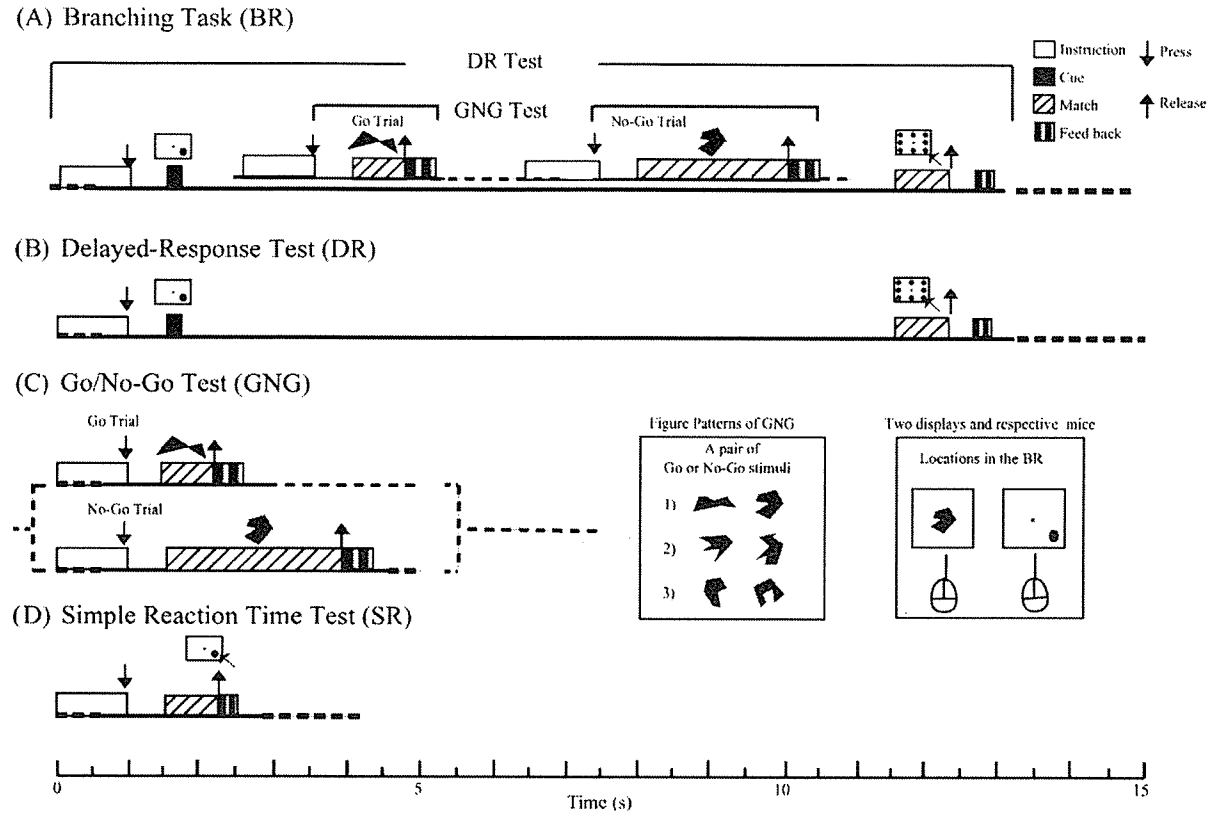

Fig. 1. Sequences of four employed task and tests: (A) branching task (BR). The subject faced two computer displays: a right display with a right mouse for the main Delayed-Response Test (DR) and a left display with a left mouse for the subroutine GNG with reversal (cf. inset in the bottom right). At first, in the right display, an instruction to press the right mouse appeared. As soon as the mouse was pressed, a Visual Cue (one of eight circles peripherally surrounded) appeared for 0.2 s followed by a 10 s delay period. During this period, the subject performed GNG trials twice. In the left display, an instruction to press the left mouse appeared and the subject pressed the mouse with the left hand. Then, one of Cues for a Go or No-Go trial in the GNG appeared (cf. inset in the bottom left). To a Cue for the Go trial, the subject released the mouse within 1 s, and to a Cue for the No-Go trial, the subject kept pressing the mouse for 2.5 s. After the subject responded, a Feed back display, indicating a correct or incorrect response, appeared for 0.5 s and an instruction for the second GNG trial appeared. Pressing the mouse initiated the second trial in a similar fashion. In GNG trials, regardless of the first or second trial, Cue figures for Go or No-Go trials appeared pseudo-randomly ((A) illustrated only one example of the GNG trial). Inset at the right bottom shows three pairs of figure patterns. These figure patterns with relations to Go or No-Go figures were reversed after seven correct responses. After completing the first pair, the second pair was used and after the second pair, the third pair was used. After two successive trials of GNG were completed in the left display, the subject had to respond to one of eight circles peripherally arranged and shown in the Visual Cue phase in the right display. After the subject responded, the Feed back display, indicating a correct or incorrect response appeared for 0.5 s. Then the trial was reset and an instruction for the next trial appeared. Thus, the subject performed the DR and GNGs during a delay of the DR, that is, the main DR and subroutine GNG a branching task. (B) Delayed-Response Test (DR). The subject used one computer activating the right display with the right-hand mouse (cf. inset in the bottom right, the right part of two displays). After pressing the mouse an instruction appeared, a Visual Cue appeared for 0.2 s followed by a 10 s delay period. After the delay period and with the mouse still pressed, eight circles of the Match phase appeared. In the Match phase, the subject released the mouse and pressed the circle shown in the Cue phase. After the subject responded, a Feed back display indicated a correct or incorrect response. After the Feed back display, an instruction for the next trial appeared. (C) Go/No-Go Test (GNG) with reversals. The subject used one computer activating the left display with the left-hand mouse (cf. inset in the bottom right, the left part of two displays). When the mouse was pressed after the instruction, one of the paired figure stimuli (Go or No-Go trial) of the Cue appeared in the center of the left display (inset at the bottom left indicates the successively used three pairs of figures pattern associations). After seven successive correct responses, the pair figure was reversed and then after completing responses to two Cue figures of the first pair, the next pair was used successively according to (1), (2), and (3) in the inset, bottom left. If a Cue indicating Go appeared, the mouse was released within 2.5 s. If a Cue indicating No-Go appeared, the mouse was withheld for 2.5 s. The association between the Go and No-Go figures was reversed after seven successive correct trials and then the figure pattern was changed into the next figure pattern. (D) Simple Reaction Time Test (SR). The subject used one computer activating the right display with the right-hand mouse (cf. inset in the bottom right, the right part of two displays). After pressing the mouse with the right hand, a Visual Cue appeared and the location on the display was pressed. After 0.25 of the Feed back display, indicating a correct or incorrect response, the trial was reset and an instruction for the next trial appeared.

for the next trial appeared. The Cue locations were selected pseudo-randomly. If the location was incorrectly pressed, the circle in the Cue phase was presented in the same location (correction method). If the subject released the hand from the mouse during the delay period, the trial was recorded as incorrect and was reset. The test was terminated when 32 trials were correctly performed. The test took about 6 min to complete.

Fig. 1C shows a symmetrically reinforced GNG, being identical to the subroutine GNG of the BR of Fig. 1A. An instruction (in Japanese) to press the mouse appeared and the subject pressed the mouse using the right hand. Half a second later, a Visual Cue for a 'Go trial' or ' No-Go trial' appeared in the center of the display in the Cue phase. After a response to the visual figures, a Feed back appeared for 0.5 s. After the Feed back display, the trial was reset and an instruction for the next trial appeared. Cue figures were presented pseudo-randomly. If seven successive correct responses occurred, the relationship between the correct response and the figures was reversed. In the case of the Go trial, as shown in the GNG trial in Fig. 1C, the subject released the mouse within 1 s, and a Feed back tone indicating a correct response sounded (pleasant tone), and the display was colored green for 0.5 s. Alternatively, in the case of the No-Go trials, as shown in the GNG trial in Fig. 1C, the subject withheld pressing the mouse for 2.5 s, and a Feed back immediately appeared for 0.5 s. After the Feed back display, the trial was reset and an instruction for the next trial appeared. There were three pairs of figure patterns (inset of Fig. 1, center bottom). Pairs were given sequentially{(1) → (2) → (3)}. In one of these pairs, after seven successive trials the association was reversed. If after the reversed trials there were seven successful trials, then the following pair was presented. The test was concluded after 90 trials. The test included six reversals in the case of the highest correct performance (correction method). The subjects took about 8 min to complete the test.

Fig. 1D shows a SR. At first, an instruction (in Japanese) to press the mouse with the right hand appeared on the display. When the mouse was pressed by the right hand, 0.5 s passed before a Visual Cue (circle, diameter: 3 cm) appeared in one of eight locations arranged peripherally in a square fashion. Releasing the right hand from the mouse, the subjects then touched the circle on the display within 10 s. Half a second after pressing, a colored feedback display and a sound appeared (correct response, green color with pleasant tone; incorrect response, red color with unpleasant tone). After the Feed back, the trial was reset and an instruction for the next trial appeared. The test was terminated when 32 trials were correctly performed, which usually took about 3 min. In all subjects, the tests were performed in the following order: SR, DR, GNG, and BR. Each test was separated by about 5–10 min. It took about 40 min to complete all the tests.

The correct performance rates were calculated as follows. The correct performance rate in the BR was the total correct number of trials (one correct trial including the correct DR and two correct GNG trials) divided by the total number of BR trials after excluding every first trial (three trials, including one DR trial and two GNG trials) when the trial of a reversed figure pattern of Go/No-Go appeared. The correct performance rate of the DR and GNG in the BR were separately calculated. In both the SR and DR, the correct performance rates were calculated as the number of total correct trials divided by the total number of trials. In the GNG, after neglecting the responses from the first trial after the figure patterns, the Go or No-Go, was reversed, and the correct performance rate was calculated as the total correct number of trials divided by the number of trials.

2.3. Maximal oxygen uptake ($\dot{V}_{O_{2max}}$) measurement

To determine the effects on aerobic fitness capacity of jogging training in the TG, the maximal oxygen uptake was measured. A graded exercise test was performed on a motorized treadmill (MAT-5500; Fukuda Denshi, Tokyo, Japan). The treadmill speed was initially set at 6.0 km/h with a 0% grade and was gradually increased by 1.2 km/h every 4 min. The heart rate was measured throughout the tests and was determined during the last minute of each submaximal stage, using a heart rate monitor (Aculex Plus; Polar Co., Tokyo, Japan). When the heart rate reached 70% of the heart rate maximum expected for the subject's age (220-age), the treadmill grade was continuously raised by 2% every minute until the subject reached exhaustion. The amounts of expired gases (O_2 and CO_2) and ventilation (VE) were autoanalyzed and the average values for every 20 s were obtained (Model 2900, SensorMedics Yorba Linda, CA). The criteria for achieving $\dot{V}_{O_{2max}}$ (Astrand, 1967) were (1) a maximal heart rate ±10 beats/min of the age-predicted maximal heart rate (heart rate = 220-age), (2) a respiratory exchange rate of at least 1.10 which was evaluated by energy metabolism to exhaustion, and (3) attained to plateau in the $\dot{V}_{O_{2max}}$. The $\dot{V}_{O_{2max}}$ values were calculated from the values of the highest 20 s collections, using Vmax software (Ver. 05-2A; Nihonkohden., Tokyo, Japan).

2.4. Data analysis

All of the analyses were performed using SPSS software for Windows (SPSS V11.0 for Windows, SPSS, Chicago, IL). A multiple comparison Tukey HSD test was used for comparing the time course changes in each group. The effect of jogging training, compared with NG subjects for 12 weeks, was evaluated using a two-way ANOVA with repeated measures. To compare the influences over the 12 weeks of no jogging periods after stopping the jogging (from weeks 12 to 24), and the aerobic fitness capacity caused by jogging training on $\dot{V}_{O_{2max}}$ during 12 weeks in TG subjects, a one-way repeated ANOVA was used. When the ANOVA revealed differences between the groups and time courses, a post-hoc comparison was done using a Tukey HSD test to identify which conditions were different each other. If an ANOVA revealed significant changes after stopping the jogging in TG subjects, the values between weeks 24 and 0 were compared using Student's t-test. Statistically significant relationships in the initial level (at week 0) and changes between $\dot{V}_{O_{2max}}$ and test performance were determined using a Pearson correlational analysis. Statistical significance was set at $P < 0.05$.

3. Results

3.1. General

Changes in the correct performance rates in the BR and three control frontal tests {DR, GNG, and SR} were examined and compared between TG and NG before (week 0), during (week 6), and after training (week 12). In the TG, these task and tests were also given at 18 and 24 weeks after stopping the jogging. The correct performance rates and reaction times of these task and tests were examined during and after jogging training. These average values were shown in the *top* and individual values except for those with SR were shown in the *bottom* of Fig. 2. A fitness test that measured maximal oxygen uptake ($\dot{V}_{O_{2max}}$), was also examined in the TG at weeks 0, 6, and 12.

3.2. Branching task (BR) performance during jogging

The correct performance rates markedly increased from week 0, through week 6, to week 12 in the TG but increased only slightly in the NG. Fig. 2A illustrates the changes in the total correct performance rate of the BR. As shown in Fig. 2A (*top*), from weeks 0 to 6, the rate was significantly increased in the TG ($P < 0.005$) but not in the NG.

From weeks 6 to 12, the rates did not increase in either group. The changes in the performance rate over 12 weeks in the TG were significantly different from those in the NG ($P < 0.005$). Between these groups, the difference in the change in performance rates was significant at weeks 0–6 ($P < 0.0001$) and also at weeks 6–12 ($P < 0.05$). Thus, the changes in the correct performance rate of the BR over 12 weeks were different between the NG and the TG.

3.3. Control tests performance

In both TG and NG, all control tests were performed at higher average correct response rates of more than 85% at all weeks tested.

3.3.1. Delayed-Response Test (DR)

The changes in the correct performance rates in the DR are shown in Fig. 2D. As shown in Fig. 2D (*top*), from weeks 0 to 6, the rate decreased significantly in the NG ($P < 0.05$) but increased significantly ($P < 0.005$) in the TG but changes did not significant from weeks 6 to 12. The rate changes over 12 weeks were not significant between the groups. Thus, the correct performance rate of the DR in the TG did not differ from that in the NG in any week tested, and both groups showed higher rates than in the BR.

3.3.2. Go/No-Go Test (GNG)

The changes in the correct performance rate in the GNG are shown in Fig. 2E. As shown in Fig. 2E (*top*), from weeks 0 to 6, the rate in the NG significantly increased ($P < 0.05$) but that in the TG did not. From weeks 6 to 12, the changes in the rate of the groups showed no significant difference. Neither did the rate changes differ between the two groups.

3.3.3. Go and No-Go performance of GNG

As for the Go performance of GNG at weeks 0–6 and 6–12, the rate in both groups did not significantly change and they were not different between groups over 12 weeks.

As for the No-Go performance of GNG from weeks 0 to 6, in the NG significantly increased ($P < 0.001$) but that in the TG did not. From weeks 6 to 12, the rate changes were not significant in either group and it was not different between groups over 12 weeks. Thus, the Go and No-Go performance did not show different changes over 12 weeks of jogging training.

3.3.4. Simple Reaction Time Test (SR)

The changes in the correct performance rate in the SR are shown in Fig. 2F. The rate was 100% in both groups over 12 weeks, and there were no significant rate changes between the NG and the TG. Thus, no performance changes were seen in the control tests over 12 weeks.

3.4. Contributions of main Delayed-Response Test (DR BR) and subroutine Go/No-Go Test (GNG BR) to branching task performance over 12 weeks

As described above, the correct performance rate in the BR increased more in the TG than in the NG. We examined which of the tests, the DR or the GNG, would contribute more to the rate changes in the BR. We measured the correct rates separately. At weeks 0, 6, and 12, the main DR BR correct performance rates of the TG and the NG were relatively higher, being more than 90% in the DR and more than 85% in the GNG.

The performance of the main DR in the BR (DR BR) is shown in Fig. 2B. As shown in Fig. 2B (*top*), at weeks 0–6, the rate increase in the NG was not significant, while that in the TG was significant ($P < 0.005$). At weeks 6 to 12, the rate increases were not significant in either group. The changes in the correct performance rates between the groups over 12 weeks were significantly different ($P < 0.05$), and there was a significant rate change between the groups at weeks 0–6 ($P < 0.01$). Thus, while the rates were relatively higher within a small range, there were rate change differences between the groups. Thus, rate changes in the DR BR increased in the TG more than in the NG.

The performance in the subroutine GNG in the BR is shown in Fig. 2C. As shown in Fig. 2C (*top*), the rate increases from weeks 0 to 6 were not significant in either group. From weeks 6 to 12, the changes in the rate showed no significant differences in the NG but increased significantly in the TG ($P < 0.01$). The rate changes over 12 weeks between the groups were significantly different ($P < 0.005$); they were different at weeks 0–6 and 6–12 ($P < 0.05$, respectively). The correct performance rate of the GNG BR over 12 weeks showed an increase in the TG. These results

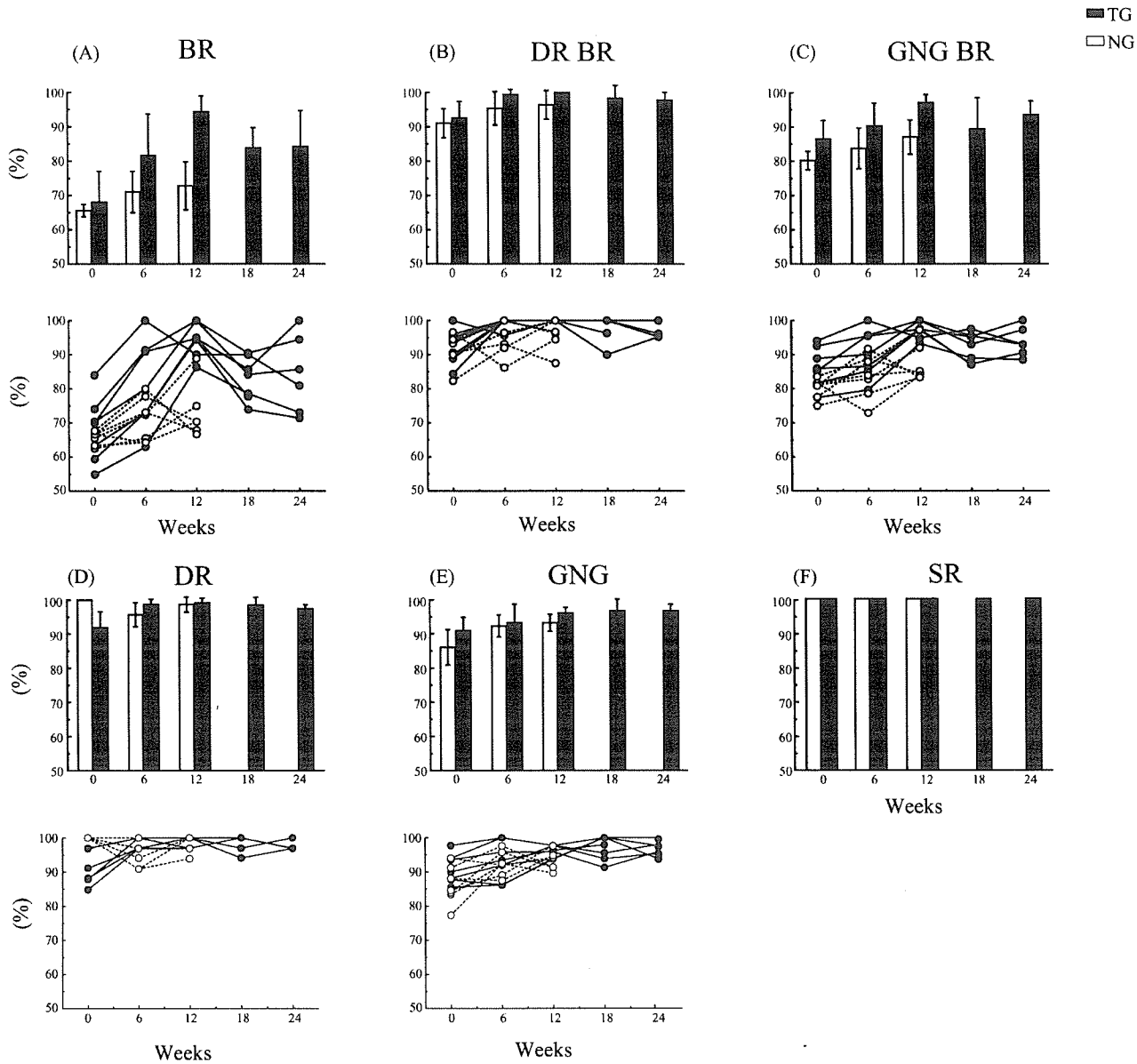

Fig. 2. Changes in the correct performance rates (%) of employed task and tests in the jogging trained group (TG; (■) and (●)) and in the non-jogging untrained group (NG; (□) and (○)). Ordinate: correct performance rate (%) in weeks 0, 6, 12, 18, and 24 in the TG, and weeks 0, 6, and 12 in the NG. During the first 12 weeks, the TG performed jogging and the NG did not. After 12 weeks, measurements were performed in the TG after stopping the jogging at weeks 18 and 24. *Top*: correct rate changes of both groups (%) are represented as the means ± S.D. by bar graphs. Below: individual rate changes by lines. (A–C) Branching task (BR) and (D–F) three control frontal tests. (A) Branching task (BR). (B) Correct performance rate of only the Delayed-Response Test (DR) of the BR Task (BR DR). (C) Correct performance rate of only the Go/No-Go Test (GNG) of the BR Task (BR GNG). (D) Delayed-Response Test (DR). (E) Go/No-Go Test with reversals (GNG). (F) Simple Reaction Time Test (SR).

indicate that the correct performance rate in the GNG BR increased in the TG. Further, the rate changes of the GNG BR between each 6 week period were similar to those in the BR rate, although the changes were smaller.

The correct performance of Go and No-Go in the GNG of BR are separately examined. The correct rate of Go trial from weeks 0 to 6, the rate increases were not significant in either group. At weeks 6–12, the rate increase in the NG was not significant, while that in the TG was significant ($P < 0.05$). The rate change of Go performance of GNG in BR showed no difference between the groups. As for the No-Go performance of GNG in BR from weeks 0 to 6, the rate increases were significant in either group ($P < 0.05$, respectively). At weeks 6–12, the rates were not changed significantly in both groups but in the TG showed statistically weak power ($P = 0.07$). The change of the rate over 12

weeks between groups in the No-Go performance showed no statistical significance but there is tendency to increase of correct performance rate ($P = 0.07$). These results in the GNG of BR showed that Go performance could not see any influence but No-Go performance could see a tendency of influence over 12 weeks of the training.

3.5. Changes in the correct performance rates at 18 and 24 weeks after stopping the jogging in the TG

3.5.1. Branching task (BR) performance after stopping the jogging

After stopping the jogging training that lasted 12 weeks, the correct performance rate in the BR, as shown in Fig. 2A (*top*), decreased at weeks 18–24. The decrease was significant over the 12 weeks after stopping the jogging ($P < 0.05$). From weeks 12 to 18, the rate decrease was significant ($P < 0.05$), but from weeks 18 to 24 it was not. The correct rate at week 24 was still significantly higher than that before jogging at week 0 ($P < 0.05$).

3.5.2. Control tests (DR, GNG, and SR) performance after stopping the jogging

After stopping the jogging training, the correct performance rate in the DR decreased slightly at week 18–24. The rate changes after stopping the jogging of the GNG were almost no change at week 18–24. The rate change of the SR after stopping the jogging show a maintenance of the rate at 100%. There were no significant changes in the control tests after 12 weeks of stopping the jogging.

Thus, there was a gradual decrease in the BR performance after stopping the jogging but the correct rate at week 24 was still higher than that in the control before the training. There were no changes seen in the control tests.

3.5.3. Main Delayed-Response Test (DR BR) and subroutine Go/No-Go Test (GNG BR) of branching task performance after stopping the jogging

In the DR BR after stopping the jogging, as shown in Fig. 2B (*top*), the correct performance rate in the DR BR decreased slightly at week 18–24. In the GNG BR after stopping the jogging training, the correct performance rate decreased slightly at week 18–24, as shown in Fig. 2C (*top*). The change in the correct performance rate of the DR BR and of the GNG BR showed no significant decrease after stopping the jogging.

3.6. Reaction time changes of employed tests

The reaction times were compared between the NG and the TG over 12 weeks and after stopping the jogging in the TG at weeks 12–24. No significant changes in reaction times occurred during or after stopping the training.

As shown in Fig. 3A, the average values of the reaction times (RT) in the SR at weeks 0–12 were 220–180 ms in the NG and 200–150 ms in the TG. After stopping the jogging, the RTs in the TG were slightly shorter than those during training being. As shown in Fig. 3B, the DR in the RT in the NG did not change, being about 320 ms and that in the TG was 360–280 ms over 12 weeks. After stopping the jogging, the RTs in the TG were about 330–310 ms. As shown in Fig. 3C, the average of the RTs from weeks 0 to 12 in the Go trials of the GNG were 690–770 ms in the NG and 700–670 ms in the TG. After stopping the jogging in the TG, the RT was about 630 ms over 12 weeks. Fig. 3D shows the average RT of the main DR in the BR. The RT at weeks 0–12 in the NG was about 550–460 ms and that of the TG was about 480–360 ms. After stopping the jogging in the TG, the RT was about 330 ms over 12 weeks. We were not at all able to detect significant changes in reaction times in tests over 12 weeks in both groups and after 12 weeks of stopping jogging in the TG. Thus, our findings indicate that jogging training did not shorten the RTs.

3.7. Aerobic fitness capacity changes associated with jogging training as revealed by maximal oxygen uptake ($\dot{V}_{O_{2max}}$)

We measured the maximal oxygen uptake in seven TG subjects over 12 weeks to evaluate their aerobic fitness capacity during jogging training. Table 2 shows our findings as measured before the jogging program at week 0, and at weeks 6 and 12 in the TG.

The yielded $\dot{V}_{O_{2max}}$ (ml/min kg) values in the present subjects were comparable to those for individuals of average fitness among normal healthy Japanese subjects (Isokawa et al., 2000). The changes were significant over 12 weeks ($P < 0.0001$). A significant change was seen from weeks 0 to 6 ($P < 0.0005$) and from weeks 6 to 12 ($P < 0.005$). Thus, the aerobic fitness capacity of these subjects is considered to have improved in response to the jogging training. We also examined the correlations between the $\dot{V}_{O_{2max}}$ values and changes in the correct performance rates (%) for all of the frontal tests we employed. We found no significant relations between changes in aerobic fitness capacity and performance in any of the frontal tests.

Table 2
Maximal oxygen uptakes ($\dot{V}_{O_{2max}}$) over 12 weeks in the trained group, measured during the control period at weeks 0, 6, and 12

Subjects	0 weeks	6 weeks	12 weeks
$\dot{V}_{O_{2max}}$ (ml/min kg)			
1	40.7	42.7	43.7
2	42.2	44.3	45.6
3	48.2	50.7	50.8
4	44.4	45.4	46.6
5	40.8	43.0	43.9
6	46.0	47.1	48.8
7	45.2	46.4	46.7
Mean ± S.D.	43.9 ± 2.6	45.7 ± 2.6	46.6 ± 2.4

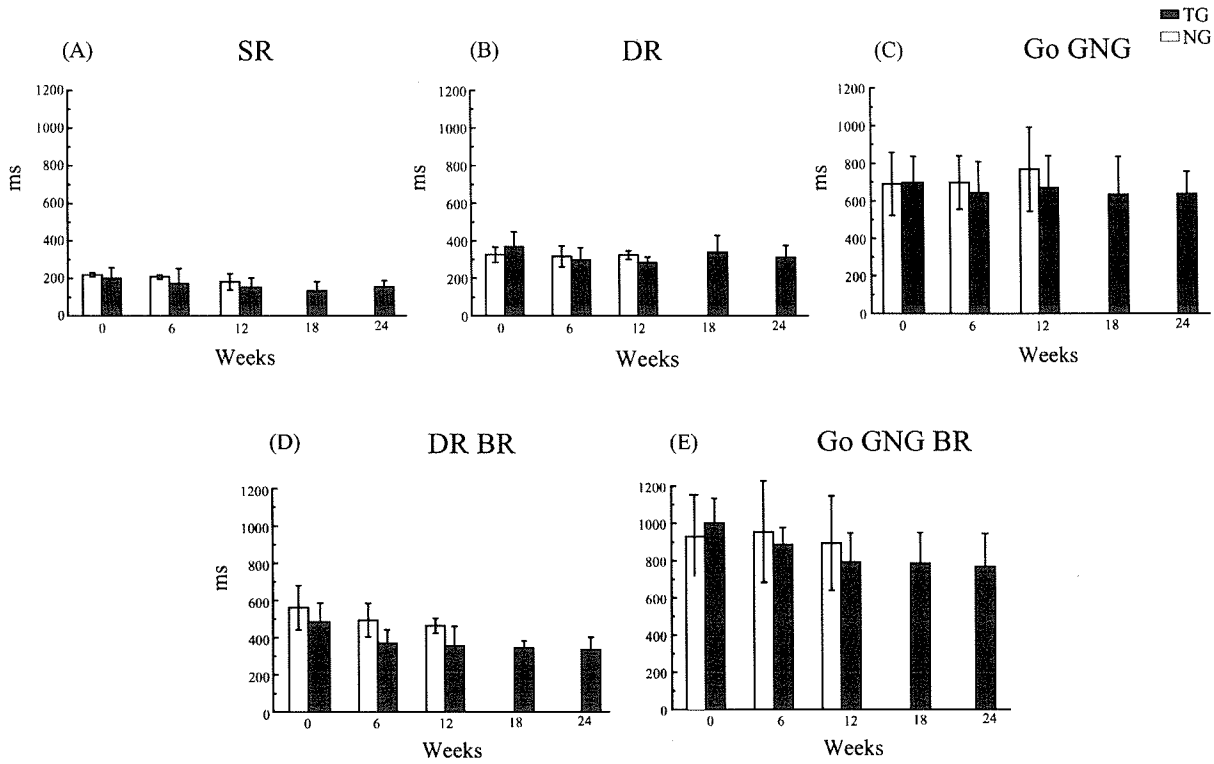

Fig. 3. Changes in reaction times of employed tests in the jogging trained group (TG; (■)) and non-jogging untrained group (NG; (□)). Ordinate: reaction times (ms) with means ± S.D. (A) Simple Reaction Time Test (SR). (B) Delayed-Response Test (DR). (C) Response times in the Go trials in the Go/No-Go Test (GNG) with reversal. (D) Response times in the DR in the branching task (BR-DR). (E) Response times in the Go trials of the GNG in the BR (BR-GNG (Go)).

4. Discussion

In the present study, we examined the effect of habitual jogging on prefrontal functions, using tests selected to allow the detection of functional changes in the prefrontal cortex. We measured the changes in the correct performance rate, which increased with repeated jogging training. The prefrontal tests included a spatial working memory test (or DR) with a 10 s delay period and a symmetrically reinforced GNG with a reversal. We developed a new test, which we used a term as a Branching Test or BR, in which these two single tests were combined in a main-subroutine fashion such that during a delay period of the main DR, a GNG was performed twice and its Visual Cue-response associations were reversed after seven successive correct responses. A SR was also given. We found that jogging training for 12 weeks gradually increased the correct performance rate in the BR, which increased from 65 to 95%, while the rates in the DR, GNG, and SR were not influenced, being maintained at approximately 90–95%. Further, after stopping the jogging training, the correct performance rate of the BR decreased while those of the other tests were unchanged.

For the prefrontal tests, we attempted to choose tests in which there was expected to be increased prefrontal activity, such as may be required for jogging in the streets. A spatial test was considered first, since spatial working memory may be required when joggers pass through certain jogging points in the streets, which may be recalled both before and during jogging. Further, since joggers at crossroads may be forced to stop or to select a road to continue on, with or without traffic signals, we included a GNG. The prefrontal neuronal activities during these two tests have been well studied in monkeys (Fuster, 2001). Specific and non-specific neuronal activities associated with a spatial working memory have been demonstrated during a Cue and the ensuing delayed periods (Fuster and Alexander, 1971; Kubota et al., 1974). Visual Cue related activity has been shown to have relatively wide visual receptive and memory fields (Mikami et al., 1982; Funahashi et al., 1989). Activity related to memory-based execution and to a decision for execution has also been investigated (Kubota and Niki, 1971; Kubota et al., 1974; Kubota and Funahashi, 1982; Kim and Shadlen, 1999). These spatial working memory-related activities have been actively studied in the periprincipal region, predominantly in Walker's area 46 (Walker, 1940). Neuronal activity related to a Go/No-Go task has been analyzed in the arcuate area (Petrides, 1985, 1986), and Go and No-Go performance-related and reversal-related activities have been demonstrated (Komatsu, 1982; Kubota and Komatsu, 1985; Watanabe, 1986). All these studies have shown that neurons

in the prefrontal cortex are activated during the correct performance of working memory and GNGs. It is thought that these prefrontal neurons are activated in the human during the correct performance of spatial working memory tests and GNGs. However, these tests are relatively easy to perform as single tasks. Even 7.5- to 12-month-old human infants and 3-month-old rhesus monkey infants (Diamond and Goldman-Rakic, 1989; Kubota, 1994) could learn and perform these tests with a 5–10 s delay. Thus, to detect changes in the prefrontal functions associated with habitual jogging in healthy adults, we had to develop a more difficult test. Recently, Baddeley et al. (2001) showed that, if two tasks were performed simultaneously (dual task condition), it was more difficult to perform them than when they were single tasks. Further, Koechlin et al. (1999) introduced a relatively difficult dual task in which, combining a visual discrimination GNG and a working memory test as the main DR, and adding a GNG subroutine (branching test), they showed that the anterior prefrontal cortex is activated during the branching test. Thus, we developed a similar branching test or task (BR), involving a main DR and a subroutine GNG. Since the performance characteristics of the task in the human studies were not available, we developed our own performance parameters, based on trial and error. First, we used a 10 s delay period as the longest delay allowed in a single trial. Second, to make the selection difficult, we chose eight Visual Cues with shorter periods (200 ms). Third, to create a heavy memory load, the subroutine Go/No-Go trials were repeated twice during each delay period of the DR with reversals after seven trial successes. These parameters were set so that the correct performance rates prior to training would be at about the 50–60% level in both the jogging group (TG) and non-jogging groups (NG), and at about the 80–90% level after the training. This allowed us to detect changes in the correct rate in the BR that appeared to reflect prefrontal function changes associated with jogging training. We did not determine the part of the prefrontal cortex that was active during Branching, or the number of trials and time sequences of the Cue and delay that were needed to complete the tasks, which should be the subjects of future studies with use of visual imaging techniques.

Recent human imaging studies have shown that spatial working memory tasks could activate various regions of the dorsolateral prefrontal cortex (Jonides et al., 1993; Courtney et al., 1997, 1998; Smith and Jonides, 1998; Fletcher et al., 1998; Duncan and Owen, 2000; Fuster, 2001). The dorsolateral prefrontal cortex activities may be related to the maintenance of spatial working memory and its execution towards a goal. Studies of a variety of Go/No-Go Tasks have shown that various regions of the prefrontal cortex are activated, such as the right frontal regions (Kawashima et al., 1996), the dorsolateral frontal cortex (Sasaki et al., 1996), Broadmann's area 45 (Konishi et al., 1999), and the middle frontal cortex (Watanabe et al., 2002; Sasaki et al., 1996). Further, when the two prefrontal tests were combined in a main and subroutine fashion, the anterior prefrontal cortex became active (Koechlin et al., 1999, 2000). We assume that our BR activates the anterior prefrontal cortex. In our preliminary studies using two kinds of frontal tests, a Delayed-Matching Test and a GNG, we found selective activities in Broadmann's areas 9 and 10 (Taira et al., 2001; Harada et al., 2002).

Habitual jogging improved the correct performance rate in the BR in the TG but not in the NG. Further, this performance change in the TG was reduced after jogging was stopped. It seems, therefore, that plastic BR performance change was influenced by jogging and may reflect use-dependent plastic changes in the synapses or vascular system of unknown prefrontal neurons induced by repeated jogging for 12 weeks. It would be interesting to know how these cortical area activities would change after repeated jogging. It may be that jogging on a road would operate like a single session of a BR, concomitantly performed as a spatial working memory test with a GNG for decision or selection. In other words, a BR could be approximated by memorizing, remembering, or representing certain spatial locations and having goals, which involves selection and decision. Further, jogging-induced task improvement may influence these neuroplastic changes even in the human brain as revealed by animal studies in which neurogenesis and angiogenesis were induced in turn. In the rat, it was shown that running on a running wheel enhanced spatial learning with increased neurotrophic factor (BDNF), nerve growth factor (NGF), or insulin-like growth factor (IGF-1) in the hippocampal region, caudal cerebral cortex, and prefrontal cortex (Van Praag et al., 1999; Cotman and Berchtold, 2002; Anderson et al., 2000; De Bruin et al., 1990; Fordyce and Farrar, 1991; Carro et al., 2001). It was also shown that neuromuscular activity is necessary to maintain a normal level of BDNF (Gomez-Pinilla et al., 2002). Further, running induced neurogenesis due to an enhanced LTP with improved spatial learning in the hippocampus (Van Praag et al., 1999) and the neocortex (Ehninger and Kempermann, 2003). Moreover, exercise has been shown to cause angiogenesis in the cerebellar cortex (Black et al., 1990) and in the primary motor cortex with increased cerebellar blood volume (Swain et al., 2003). Since these animal studies suggest that jogging could enhance neuronal plasticity and/or vascular improvement, then it is understandable that habitual jogging would improve performance in the BR and that cessation of this activity would likely decrease performance.

Previous studies using aerobic exercise training in elderly subjects showed that exercise improved executive performance in cognitive tests, and they suggested that this may be related to improvements in cardiovascular fitness caused by the training (Hall et al., 2001). After 4 months of aerobic exercise training, improved digit symbol and Stroop test performance, together with a significant increase of cardiovascular function, have been reported (Dustman et al., 1984). After 10 weeks of aerobic exercise, improvements in reaction time and attentional tests, which comprised a time-sharing task and an attentional flexibility task, have also been shown (Hawkins et al., 1992). Recently, Kramer et al.

(1999) showed that 6 months of walking training, associated with a slight improvement of cardiovascular function, resulted in decreased reaction times in a task-switching test, response-compatible test, and stopping test. In the present study, however, the reaction times did not show significant changes over 12 weeks of training, although significant improvement of cardiovascular function was observed. There are several reports in which the reaction times were different between the young and the elderly (Spirduso, 1980; Rypma and D'Esposito, 2000). It appears that the initial performance seems to be impaired in elderly but not in young subjects. Therefore, it is possible that the differential changes of reaction times by training might be due to an age difference. Further, the task improvement by the training was only seen in the BR and not in the control spatial working memory test (DR) and decision/inhibitory control test (GNG). In studies in which aerobic exercise induced performance changes in executive tests, some reports showed no clear changes of executive test performance using a neuropsychological battery. Further, long-term aerobic training did not influence cognitive tasks in a study of the elderly (Madden et al., 1989; Blumenthal et al., 1991; Hill et al., 1993). Kramer et al. (1999) and Colcombe and Kramer (2003) claimed that after the aerobic training in elderly subjects, selective task improvement, including frontally mediated task demands such as coordination, inhibition, planning, and working memory, would occur. In addition, Hall et al. (2001) showed that exercise training with improved cardiovascular fitness would specifically affect frontally mediated executive processes. Our tests, which are considered to involve a frontally mediated executive process in the young subjects, did not necessarily show improvement with exercise. These differences in exercise training might reflect the test sensitivity and/or changes in ability with age. Since our BR included aspects of working memory, inhibitory control, and task switching, it seems to be useful and appropriate for assessing the aerobic training of frontally mediated executive functions, and we found that the jogging training clearly improved this performance in the young subjects but not in the elderly. Thus, training-induced cortical plasticity appears to be task-specific, since training may selectively activate some of the prefrontal–premotor cortical circuitry. We suggest that training may improve task performance-mediated prefrontal function and that this reflects also regional functional ability.

Our data showed that the performance improvement in the BR was greater in the subroutine GNG component than in the main DR component. The performance of the subroutine task required the rapid switching and dividing of attention from the main task to the subroutine task during the BR. The observed improvement in the performance of the subroutine task associated with jogging training may reflect an improvement in attentional control.

Finally, in the present study, we asked joggers to draw their courses as road maps, before and after jogging session but we did not ask non-joggers to do so. Improved BR in the present study might be due to working memory task training, as drawing maps. Recently, it was shown that daily working memory task training for 5 weeks improved performance and increased the prefrontal and parietal regional activities (Olesen et al., 2004). It is possible that the training as map drawing procedure might have affected positively their spatial working memory performances and resulted in an improved BR performance. However, we cannot extract separately the influence of jogging training with or without map drawing administration in this study. In the future studies, it is necessary to abstract effects only due to jogging, and also to identify and understand changes in prefrontal activities in the human associated with aerobic exercise training with jogging as well as walking.

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RESEARCH ARTICLE

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Effect of body weight support on cortical activation during gait in patients with stroke

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Abstract Treadmill training with body weight support (BWS) was shown to improve locomotion after stroke. We investigated whether BWS affected cortical activation during gait using an optical imaging system. In six patients with subcortical stroke, BWS lowered activation in the sensorimotor cortex (SMC) as assessed by task-related changes of oxygenated hemoglobin levels ($P < 0.01$). The changes of SMC activation correlated with those of cadence ($P < 0.05$). Improvement of asymmetry in SMC activation also correlated with improvement of asymmetric gait ($P < 0.05$). In five age-matched controls, BWS increased overall activation ($P < 0.05$) but did not modify gait parameters and there was no correlation between gait parameters and SMC activation. It is suggested that BWS might improve efficacy of SMC function in patients with stroke.

Keywords Stroke · Body weight support · Gait · Recovery · NIRS · Rehabilitation · Optical imaging

Introduction

There is abundant evidence that functional recovery after stroke depends on reorganization of damaged neuronal networks (Ward and Frackowiak 2004). Task-oriented strategies of neurorehabilitation appear to improve functional outcome but also modify cortical motor maps. For instance, reorganization of hand area in the primary motor cortex in the affected hemisphere was associated with functional improvement after constraint-induced movement therapy (Liepert et al. 2000). In terms of gait training, several studies have demonstrated that treadmill training with partial body weight support (BWS) improve locomotor outcome of patients with stroke (Hesse et al. 1994, 1995; Visintin et al. 1998; Pohl et al. 2002; Sullivan et al. 2002). Neural mechanisms underlying the efficacy remain unclear although both the spinal and cerebral neural networks are likely to be involved (Wickelgren 1998; Miyai et al. 2002a). Optical imaging technique using near infrared spectroscopy (NIRS) enables measurement of cortical activation as assessed by changes in hemoglobin oxygenation during human gait. In healthy subjects, cortical activation as assessed by task related increase of oxygenated hemoglobin (oxyHb) during gait centered in medical sensorimotor cortices (SMC) and supplementary motor areas (SMA) (Miyai et al. 2001). In patients with hemiparetic stroke, sensorimotor activation was asymmetrical and there was an enhanced activation in the premotor regions (Miyai et al. 2002a). Subsequent follow-up study showed that locomotor recovery was associated with improved asymmetry of sensorimotor activation (Miyai et al. 2003). In this study, we tested whether BWS altered gait parameters and cortical activation patterns in patients with stroke. To eliminate possible effect of physical assistance on cortical activation by therapists (Miyai et al. 2002a), we studied patients with subcortical stroke who could ambulate at least with supervision.

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Methods

We studied six patients with hemiparesis due to initial subcortical stroke (five males, one female, two with right and four with left hemiparesis, four with cerebral infarction, two with cerebral hemorrhage, 57 ± 6 years old on average, and 75 ± 27 days poststroke, 159.2 ± 6.5 cm in height, Table 1) with mild to moderate hemiparesis who were able to ambulate with supervision using a cane. They had similar subcortical lesions involving the internal capsule or corona radiata. All were right handed. Fugl-Meyer motor scale (Fugl-Meyer et al. 1975) for the lower extremity (mean ± SD) was

Table 1 Clinical characteristics of patients with subcortical stroke

No.	Age	Sex	Type	Days	Lesion	Side	FM/UE	FM/LE
1	56	M	H	47	IC, Th	R	60	29
2	47	F	I	107	CR	L	8	9
3	58	M	H	108	IC, Th	R	30	8
4	54	M	I	73	Pt, CR	L	6	20
5	60	M	I	60	CR	L	10	27
6	64	M	I	53	CR	L	5	5
Mean ± SD	57±6			75±27			20±22	16±9

M male, *F* female, *H* hemorrhage, *I* infarction, *Days* days poststroke, *IC* internal capsule, *Th* thalamus, *CR* corona radiata, *Pt* putamen, *R* right, *L* left, *FM* Fugl-Meyer motor scale (16), *UE* upper extremity, *LE* lower extremity, *FM/UE full*=66, *FM/LE full*=34

16±9 (full=34). We also studied five age-matched healthy controls with no neurological abnormality (three males, two females, 53±11 years old, 159.0±8.5 cm in height). This study was approved by the ethical committee of our hospital and has been performed according to the Declaration of Helsinki. Written informed consent was obtained from each subject. Each individual had at least 24 h to consider before signing consent.

We evaluated cortical activation patterns using a 36-channel optical imaging system during gait on the treadmill with partial BWS (10%) using an overhead harness with a pelvic belt and thigh strips (Miyai et al. 2002a,b) and with no BWS (NBWS). The degree of BWS (10%) was chosen since these patients with mild gait disturbance preferred low degree of BWS. Reported tightness of leg straps was not subjectively different between BWS and NBWS condition. The order of the two tasks was randomized. All patients and controls have never experienced treadmill training with BWS before this study. Since patients and controls were not used to walking on the treadmill with BWS, relatively low speed (1 km/h) were chosen to minimize additional cortical activation due to the novelty of the task, anxiety for safety, and uncomfortable condition. Patients' self-selected walking speeds (1.4±0.3 km/h, ranging from 1.0 to 1.8) were close to the experimental speed. For NIRS recording, each 30 s task (walking) period was alternated by 30 s rest (standing) period for four times. Patients held to rails during task and rest periods with their unaffected hands. For objective measurements of gait performance, we videotaped each walking task and evaluated cadence (steps/min) and swing phase laterality index (LI) that was defined as (time for swing phase of the sound leg − time for swing phase of the paretic leg)/(time for swing phase of the sound leg + time for swing phase of the paretic leg). We also monitored blood pressure, heart rate, and arterial oxygen saturation by using a pulse-oxymetry at the baseline and after completing each task.

Details of the optical imaging system (OMM-2001, Shimadzu, Kyoto, Japan) using continuous wave laser diodes with wavelengths of 780, 805, and 830 nm were described previously (Miyai et al. 2001, 2002a, 2003; Suzuki et al. 2004). In brief, it consisted of 24 optodes including 12 light source and 12 detector fibers that enabled 36-channel recording covering bilateral fronto-parietal cortices (Fig. 1). The system can detect changes in oxyHb, deoxygenated hemoglobin (deoxyHb), and total hemoglobin (totalHb) levels (mM×cm) within a few centimeters depth of the skull surface covering the cerebral cortex after setting the inter-optode distance to 3.0 cm. The light source fiber next to the posterior one in the center row was located in Cz portion (Fig. 1). The optodes were placed tightly on the skull using a holder cap fabricated from custom-made thermoplastic resin. An anatomical 3D T1-weighted MRI scan was performed with marking the optode location on the skull by vitamin D capsules. In two subjects, the anatomical MRI was normalized to a standard stereotaxic space (Friston et al. 1995; Ashburner et al. 1997; Ashburner and Friston 1999), using a Montreal Neurological Institute (MNI) brain template, which corresponds to the space described by Talairach and Tournoux (1988). The normalization was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Coordinates of each optode were then converted into MNI coordinates. Thus anatomical MRI scan revealed that the optodes were located over the bilateral fronto-parietal cortices covering an area of 13×13 cm including the primary SMC, premotor cortices (PMC), SMA, prefrontal cortices and the superior parietal lobes. Based on information from anatomical MRI and our previous work regarding cortical mapping of human gait in normal subjects (10), we defined SMC as the medial parts of the posterior channels (Ch 16, 17, 22 and 23), SMA as the medial parts of the middle channels (Ch 14, 15, 20 and 21), and PMC as the lateral parts of the middle channels (Ch 2, 8, 3, 9, 26, 27, 32, and 33). Prefrontal regions were partially covered by the anterior channels (Ch 1, 7, 13, 19, 25, and 31, See Fig. 1).

Although it remains to be determined how changes in hemoglobin oxygenation correlate with neural activities (Villringer and Obrig, 2002), we used oxyHb value as a marker for cortical activation based on the following findings. There was a task related increase of oxyHb levels without apparent changes in deoxyHb levels in the medial cortical areas although task related decrease was seen in the lateral sensorimotor regions (Miyai et al. 2001) The cortical maps based on changes in oxyHb levels were similar to fMRI findings during foot

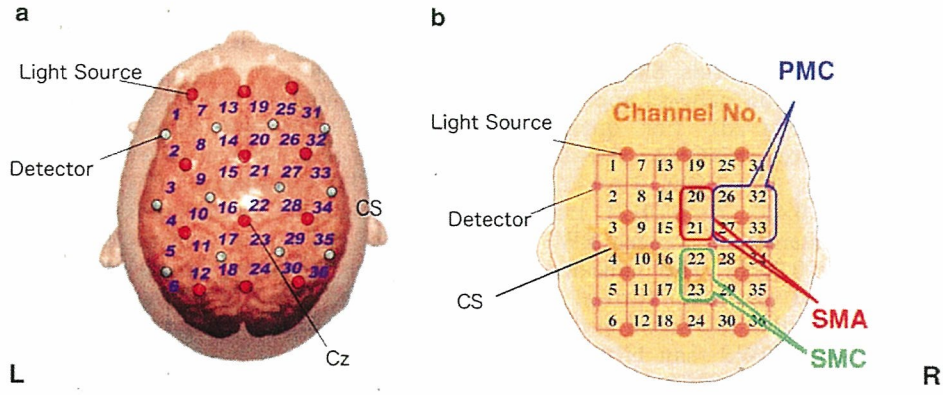

Fig. 1 Anatomical location of optodes **a** The anatomical location of the optodes including 12 light source (*large circles*) and 12 detector fibers (*small circles*) was exposed onto the normalized brain surface using a MNI brain template, which corresponds to the space described by Talairach and Tournoux. See text for details. **b** Schema for location of 24 optodes and corresponding 36 channels. The channels covering the SMC, SMA, and PMC in the right hemisphere were defined based on information from anatomical MRI. See text for details. *L* left, *R* right, *CS* central sulcus

movements and gait imagery in our experimental setting (Miyai et al. 2001). Several experimental data have also shown that oxyHb is more sensitive to activity dependent changes in regional cerebral blood flow than deoxyHb (Hoshi et al. 2001; Wolf et al. 2002; Strangman et al. 2002).

We obtained images depicting average changes in oxyHb during the four cycles of task after adapting the linear interpolation to the simultaneously acquired 36 data. Each topographic map was corrected to match the anatomical location of the optodes on the brain surface and was overlaid on an anatomical MRI surface image (Tsuchiya et al. 1996). For quantification of cortical activation, we calculated ΔoxyHb that is "oxy Hb during task period — oxyHb during rest period" in each channel. Data from the latter 20 s of the 30 s task periods and the middle 20 s of the 30 s rest periods were used since there was approximately 3–5 s delay in the response of hemoglobin oxygenation related to the tasks (Miyai et al. 2001). Activation of each cortical region was defined as average activation of the corresponding channels. To evaluate inter-hemisphere asymmetry of regional activation, we calculated regional LI (Miyai et al. 2002b, 2003) (LI) that was defined as (ΔoxyHb in the affected hemisphere − ΔoxyHb in the unaffected hemisphere)/(ΔoxyHb in the affected hemisphere + ΔoxyHb in the unaffected hemisphere) in each region (SMC, PMC, and SMA).

Changes of walking performance (cadence and LI of swing phase period) with BWS were analyzed using paired *t* test. In comparing amount of regional activation and LI during gait with the rehabilitative intervention, we performed repeated measures ANOVA with type of intervention (BWS vs. NBWS) as within-subject factor, site of regions (SMC, PMC, and SMA) as between-subject factor. To minimize the effect of individual and regional variations of differential pathlength factor on the measurements, we focused on significant interactions between the factors. Fisher's least significant difference test was used as post-hoc test. Simple regression analysis was used to evaluate correlation between regional activation and gait performance (cadence and LI of swing phase period). Statistical significance was set at $P < 0.05$ after correction for multiple comparisons if applicable.

Results

In patients with stroke, BWS significantly decreased time for swing phase for paretic leg (NBWS/BWS = 0.42 ± 0.10/0.36 ± 0.07, $P = 0.03$), significantly improved the asymmetry of swing phase during hemiparetic gait (swing phase LI ± SD; –0.12 ± 0.06/–0.07 ± 0.07, $P = 0.009$), and tended to increase cadence (60 ± 21/68 ± 23, $P = 0.06$). In controls, BWS did not affect either time for swing phase (0.32 ± 0.02/0.32 ± 0.02 for the right leg, $P = 0.36$), swing phase LI (0.005 ± 0.007/0.008 ± 0.012, $P = 0.51$), or cadence (113 ± 9/115 ± 9 steps/min, $P = 0.39$). There were no significant changes in arterial oxygen saturation before and after completing the tasks in controls (pre/post = 98 ± 1/97 ± 1%) and patients (97 ± 1/97 ± 1) in either condition (BWS or NBWS). After walking tasks, there was significant increase in systolic blood pressure in both NBWS condition (controls: pre/post = 123 ± 10/133 ± 14 mmHg; patients: 120 ± 9/129 ± 10, $P < 0.05$) and BWS condition (controls: pre/post = 124 ± 11/133 ± 12 mmHg; patients: 122 ± 9/130 ± 11, $P < 0.05$). There were no significant changes in diastolic blood pressure although heart rate tended to increase during NBWS condition (controls: pre/post = 70 ± 11/73 ± 12; patients: 74 ± 14/77 ± 11, n.s.).

Individual mapping showed that cortical activation centered in the medial SMC less in the affected hemisphere than in the unaffected hemisphere in

patients with stroke, (Fig. 2a–c). SMC activation appeared to be smaller and more symmetrical in BWS than in NBWS condition. In controls, SMC activation was symmetrical and activation patterns appear to be less affected by BWS (Fig. 2d). For quantitative analyses, repeated measures ANOVA revealed no main effect for BWS ($F[1, 33]=1.900$, $P=0.1773$) or site of region ($F[2, 33]=0.451$, $P=0.6412$). However there was a significant interaction between BWS and site ($F[2, 33]=8.626$, $P=0.0010$). This indicated that BWS had distinct regional effects on cortical activation. Post hoc test revealed that activation in the SMC was significantly smaller in BWS than NBWS condition ($P=0.0081$), but not in the SMA ($P=0.1067$) or PMC ($P=0.0863$), suggesting that BWS significantly lowered SMC activation during hemiparetic gait (Fig. 3a). In healthy subjects, there was a significant main effect for BWS ($F[1, 27]=4.321$, $P=0.0473$) but not for region ($F[2, 27]=1.220$, $P=0.3110$). There was no interaction between BWS and site ($F[2, 27]=0.397$, $P=0.6742$), suggesting that BWS generally increased cortical activation in a non-specific manner in controls (Fig. 3b).

Importantly in patients with stroke, there was significant correlation between the changes of SMC activation and those in cadence ($P=0.0451$, $\Delta SMC = -0.183+0.01\times\Delta Cadence$; $R^2=0.644$, Fig. 4a). These suggest that SMC activation is smaller under BWS than under NBWS during comparable walking performance. In controls, however, there was no correlation between these parameters. Concerning regional LI, there was no main effect of BWS, site, or interaction between BWS and site both in patients or controls. However in stroke patients, there was a significant correlation between the changes of LI of SMC activation and the changes LI of swing phase period (ΔLI of $SMC=-0.08+3.326\times\Delta LI$ of swing phase period; $R^2=0.648$, $P=0.0434$, Fig. 4b). Such significant correlation was not seen in the SMA or PMC. In controls, there was no correlation between changes of regional LI and gait parameters.

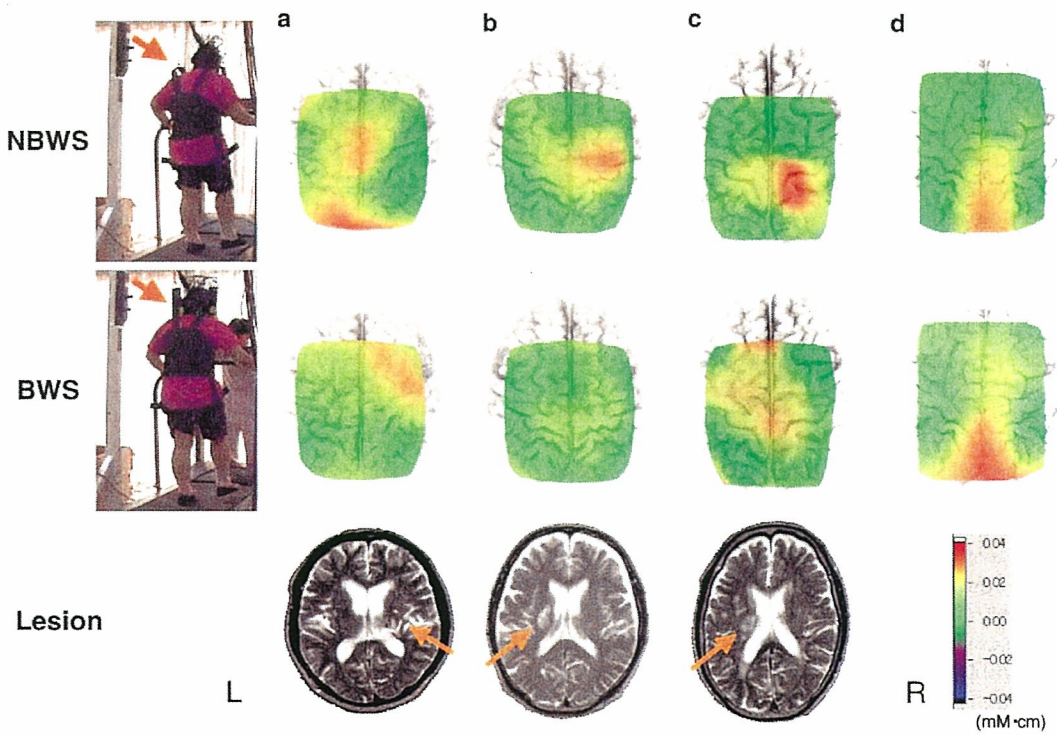

Fig. 2 Cortical maps based on increased levels of oxyHb during gait with and without BWS (NBWS) in three patients with subcortical stroke and a healthy subject. **a** Case 3: in NBWS condition, SMC and PMC activations are less in the affected hemisphere than in the unaffected hemisphere. Activation is also noted in the SMA and parietal regions. In BWS condition, SMC and SMA activation appears to decrease, but there is enhanced activation in the prefrontal regions. **b** Case 5: both in NBWS and BWS condition, SMC and PMC activations are asymmetrical with less activation in the affected hemisphere. BWS results in reduction of overall activation and SMC activation appears to be symmetrical. **c** Case 6: SMC activation is less in the affected hemisphere than in the unaffected hemisphere. In BWS condition, the SMC activation appears to be less but more symmetrical than in NBWS condition. Additional activations are seen in the PMC and prefrontal regions especially in the affected hemisphere. **d** A 45 year old healthy female. BWS does not appear to affect SMC activation but induces prefrontal activation. The scale indicates the color coordinates of concentration changes (mmol·cm). *Short arrows* in the left column indicate loose (NBWS condition) or tight belts (BWS condition) of the jacket for suspension of the patient. *Long arrows* in the lowest row indicate site of subcortical lesion. *L* left, *R* right

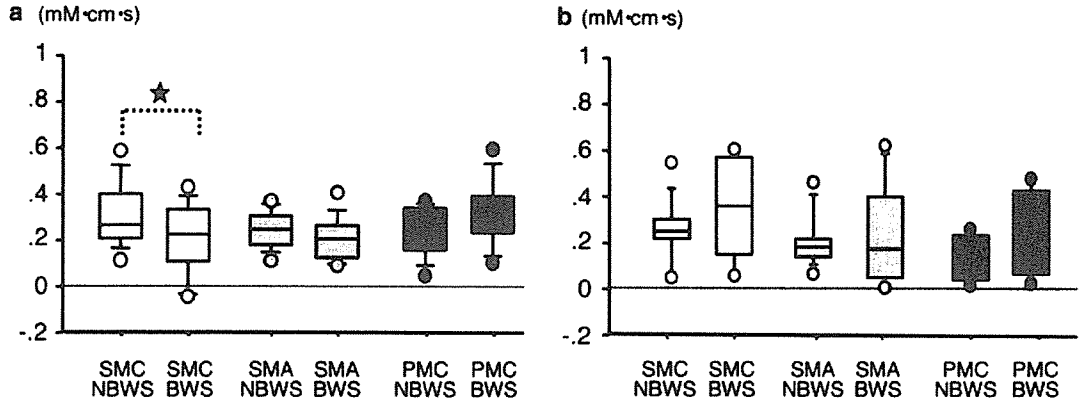

Fig. 3 Effect of BWS on regional activation during gait **a** In patients with stroke ($n=6$), the SMC activation was significantly smaller during treadmill gait with BWS than during treadmill gait without BWS (*$P=0.0081$). **b** In controls ($n=5$), BWS significantly increased overall activation ($P=0.0473$) but not in a region specific manner. See text for details. The *lower*, *middle*, and *upper horizontal lines* of the *boxes* represent 25th, 50th, and 75th percentiles, respectively. The *vertical lines* extend from the 10th to the 90th percentiles

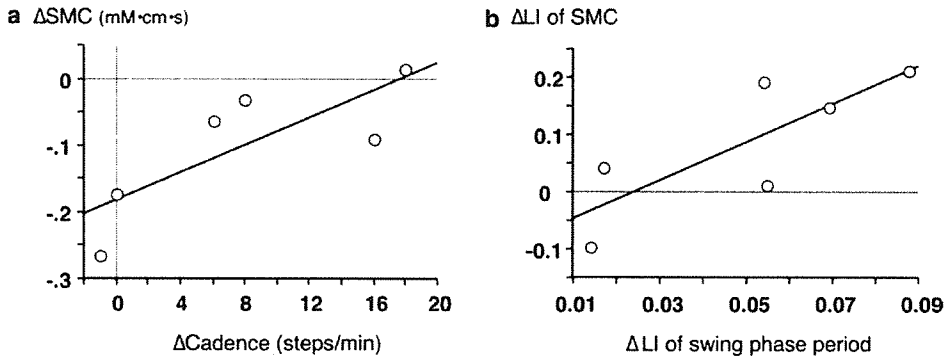

Fig. 4 Relationship between gait parameters and SMC activation in patients with stroke ($n=6$). **a** There was significant correlation between the changes of the SMC activation and those in cadence ($\Delta SMC = -0.183 + 0.01 \times \Delta cadence$; $R^2=0.644$, $P=0.0451$). **b** There was a significant correlation between the changes of LI of SMC and the changes of LI of swing phase period (ΔLI of $SMC = -0.08 + 3.326 \times \Delta LI$ of swing phase period; $R^2=0.648$, $P=0.0434$)

Discussion

We demonstrated that 10% of BWS affected both gait performance and activation in the medial SMC controlling foot movements in patients with stroke although this was not the case with controls walking with similar condition. In patients with stroke, there was a positive relationship between changes of cadence induced by BWS and changes in SMC activation. Although patients with increased cadence under BWS condition showed comparable SMC activation, those who had less changes in cadence revealed decreased SMC activation under BWS. Our finding might be at least partially explained by the fact that locomotion is controlled by hierarchy including the spinal central pattern generators (CPGs) and supraspinal multiple motor centers such as the subthalamic and brainstem locomotor regions, and the cerebellum and cortico-basal ganglia loops (Armstrong 1988; Drew 1988; Dietz et al. 2002). Although it is difficult to directly evaluate to which extent the CPGs or other subcortical locomotor regions contribute locomotor performance, the decrease in SMC activation induced by BWS might reflect the shift of locomotor control center to the lower levels when patients performed the task more automatically as suggested by increased cadence and improved gait asymmetry. Decreased somatosensory inputs due to less loading of each leg in BWS condition might also reduce SMC activation. However in healthy subjects walking or running at different speed on the treadmill (Suzuki et al. 2004), SMC activation also tended to decrease as the locomotor speed increased although somatosensory input might increase with higher speed. It might be also possible that BWS reduced SMC activation because of the less effort for walking. Although it is difficult to assess effort changes in physiological parameters including heart rate, blood pressure, and arterial oxygen saturation were comparable. Since earlier studies have shown that 30% or larger BWS but not 10% BWS significantly change oxygen consumption in healthy subjects (Threlkeld et al

2003, Grabowski et al 2005), it might be possible that 10% BWS could also induce significant changes in hemiparetic patients. Another possibility might be that the modest change in load might have altered sensorimotor drive within the SMC. These hierarchical mechanisms for controlling locomotion might be associated with higher possibility for regaining independent locomotor function than achieving functional use of the affected hand in patients with severely disabled stroke (Yagura et al. 2003) since similar hierarchical mechanisms are not seen in motor control of hand. In contrast, BWS did not alter the SMC activation in controls but generally increased cortical activation possibly because BWS was rather an uncomfortable condition for controls to walk. However it should be elucidated whether SMC activation and gait performance might be modified by BWS in controls walking at their optimal or self-selected speed.

Secondarily, improved walking performance with less prolonged swing phase of the paretic leg was associated with improved asymmetry in SMC activation. This indicates that at least patients with improved gait performance under BWS showed more balanced SMC activation. Thus changes of asymmetry in SMC activation are likely to depend on changes of walking performance induced by BWS but not by BWS itself. Although we evaluated immediate effects of BWS on gait performance and cortical activation, our observation is also in accordance with a longitudinal study demonstrating that improved gait performance after 2 months of inpatient rehabilitation paralleled improved asymmetry in SMC activation (Miyai et al. 2003). These suggest that SMC activation reflects physiological parameters of gait and that locomotion is actively controlled at the level of the SMC in patients with stroke. Thus improved asymmetry of SMC activation might be one of the common mechanisms underlying locomotor recovery after stroke. BWS might enable patients with mild to moderate hemiparesis to control locomotion symmetrically at the cortical level.

Using changes in oxyHb as a marker for cortical activation might be controversial. Both the blood oxygenation-dependent (BOLD) fMRI (Ogawa et al. 1992) and NIRS (Frostig et al. 1990) detect hemodynamic changes assumed to link with neural activities (Roy and Sherrington 1890). Correlation between BOLD signals and deoxyHb or oxyHb levels in NIRS signals has been controversial (Kleinschmidt et al. 1996; Toronov et al. 2001; Mehagnoul-Schipper et al. 2002; Strangman et al. 2002) although some literature reporting significant correlation between BOLD fMRI and deoxyHb in NIRS did not analyze oxyHb values. One explanation is that NIRS imaging is more likely to reflect hemodynamic changes in capillaries while BOLD fMRI reflects those in small veins (Yamamoto and Kato 2002). Since changes in deoxyHb levels related to tasks might vary while oxyHb consistently increase, most reliable marker for hemodynamic response could be oxyHb (Hoshi et al. 2001). Although deoxyHb remained unchanged during foot movements in the medial channel in our experimental setting, maps based on oxyHb by NIRS was quite similar to maps based on BOLD fMRI in the same subject performing the same task (Miyai et al. 2001). In the same experiment, deoxyHb levels in the lateral channels covering hand-arm area of sensorimotor cortex decreased along with increase in oxyHb as reported in most studies (Miyai et al. 2001).

There might be another claim that locomotor tasks using a block design might induce signals outside of the brain such as signals related to breathing, heart rate, and arterial pressure fluctuations inducing a systemic increase in oxygenation and blood volume (Wobst et al. 2001; Boas et al. 2002; Jasdzewski et al. 2003). Indeed there was task-related increase of systolic blood pressure in both controls and patients while changes were not significant in other physiological parameters. However increment of oxyHb was mostly localized in the medial regions. Changes in oxyHb levels in the region covering the medial sensorimotor cortex detected with shorter optode distance (2 cm) were smaller while those with longer optode distance (4 cm) were higher (unpublished data). The close relationship with physiological parameters of gait and changes in oxyHb levels including laterality observed in this study and the other (Miyai et al. 2003) might also support the brain origin of the measured oxyHb levels in our study. Hemodynamic response might be altered in patients with stroke. To minimize this problem, we studied chronic patients with subcortical lesion. The studied patients showed decreased deoxyHb levels as well as increased oxyHb levels in the lateral sensorimotor cortex of the affected hemisphere during mass grasping of the affected hand supporting the relatively preserved hemodynamic response (data not shown). Thus our findings might add further evidence that a specific rehabilitative intervention alters brain activation as well as motor performance of patients with cerebral lesion.

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Patients with Severe Stroke Benefit Most by Interdisciplinary Rehabilitation Team Approach

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Key Words
Interdisciplinary rehabilitation · Multidisciplinary rehabilitation · Stroke rehabilitation unit · General rehabilitation ward

Abstract
Background: We evaluated the efficacy of a regular interdisciplinary stroke team approach on rehabilitation outcome. ***Methods:*** We compared a stroke rehabilitation unit (SRU) with regular interdisciplinary stroke team conferences with general rehabilitation ward (GRW) without such conferences in the same rehabilitation hospital. One hundred and seventy-eight patients within 3 months after stroke were allocated to SRU or GRW, based on bed availability. Main outcome measures were the Functional Independence Measure, Stroke Impairment Assessment Set, length of hospital stay, discharge disposition and cost of hospitalization. ***Results:*** The interval between stroke onset and admission to our hospital was significantly longer in the SRU (n = 91) group compared with the GRW group (n = 87, $p < 0.05$). Although comparable numbers of patients were discharged home (74.7% in the SRU vs. 71.3% in the GRW), significantly more patients ($p < 0.0001$) with severe disability were discharged home in the SRU group (47.4%) compared with the GRW group (0%). There were no significant differences in the increase in Functional Independence Measure score, Stroke Impairment Assessment Set score, length of hospital stay, or cost. ***Conclusion:*** Patients with severe stroke appeared to benefit most from regular interdisciplinary stroke team conferences in the SRU and had an improved discharge disposition.

Introduction

There are many studies advocating the benefit of the stroke unit, and several papers reported that multidisciplinary rehabilitation in the stroke unit improved activities of daily living (ADL), gait, length of hospital stay (LOHS) and rate of discharge to home [1–8]. A recent systematic review demonstrated that there could be a substantial benefit with lower risk of death, institutionalization and dependency from organized inpatient multidisciplinary rehabilitation in the postacute period [1]. However, only few papers have identified specific factors in the stroke unit that contribute to favorable outcome and types of patients who benefit most. In a randomized controlled trial, Indredavik et al. [2] found that early rehabilitative intervention was the most important factor associated with discharge to home. In a community-based study, Jorgensen et al. [3] found that patients who had the most severe stroke appeared to benefit most in the stroke unit. Finally, Feigenson et al. [4] reported in their nonrandomized controlled trial that patients who were admitted to a stroke rehabilitation ward had better func-

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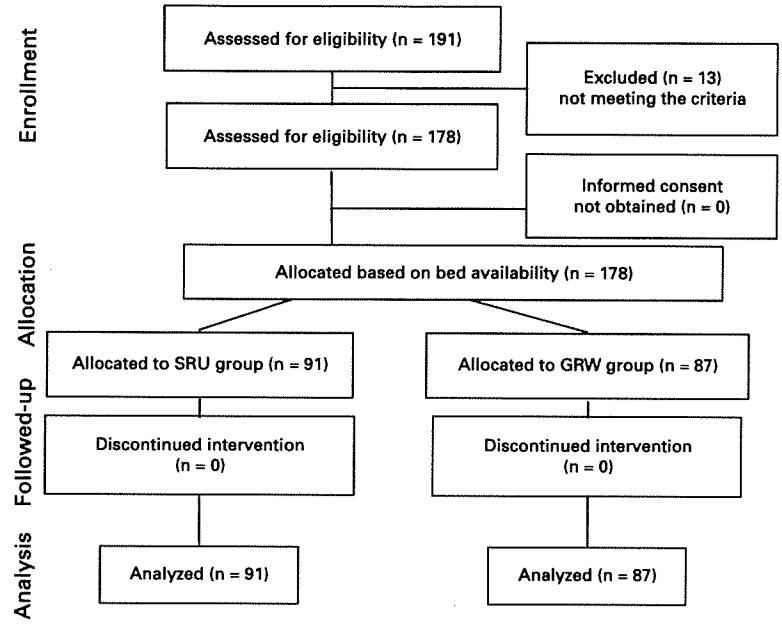

Fig. 1. Flow of patient participation through each stage of the study.

tional outcome than those who were admitted to a general rehabilitation ward (GRW) even in the same rehabilitation hospital. Although some of those stroke units provide a combination of acute care and subsequent rehabilitation [1–3], those results raised a possibility that a focused multidisciplinary team approach might contribute to a better functional outcome for patients after stroke.

There are two types of inpatient rehabilitation wards in our hospital with approximately 200 beds allocated to patients with stroke. One is the stroke rehabilitation unit (SRU) with weekly regular interdisciplinary rehabilitation team conferences, where each patient is evaluated for impairment and disabilities, complications, social factors, goals achieved, goals to be achieved and discharge disposition. This SRU has 54 beds and was opened in July, 2000, in response to changes in the health insurance policy in Japan, allowing more coordinated rehabilitation efforts for patients within 3 months after stroke onset. In this unit, we are allowed to charge an additional cost of 16,800 yen (approximately 140 USD, assuming a dollar is equal to 120 yen) per hospital day. This additional cost also covers laboratory and radiological examinations, but the cost of rehabilitative intervention is reimbursed separately. Another type of ward with a total of 156 beds is the GRW, where weekly interdisciplinary rehabilitation team conferences are not offered, but patients receive daily rehabilitative intervention including rehabilitation nursing care, physical therapy, occupational therapy and/or speech therapy, and receive discharge planning by medical social workers. The only difference between those two types of wards is the presence or absence of weekly regular interdisciplinary rehabilitation team conferences. In the present study, we compared the functional outcome of those two types of stroke rehabilitation programs at the inception of the SRU.

Patients and Methods

One hundred and seventy-eight consecutive patients who were admitted to our hospital after experiencing initial stroke in less than 3 months were randomly assigned to the SRU or GRW, depending on bed availability at the time of hospitalization. Patients who required any physical assistance prior to stroke were excluded. In our rehabilitation hospital, medical social workers handle the availability of the beds and assign patients to the vacant beds in a random manner, and other staff members do not deal with patient admission [9, 10]. Thus, patients were allocated to SRU or GRW with little bias, although this is not strictly a randomized controlled study. Written informed consent was obtained from each patient (fig. 1). Although patients recognized which types of bed they were assigned to in the present study, they did not know whether the ward held regular team conferences or not. They were transferred

to our hospital primarily because they still needed assistance in ambulation or ADL after staying in acute care hospitals, where they received only physical therapy sessions 3–5 days a week. In our hospital, the SRU group received weekly regular interdisciplinary stroke team conferences, but the GRW group did not. In the GRW group, irregular team conferences were held as needed, especially for all patients who were severely disabled. For both groups, the multidisciplinary rehabilitation program consisted of a 40-min session of physical therapy, occupational therapy and/or speech therapy, as needed, 5 days a week. All received our standard rehabilitation nursing care. For the SRU group, discharge planning was provided to patients by social workers based on the information presented at the weekly interdisciplinary stroke team conferences, where various professionals including physicians, nurses, physical therapists, occupational therapists, speech therapists, clinical psychologists and medical social workers joined together. Neither the patients nor their caregivers attended the team conferences, but they discussed discharge planning with attending physicians or medical social workers. For the GRW group, discharge planning was provided by social workers based on the information gathered from physicians, nurses, physical therapists, occupational therapists, speech therapists and clinical psychologists, but rehabilitation conferences were held irregularly only for selected patients with unsolved medical or social problems. Since those rehabilitation staff members, except nurses, participated in the treatment of patients in both groups, it is unlikely that there were any significant differences between the two groups in the quality and quantity of rehabilitative therapy.

On admission and discharge, functional outcome was evaluated utilizing the Functional Independence Measure (FIM) for disability [11] and the motor subscore of the Stroke Impairment Assessment Set (SIAS) for neurological impairment [12]. The motor subscore of the SIAS (score range 0–25) consists of two tests for upper extremities (0–10) and three tests for lower extremities (0–15) [12]. Follow-up assessments were carried out in a single-blinded manner by the examiners who were blinded to the study. Inter-rater reliabilities for individual items of the SIAS and the FIM at our hospital have been reported previously [13]. Other outcome measures included length of hospital stay, cost of hospitalization per day and discharge disposition. Primary outcome included the FIM and discharge disposition. According to the FIM score on admission, we divided each group into 3 subgroups (FIM $\leqq$ 53: subgroup A, 54 $\leqq$ FIM $\leqq$ 107: subgroup B, FIM $\geqq$ 108: subgroup C), in order to analyze the effect of weekly interdisciplinary stroke team conferences on the functional outcome of patients with different initial disabilities.

For the comparison of demographic data, LOHS, discharge disposition and cost of hospitalization among subgroups, we used χ^2 test or twofactorial ANOVA with the type of ward and initial disability as independent variables. Fisher's least significant difference was tested as a post-hoc test for ANOVA. To compare FIM and SIAS scores, we used Mann-Whitney test. Statistical significance was set at $p < 0.05$.

Results

Of 178 patients, 91 were admitted to the SRU and 87 to the GRW. No patient died or was transferred to other acute care hospitals because of complications or acute illnesses including recurrence of stroke while in our hospital. There were no significant differences in age, sex, type of stroke, affected side and complications between the two groups. Mean interval (± SD) between onset of stroke and admission to our hospital was significantly longer ($p < 0.05$) in the SRU group (60.4 ± 19.9 days) than the GRW group (53.8 ± 17.7 days). However, there was no significant difference in the baseline FIM or SIAS scores or the increase in FIM or SIAS scores between the two groups (table 1). The number of patients discharged home

Table 1. Demographic features and functional state on admission and discharge in SRU and GRW groups

	SRU group	GRW group
Demography		
Patients	91	87
Days after stroke (SD)	60.4 (19.9)*	53.8 (17.7)
Age, years (SD)	60.7 (11.3)	59.1 (11.6)
Sex, m/f	61/30	55/32
Type of stroke, I/H	54/37	44/43
Side of stroke, r/l/both	46/42/3	44/42/1
Complications		
Hypertension, %	65.9	73.6
Diabetes mellitus, %	25.3	19.5
Hyperlipidemia, %	27.5	33.3
Ischemic heart disease, %	7.7	13.8
Arrhythmia, %	8.8	6.9
Functional status on admission		
FIM (total) on admission (SD)	86.0 (28.9)	88.0 (23.3)
FIM (motor) on admission (SD)	59.7 (21.4)	60.3 (18.4)
FIM (cognition) on admission (SD)	26.3 (9.2)	27.6 (7.5)
SIAS (motor) on admission (SD)	11.3 (7.1)	10.8 (6.8)
Functional improvement after inpatient rehabilitation		
Increase in FIM (SD)	18.7 (14.2)	18.2 (15.4)
Increase in FIM, motor (SD)	15.2 (10.9)	15.0 (12.0)
Increase in FIM, cognition (SD)	3.5 (5.5)	3.2 (5.0)
Increase in SIAS, motor (SD)	3.2 (3.1)	3.8 (3.1)
Increase in SIAS, UE (SD)	1.3 (1.6)	1.3 (1.4)
Increase in SIAS, LE (SD)	1.9 (1.9)	2.5 (2.3)
LOHS, discharge disposition and cost		
LOHS (SD)	97.7 (18.0)	95.2 (17.0)
Patients discharged home (%)	68/91 (74.7)	62/87 (71.3)
Cost per hospital day, USD (SD)	248 (101)	228 (14)

SRU = Stroke rehabilitation unit; GRW = general rehabilitation ward; SD = standard deviation; I = infarction; H = hemorrhage; LOHS = length of hospital stay; FIM = Functional Independence Measure; SIAS = Stroke Impairment Assessment Set; UE = upper extremity; LE = lower extremity. * $p < 0.05$ vs. GRW group. USD was calculated at a rate of 120 Japanese yen per USD.