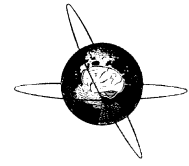




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## Fluoxetine facilitates use-dependent excitability of human primary motor cortex

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### Abstract

**Objectives:** In poststroke patients, fluoxetine, a selective serotonin-reuptake inhibitor, as an adjunct to physical therapy provided a better functional recovery from motor deficits. The aim of this study was to investigate the effect of a single dose of 20 mg fluoxetine on motor learning and associated cortical changes in healthy right-handed subjects in order to get deeper insight into its facilitating influence on human motor cortex.

**Methods:** Subjects performed a motor task consisting of a simultaneous co-contraction of the abductor pollicis brevis (APB) and the deltoid muscle with and without fluoxetine in a placebo-controlled double-blinded crossover study design. Immediately before and after motor learning motor output maps of the APB muscle were assessed in order to get insight into plastic changes of the muscle representation.

**Results:** We found a significantly improved motor performance under both conditions without having substantial differences between placebo and fluoxetine. After the completion of the motor task there was a medial shift of the APB muscle motor output map. Only after the administration of fluoxetine the sum of MEP amplitudes (SOA) increased and the motor output map enlarged.

**Conclusions:** These findings provide evidence for a use-dependent facilitating effect of fluoxetine on cortical excitability but not on motor performance.

**Significance:** Our findings are not in line with previous experiments in poststroke patients. However, long-term treatment with fluoxetine may additionally improve motor function by upregulating serotonergic receptors. Further studies investigating the influence of long-term treatment on cortical excitability and psychophysics may therefore provide deeper insight into a possible therapeutical efficiency of fluoxetine in poststroke patients.

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*Keywords:* Transcranial magnetic stimulation; Primary motor cortex; Plasticity; Fluoxetine; Serotonin

### 1. Introduction

The application of the endogenous transmitter 5-hydroxytryptamine (5-HT, serotonin) into cell cultures causes long-term facilitation of sensorimotor synapses due in part to growth of new presynaptic varicosities (Glanzman, 1994). In several animal experiments, 5-HT showed the capacity to modulate purposeful motor responses (Barbeau and Rossignol, 1991; Bieger, 1981; Cazalets et al., 1992; Mangan et al., 1994). In humans, the 5-HT reuptake inhibitor fluoxetine accumulates in the brain relative to the plasma and promotes an amplified serotonin concentration

(Karson et al., 1993; Sommi et al., 1987). Among other antidepressants, it inhibits 5-HT reuptake selectively, with no anticholinergic activity and limited side-effects (Gram and Fluoxetine, 1994). In poststroke patients, fluoxetine as an adjunct to physical therapy provided a better functional recovery from motor deficits (Dam et al., 1996). In first functional magnetic resonance imaging experiments, Pariente et al. found a fluoxetine-dependent hyperactivation in the ipsilesional primary motor cortex giving rise to an enhanced hemodynamic response of the perilesional tissue (Pariente et al., 2001).

In the present study we investigated the effect of a single dose of 20 mg fluoxetine on psychophysical and cortical changes in healthy right-handed subjects in order to get deeper insight into its facilitating influence on

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human motor system. In previous studies synchronised movement of two limb muscles led to rapid plastic changes of the motor output map (Cohen et al., 1995; Liepert et al., 1999; Tegenthoff et al., 1999, 2004). In the present study subjects performed a so-called co-contraction task consisting of a simultaneous contraction of the abductor pollicis brevis (APB) and the deltoid muscle (Pleger et al., 2003a; Schwenkreis et al., 2001; Tegenthoff et al., 2004) in a placebo-controlled double-blinded crossover study design. In all subjects motor output map of the APB muscle was assessed by transcranial magnetic stimulation (TMS) of the primary motor cortex.

## 2. Material and methods

### 2.1. Subjects and study design

We examined ten healthy right-handed subjects (five men and four women, aged 25–29 years,  $27.3 \pm 3.3$  years, mean  $\pm$  standard error). They all gave their written informed consent, and the protocol of the study was approved by the local ethical committee.

The study was performed in a placebo-controlled double-blinded crossover design. The subjects had to participate in two sessions. Therefore, the supervisor (M.T.) randomly divided them into two groups, each consisting of five subjects. The first group started after the administration of a single dose of 20 mg fluoxetine, whereas the subjects of the second group first received placebo. In line with previous co-contraction studies (Pleger et al., 2003a; Schwenkreis et al., 2001; Tegenthoff et al., 1999, 2004), the groups were reversed after an interval of two weeks in order to avoid a carry over effect. The investigators did not know if the subjects had taken placebo or fluoxetine prior to each session. The randomization code was kept by the supervisor and broken at the end of the study after the individual data analysis had been completed.

Under both conditions, subjects had to perform a motor task 6 h after drug intake to guarantee peak plasma concentration after fluoxetine administration (Altamura et al., 1994; Sommi et al., 1987). The motor task consisted of a synchronised movement of the abductor pollicis brevis (APB) muscle and the deltoid muscle (for a detailed description see Pleger et al., 2003a). The subjects were instructed to make brisk and short movements of both muscles as synchronously as possible. Over 1 h, three co-contractions per minute had to be performed. During each single co-contraction we measured the latency difference between the onsets of both muscle contractions using EMG-monitoring from surface electrodes. We used the differences between the muscle onsets as a marker of motor performance. After each co-contraction the subjects were informed of the results and encouraged to improve them.

### 2.2. Motor evoked potential mapping

TMS was applied using a figure-of-eight-shaped coil (outside diameter 8.7 cm, peak magnetic field strength 2.2 T, peak electric field strength 660 V/m) that was connected with a Magstim 200 HP device (monopolar waveform/The Magstim Company). The TMS measurement was performed immediately before and after the co-contraction task. The subjects were seated comfortably in a chair. Motor evoked potentials (MEP) were recorded on an EMG device (sampling rate: 5000 Hz/Neuropack 8, Nihon Kohden) with surface electrodes from the APB muscle of the dominant hand. The band pass filter was set from 20 Hz to 2 kHz, the gain from 0.1 to 1 mV/D. The sufficient muscle relaxation during the examination was continuously monitored by EMG (gain 0.1 mV/D). The TMS coil was held tangentially to the head in an anterior–posterior direction, with the grip pointing backwards. Motor threshold (MT) was defined as the minimum intensity which produced five motor evoked potentials  $> 50 \mu\text{V}$  out of ten trials. It was determined over that scalp position were TMS previously elicited the highest amplitude. Stimulation intensity was set to 110% of the motor threshold. Starting at the scalp position of the highest amplitudes, the motor cortex was examined in dorsal, rostral, lateral and medial direction in steps of 1 cm until no further MEP could be elicited. For a systematic examination of the primary motor cortex we used a tight fitting cap with a coordinate system on it ( $1 \times 1$  cm width). The coordinate system was arranged relative to Cz, which was identified as the intersection of the interaural line (y-axis), and the connection between nasion andinion (x-axis). Eight stimuli were applied to each position, and the responses (peak-to-peak amplitudes) were averaged. These averaged amplitudes were considered for further statistical analysis. Averaged amplitudes smaller than  $10 \mu\text{V}$  were rejected. Afterwards, we calculated the sum of all MEP-amplitudes of the motor output map (SOA), and its amplitude-weighted centre of gravity (COG). The centre of gravity (COG) is a single  $x$ – $y$  coordinate derived from the distribution of MEP amplitudes within the motor output area. It was calculated according to the following formula:  $[\sum(x \times y)/\sum z]$  (Liepert et al., 1999). Additionally, the number of positions from which MEPs could be elicited was used as a marker for the area size of the motor output map.

### 2.3. Statistical analysis

To evaluate differences of the TMS parameters assessed under placebo and fluoxetine we used an ANOVA for repeated measurements (pre vs. post training) with the within-subject factor ‘condition’ (placebo vs. fluoxetine). For post-hoc analysis we then used the student’s paired  $t$ -test to compare the TMS parameters obtained before and after the task within each session. We also checked the reproducibility of the neurophysiological data

by comparing the maps obtained prior to motor learning of both sessions.

To evaluate the effect of repetitive co-contraction on motor performance, the mean latency differences between the onsets of both muscles for the intervals 0–10, 10–20, 20–30, 30–40, 40–50 and 50–60 min were calculated in each subject and for each session. We used an ANOVA for repeated measurements and post-hoc *t*-test analysis (Bonferroni-corrected for multiple comparisons) to express psychophysical improvement during the motor task statistically.

### 3. Results

#### 3.1. Co-contraction task (Fig. 1)

Comparing the baseline performance during the first 10 min we found no significant differences between placebo ( $31.53 \pm 4$  ms, mean  $\pm$  standard error) and fluoxetine condition ( $29.45 \pm 2.4$  ms; paired *t*-test:  $P = 0.59$ ). During the course of the task we found a significant shortening of the latency differences between the onset of the APB and deltoid muscle contraction (ANOVA with within-subject factor ‘time’: placebo:  $F_{(1,8)} = 23.93$ ,  $P = 0.001$ ; fluoxetine:  $F_{(1,8)} = 49.96$ ,  $P = 0.0001$ ) indicating a significant motor performance improvement under both conditions. In the placebo session, the mean latency during the first 10 min was  $31.53 \pm 4$  ms, and during the last 10 min  $12.38 \pm 1.1$  ms (*t*-test:  $P = 0.001$ ). The Bonferroni-corrected post-hoc *t*-tests showed non-significant differences between the first and the successive 10 min (1–10 vs. 11–20:  $P = 0.2$ ). Afterwards subjects showed increasingly reduced time differences between the onsets of both muscles in the following periods that all reached significant level (1–10 vs. 21–30:  $P = 0.03$ ; 1–10 vs. 31–40:  $P = 0.04$ ; 1–10 vs. 41–50:  $P = 0.01$ ; 1–10 vs. 51–60:  $P = 0.009$ ). In the fluoxetine session we also found significantly reduced latencies (from  $29.45 \pm 2.4$  ms to

$12.41 \pm 1$  ms;  $P < 0.001$ ). Using post-hoc *t*-test, we found significantly reduced time differences between the first and the successive sessions (1–10 vs. 11–20:  $P = 0.003$ ; 1–10 vs. 21–30:  $P = 0.0003$ ; 1–10 vs. 31–40:  $P = 0.001$ ; 1–10 vs. 41–50:  $P = 0.0005$ ; 1–10 vs. 51–60:  $P = 0.0004$ ). Using the ANOVA for repeated measurements and the within-subject factor ‘time  $\times$  condition’, we found no differences between placebo and fluoxetine ( $F_{(5,80)} = 0.59$ ,  $P = 0.7$ ; ‘time’:  $F_{(5,80)} = 39.59$ ,  $P < 0.001$ ; between-subject factor ‘condition’:  $F_{(1,16)} = 0.0008$ ,  $P = 0.97$ ).

#### 3.2. TMS mapping (Table 1)

##### 3.2.1. Sum of amplitudes (SOA)

As a marker for the reproducibility of the neurophysiological data we found no differences in the SOA between placebo and fluoxetine prior to the motor task (placebo:  $1375 \pm 118$   $\mu$ V, fluoxetine:  $1185 \pm 133$   $\mu$ V, *t*-test:  $P = 0.31$ ). Using the ANOVA for repeated measurements with the within-subject factor ‘time  $\times$  condition’ we found significantly increased SOA ( $F_{(1,16)} = 13.33$ ,  $P = 0.002$ , post-hoc *t*-test: pre- vs. post-fluoxetine:  $P = 0.001$ ; post:  $1446 \pm 168$   $\mu$ V, Table 1). Under placebo we found no changes of the SOA after the completion of the task (post:  $1379 \pm 127$   $\mu$ V, *t*-test:  $P = 0.92$ ).

##### 3.2.2. Centre of gravity (COG)

We found no differences in the COG between placebo and fluoxetine prior to the motor task using paired *t*-test (*x*-coordinate:  $P = 0.25$ , *y*-coordinate:  $P = 0.51$ , Table 1). In the placebo session, we found a significant medial shift of the *y*-coordinate of the COG after the completion of the motor task (pre:  $-4.66 \pm 0.26$  cm, post:  $-4.54 \pm 0.26$  cm, *t*-test:  $P < 0.001$ ). We also found a significant medial shift under fluoxetine (pre:  $-4.93 \pm 0.24$  cm, post:  $-4.59 \pm 0.23$  cm, *t*-test:  $P < 0.001$ ; ANOVA, within-subject factor ‘time  $\times$  condition’:  $F_{(1,16)} = 24.95$ ,  $P = 0.0001$ ). Contrarily, we found no significant differences for

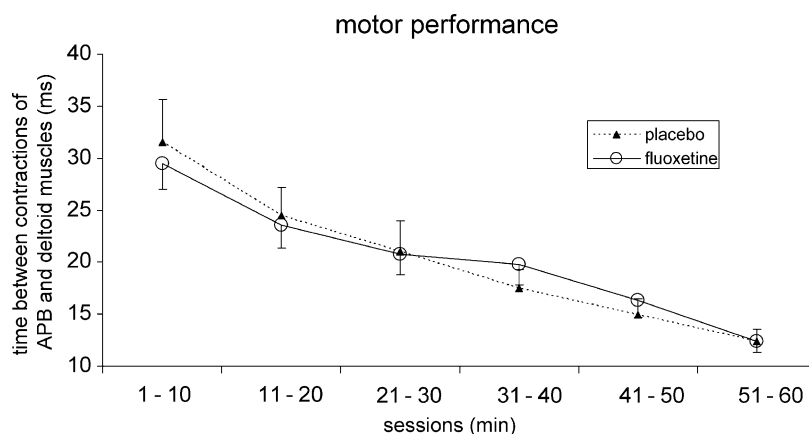


Fig. 1. A: Shown is the motor improvement during each session of the co-contraction task. Shown are the results obtained under placebo and fluoxetine condition. The whiskers represent the standard error.

Table 1

Shown are the individual SOA ( $\mu\text{V}$ ), the  $y$ - (refers to the lateral-to-medial axis) and  $x$ -coordinate (refers to the posterior-to-anterior axis) of the COG (cm) and the size of the area ( $\text{cm}^2$ ) elicited by TMS under placebo and fluoxetine condition

Subject	Sum of amplitudes (SOA)				$y$ -coordinate of COG				$x$ -coordinate of COG				Area			
	Placebo		Fluoxetine		Placebo		Fluoxetine		Placebo		Fluoxetine		Placebo		Fluoxetine	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1471	1433	497	685	-5.67	-5.56	-4.15	-3.94	-0.11	-0.13	-0.1	-0.05	16	16	8	9
2	1538	1536	1568	1955	-6.12	-5.97	-5.87	-5.48	-0.98	-1.04	-0.99	-0.93	10	10	11	12
3	1695	1388	1264	1576	-4.42	-4.3	-5.37	-4.94	-0.03	0.1	-0.43	-0.34	10	11	12	16
4	1804	1896	1745	2033	-5.17	-5.01	-4.15	-3.99	1	1.02	1.47	1.44	14	14	13	13
5	1178	1173	1298	1394	-4.17	-4.02	-5.04	-4.72	-1.03	-1.04	-0.96	-0.9	10	10	9	11
6	805	807	955	1084	-4.01	-3.91	-5.84	-5.47	-0.21	-0.29	-0.91	-0.87	9	9	9	10
7	938	988	1048	1345	-3.9	-3.82	-3.72	-3.23	-0.2	-0.2	-0.17	-0.22	9	9	12	14
8	1136	1151	1589	2154	-4.88	-4.69	-4.89	-4.67	0.2	0.3	0.08	0.01	10	11	12	15
9	1806	2039	706	791	-3.64	-3.58	-5.32	-4.83	-0.14	0.46	-1.06	-1	9	10	9	9
Mean	1375	1379	1185	1446	-4.66	-4.54	-4.93	-4.59	-0.17	-0.09	-0.34	-0.31	10.7	11.1	10.5	12.1
SE	118	127	133	168	0.26	0.26	0.24	0.23	0.19	0.21	0.25	0.24	0.78	0.74	0.57	0.81
<i>ANOVA</i>																
Within-subject factor 'time $\times$ condition'	$F_{(1,16)} = 13.33, P = 0.002$				$F_{(1,16)} = 24.95, P = 0.0001$				$F_{(1,16)} = 0.52, P = 0.47$				$F_{(1,16)} = 6.63, P = 0.02$			
Within-subject factor 'time'	$F_{(1,16)} = 14.29, P = 0.001$				$F_{(1,16)} = 116.5, P < 0.001$				$F_{(1,16)} = 1.92, P = 0.18$				$F_{(1,16)} = 15.83, P = 0.001$			
Between-subject factor 'condition'	$F_{(1,16)} = 0.09, P = 0.76$				$F_{(1,16)} = 0.17, P = 0.68$				$F_{(1,16)} = 0.34, P = 0.56$				$F_{(1,16)} = 0.13, P = 0.72$			
Post-hoc paired $t$ -test	$P = 0.92$		$P = 0.001$		$P < 0.001$		$P < 0.001$		-		-		$P = 0.08$		$P = 0.008$	

Below we show group data (mean, standard error) as well as the results of statistical analysis (ANOVA for repeated measurements, post-hoc  $t$ -test).

the  $x$ -coordinate of the COG (placebo: pre:  $-0.17 \pm 0.19$  cm, post:  $-0.09 \pm 0.21$  cm; fluoxetine: pre:  $-0.34 \pm 0.25$  cm, post:  $-0.31 \pm 0.24$  cm; ANOVA, within-subject factor ‘time  $\times$  condition’:  $F_{(1,16)} = 0.52$ ,  $P = 0.47$ ).

### 3.2.3. Area

Before the motor task we found non-significant differences in the size of the area between placebo and fluoxetine that was also indicative for the reproducibility of the motor maps (placebo:  $10.7 \pm 0.78$  cm<sup>2</sup>, fluoxetine:  $10.5 \pm 0.57$  cm<sup>2</sup>,  $t$ -test:  $P = 0.84$ , Table 1). Afterwards motor maps significantly enlarged (ANOVA, within-subject factor ‘time  $\times$  condition’:  $F_{(1,16)} = 6.63$ ,  $P = 0.02$ ). Under placebo we found a tendentious enlargement of the motor map after the motor task (post:  $11.1 \pm 0.74$  cm<sup>2</sup>,  $t$ -test pre vs. post:  $P = 0.08$ ). Under fluoxetine the enlargement of the motor map, however, reached significant level (post:  $12.1 \pm 0.81$  cm<sup>2</sup>,  $t$ -test pre vs. post:  $P = 0.008$ ). The Fig. 2 shows the results of the MEP mapping performed immediately before and after the completion of the motor task under both conditions in one single-subject and the changes in motor performance during the course of the task.

### 3.2.4. Motor threshold (MT)

We found no differences in the MT between placebo and fluoxetine prior to the motor task ( $P = 0.31$ ). In the pre and

post-session, we found equal motor thresholds (placebo:  $41.6 \pm 1.9\%$ , fluoxetine:  $43.3 \pm 1.1\%$ ).

## 4. Discussion

In the present study we investigated the influence of the selective 5-HT reuptake inhibitor fluoxetine on use-dependent plastic changes in human primary motor cortex. Healthy right-handed subjects performed a motor task consisting of a co-contraction of two limb muscles. This paradigm has been proved to be an appropriate model to study the pharmacological modulation of training-induced cortical reorganization (Cohen et al., 1995; Tegenthoff et al., 1999, 2004). In line with previous studies, repetitive co-contraction resulted in progressively shortened time intervals between the onsets of both muscles (Pleger et al., 2003a; Schwenkreis et al., 2001; Tegenthoff et al., 1999, 2004) without significant differences between both conditions. This lack of pharmacological effects on psychophysical level was surprising as Pariente et al. previously reported a significantly improved finger tapping rate and grip force of the hemiparetic side in post-stroke patients under a single dose of fluoxetine (Pariente et al., 2001).

However, our findings are in line with previous studies that also failed to show pharmacological influences on

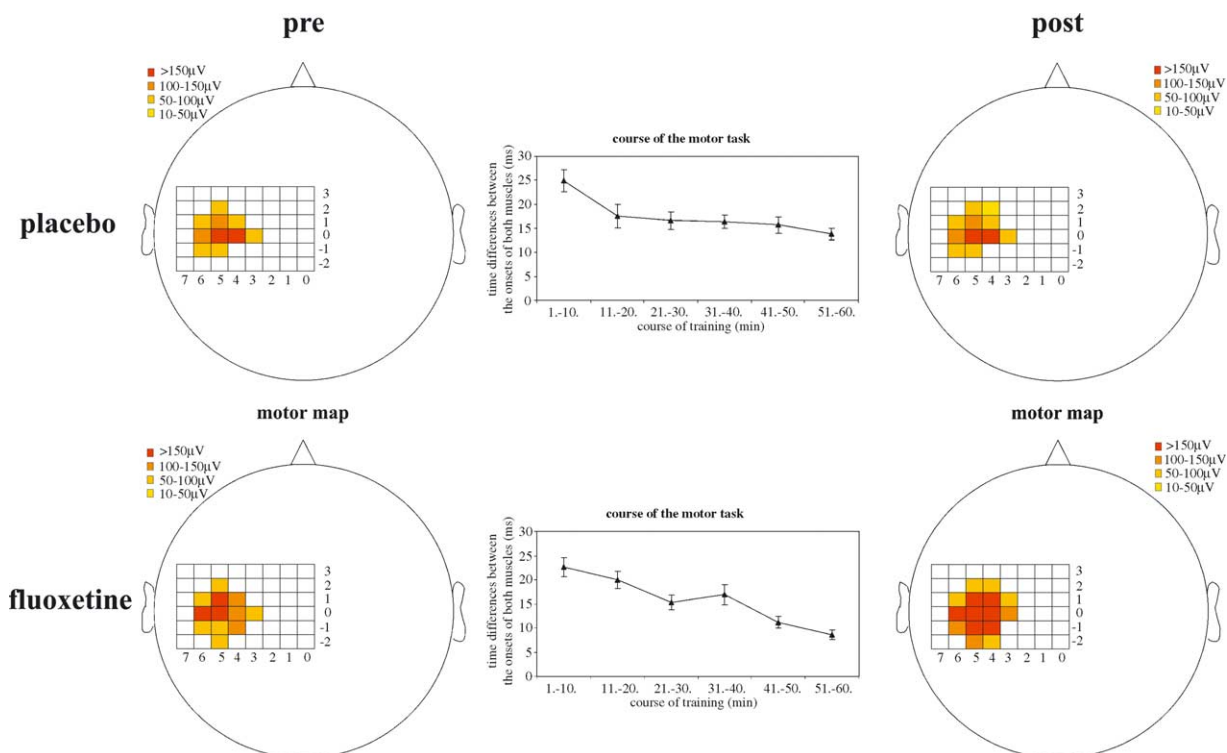


Fig. 2. Single-subject co-contraction effect: shown are the results of the TMS mapping performed before and after the completion of the motor task under both conditions (placebo: above; fluoxetine: below). The graphs between both motor maps show the changes in motor performance during the course of the task (placebo: from  $24.9 \pm 2.3$  (mean values  $\pm$  standard error) to  $13.8 \pm 1.2$  ms, paired  $t$ -test 0–10 vs. 51–60 min  $P < 0.001$ ; fluoxetine: from  $27.5 \pm 2$  to  $15.8 \pm 1$  ms;  $P < 0.001$ ). Note the differences of changes in motor maps between placebo (above) and fluoxetine condition (below), especially the enlargement of the area and the gain in SOAs.

co-contraction tasks (Tegenthoff et al., 1999, 2004). One hour of co-contraction resulted in significantly shortened time intervals between the onsets of the APB and the deltoid muscle, which was not affected by the administration of amphetamine. Motor improvement, however, resulted in a significant medial shift of the APB output map. Consequently, the co-contraction task may be considered as an appropriate task to investigate facilitating influences on re-organizational changes of human primary motor cortex. But it seems not appropriate to study parallel effects on behavioral level. In line with previous studies, we also found a medial shift of the APB motor output map under both conditions. This shift was orientated towards the representation of the deltoid muscle. Therefore it might be indicative of a change in the underlying cortical representation (Tegenthoff et al., 2004).

Synchronised neuronal activity that parallels cortical reorganization can be referred to a principle presented by Hebb (Dinse et al., 2003; Pleger et al., 2003b). He suggested that individual neurons could participate in different cell assemblies and be involved in multiple functions and representations (Hebb, 1949). Long-term potentiation (LTP) of motor synapses can be induced in Hebbian fashion by pairing weak presynaptic stimulation with strong post-synaptic depolarization (for a review see Glanzman, 1994). This mechanism can also function only at proximal synapses, suggesting that dendritic spikes participate generally in a form of synaptic potentiation that does not require post-synaptic action potential firing in the axon (Golding et al., 2002). The changes of the cortical APB representation, which are suggested by our results might therefore depend on the synchronicity of the co-contraction movement. This in turn might induce LTP-like processes that promote re-organizational changes of the participating cell assemblies.

Several animal experiments showed purposeful motor responses due to the application of 5-HT (Barbeau and Rossignol, 1991; Mangan et al., 1994). In rats, serotonergic neurons were activated in association with increased muscle motor activity, especially if the motor activity is in the repetitive or central pattern generator mode (Jacobs and Fornal, 1999). Thus, serotonergic neurons seem to promote motor output if it is generated in Hebbian fashion. The present findings corroborate the hypothesis of a facilitating effect of fluoxetine on use-dependent reorganization processes of the APB representation. Using TMS, Ilic et al. previously investigated the effects of the selective 5-HT reuptake inhibitor sertraline on human motor cortex excitability in healthy subjects (Ilic et al., 2002). Under the influence of sertraline, they found a steeper intensity curve suggesting an increased excitability of the cortico-spinal neurone. In the present study, under the influence of fluoxetine the repetitive co-contraction of the APB and the deltoid muscle resulted in an increase of the SOA and an enlargement of the APB representation. Selective 5-HT reuptake inhibitors like sertraline and

fluoxetine seem therefore to have complex influences on different parameters of cortical excitability.

In summary, our findings provide evidence for a use-dependent facilitating effect of fluoxetine on human motor cortex excitability. However, we found no gain in motor performance after a single dose of fluoxetine. Long-term treatment may additionally improve motor function by upregulating 5-HT<sub>2</sub> (Chen et al., 1992; Hrdina and Vu, 1993; Yamazaki et al., 1992) and also  $\beta$ -adrenergic receptors (Palvimaki et al., 1994). Further studies investigating the influence of long-term treatment with selective 5-HT reuptake inhibitors as an adjunct to physical therapy may therefore provide deeper insight into their possible therapeutical efficiency in post-stroke patients.

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