplitude ratios for the younger (open circles) and the older (filled circles) group at each ISI. Error bars show the 95% confidence limits. Points are offset slightly on the abscissa for clarity.

Figure 2. The relationship between SICF at interstimulus intervals of 1.5 ms (top panels) and 2.5 ms (bottom panels) and performance on the four sub-tests of the Purdue Pegboard test. Panels A through C represent the relationship between SICF and the number of pegs inserted by each participant with the left hand (A), the right hand (B) and both hands (C). Panel D represents the relationship between SICF and the number of objects assembled by each participant. Open circles represent the young subjects and filled circles represent the old subjects.



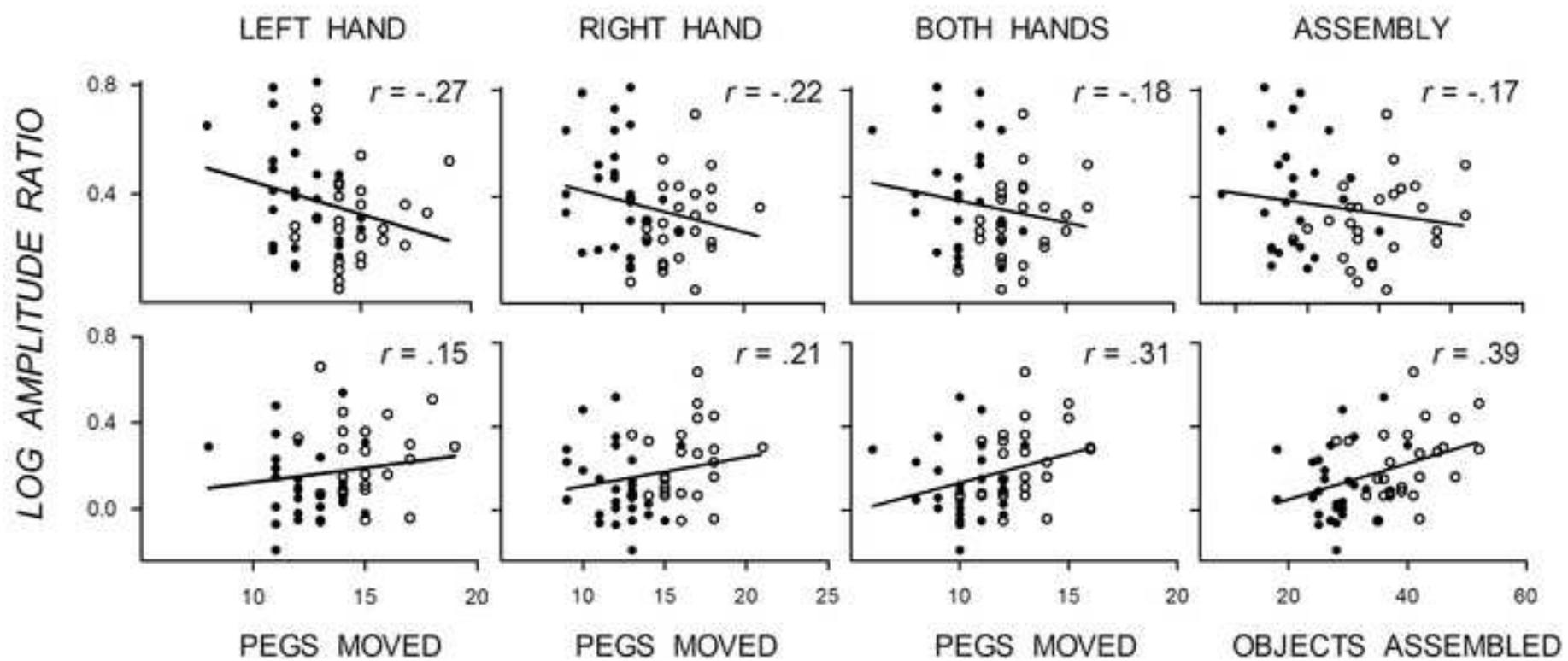


Table 1

The mean number of pegs inserted and objects assembled in the four subtests of the Purdue Pegboard test by the young and old groups. Standard deviations are in parentheses.

	Peg Moving Subtests			Assembly Subtest
	Left hand	Right hand	Both hands	
Young	15 (2)	16 (2)	13 (1)	40 (6)
Old	12 (2)	12 (2)	10 (1)	28 (5)

Table 2

Pearson's correlation coefficients between each subtest of the Purdue Pegboard test and SICF at interstimulus intervals of 1.5 and 2.5 ms. The 95% confidence intervals for the correlation coefficients are in parentheses.

	Peg Moving Subtests			Assembly Subtest
	Left hand	Right hand	Both hands	
SICF 1.5	-.27(-.50, .00)	-.22(-.46, .05)	-.18(-.43, .09)	-.17(-.43, .10)
SICF 2.5	.15(-.12, .41)	.21(-.06, .46)	.31 (.05, .54)	.39 (.14, .60)

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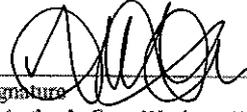
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