

# Amphetamine enhances training-induced motor cortex plasticity

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**Objectives** – Repetitive synchronized movements lead to short-term plastic changes in the primary motor cortex, which can be assessed by transcranial magnetic stimulation (TMS). Drugs which enhance such plastic changes could be of therapeutical interest, e.g. in patients with cerebral lesions. **Material and methods** – We studied the effect of amphetamine on motor performance and plastic changes in the motor cortex as revealed by TMS mapping in healthy humans, who had to train a repetitive synchronized movement over 1 h. **Results** – Cortical plastic changes observed after 1 h of training were more pronounced with amphetamine, whereas motor performance did not differ between training sessions with and without amphetamine. **Conclusion** – We conclude that amphetamine is able to enhance training-induced motor cortex plasticity. This effect could be due to its known influence on the GABAergic and glutamatergic system, but might also result from its role as an indirect catecholaminergic agonist.

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Repetitive performance of a motor task consisting of a synchronized movement of two limb muscles leads to rapid plastic changes in the motor output map assessed by means of transcranial magnetic stimulation (TMS). This was demonstrated by a shift of the centre of gravity (COG) of the motor output map derived from a small hand muscle towards the representation of the co-contracted shoulder (1, 2) or leg muscle (3). Findings of training-induced motor plasticity were also reported from TMS studies in humans (4, 5), and animal experiments suggest that such alterations take place in the primary motor cortex (M1) (6). Similar short-term representational changes after synchronous tactile co-stimulation have been observed in the primary somatosensory cortex (S1) of rats (7). One mechanism, which may contribute to such short-term plastic changes, includes the removal of local (presumably GABAergic) inhibition leading to an unmasking of pre-existing synaptic connections (8, 9). This is supported by the findings of an enhanced intracortical inhibition (10) and a prevention of practice-induced short-term plastic changes (11) in the motor cortex after administration of the GABA<sub>A</sub> agonist lorazepam. Long-term potentiation (LTP)-like changes in synaptic efficacy may

constitute another important mechanism of cortical reorganization which is mediated through *N*-methyl-D-aspartate (NMDA) receptor activation (12–14). Its relevance was recently demonstrated in humans by NMDA receptor blockade reducing intracortical facilitation (15) and preventing use-dependent plasticity in the human motor cortex (11). A contribution made by other neurotransmitting systems (cholinergic and adrenergic) in cortical plastic changes is also discussed (14, 16, 17).

Although various experiments have been addressed to investigate drugs which block plastic changes in the human motor cortex, less is known about drugs, which could enhance cortical plasticity. In this context, attention has been recently drawn to amphetamine, a drug which increases the synaptic concentrations of dopamine, serotonin and especially noradrenaline in the CNS. It has been reported to increase intracortical facilitation and short-lasting corticospinal excitability (18), to accelerate the development of use-dependent plasticity in the human motor cortex (19, 20), and it seems to have a certain therapeutic benefit, which aids recovery from a stroke (21–24). Therefore the aim of our study was to examine the effect of a single dose of amphetamine on the changes in the

motor output map after a synchronized repetitive movement of two limb muscles. This paradigm has been proved to be an appropriate model to study short-term training-induced plasticity in the human motor cortex, and its pharmacological modulation in previous studies (1–3). It therefore should allow us to get insight into the possible role of amphetamine in cortical plasticity. We hypothesized that amphetamine would enhance training-induced cortical plasticity, which should lead to a more pronounced directional shift of the motor output map of the co-contracted muscles. As cortical plasticity might be important for the recovery from lesions of the CNS (e.g. after stroke), this would give a rational base for further research to study the therapeutic efficacy of amphetamine in patients.

### Material and methods

#### Transcranial magnetic stimulation

TMS was performed with a Magstim 200 HP device (The Magstim Company, Whitland, UK) and a figure of eight coil (outside diameter 8.7 cm, peak magnetic field strength 2.2T, peak electric field strength 660 V/m), which predominantly stimulates neural structures under its centre. Motor-evoked potentials (MEPs) were recorded with surface electrodes from the abductor pollicis brevis muscle (APB) contralateral to the dominant hemisphere and stored on an EMG device (Neuro-pack 8, Nihon Kohden, Tokyo, Japan). The band pass was 20 Hz to 2 kHz, the gain 0.1–1 mV/D. The magnetic stimuli were delivered while the subjects were seated comfortably in a chair. During the whole examination, muscle relaxation was monitored with surface electrodes by EMG (gain 0.1 mV/D). Motor threshold was determined at rest to the nearest 1% of the stimulator output, and was defined as the minimum intensity which produced five MEPs > 50  $\mu$ V of 10 trials (25). Threshold was determined over that scalp position where TMS previously elicited the highest amplitude. Stimulation intensity was set to 110% of the motor threshold. Eight stimuli were applied to each position, and the mean peak-to-peak amplitude was considered for statistical analysis. Amplitudes smaller than 10  $\mu$ V were regarded as zero value. Starting at the scalp position where TMS previously elicited the highest amplitude, the motor cortex was examined systematically in rostral, dorsal, medial and lateral direction in steps of 1 cm until no further MEP could be elicited. The positions were identified with the help of a tight fitting cap with a co-ordinate system on it

(1  $\times$  1 cm width). Cz was identified as the intersection of the interaural line and the connection between nasion and inion, which made it possible to localize the co-ordinates relative to Cz. During the whole mapping procedure the coil was held tangentially to the head in an anterior–posterior direction, with the grip pointing backwards. Both the amplitude-weighted COG and the sum of MEP amplitudes (SOA) were calculated. Additionally, the number of positions from which MEP could be elicited was calculated and expressed as an area where each position equals 1 cm<sup>2</sup>.

#### Subjects and study design

We investigated 10 healthy right-handed subjects (seven men and three women, aged 22–43 years, mean age  $30.2 \pm 6.9$  years), who were all unrelated to the medical field. They all gave their written informed consent, and the protocol was approved by the local ethical committee.

Each subject had to participate in two experimental sessions: they were randomly split into two groups. The first group, made up of five subjects, started with a session including the administration of amphetamine, the other group without drug administration. This was reversed after an interval of at least 10 days.

In the drug session, each subject had to perform a definite motor task 3 h after the intake of a single dose of 20 mg amphetamine sulphate (racemate). This motor task consisted of a synchronized contraction of the deltoid and APB muscle. The participants were instructed to make brisk and short movements of both muscles as synchronously as possible. Approximately three co-contractions per minute had to be performed over 1 h. After each single co-contraction, the latency difference between the onset of muscle contractions was determined using EMG-monitoring with surface electrodes on both muscles. These latency differences of voluntary EMG activity allowed us to evaluate motor performance. The subjects were informed about the results of their performance and encouraged to improve it (2). In the no-drug session, the same motor task had to be performed over 1 h without administration of amphetamine.

In a subgroup of six subjects, in which the order of sessions (first session with amphetamine vs without amphetamine) was also balanced, a TMS mapping of the APB muscle was performed twice in each session as described above. In these subjects the session started with a TMS mapping. In the amphetamine session, the drug was administered immediately after finishing this map, and serum levels of amphetamine were drawn five times after

drug ingestion at intervals of 1 h. Immediately after the motor training, a second TMS mapping was performed, and changes in the motor output map of the APB muscle were compared between both sessions in order to determine the effect of amphetamine on short-term motor cortex plasticity.

Control experiments

In four healthy volunteers 20 mg of amphetamine were administered after a first TMS mapping of the APB muscle as described above. Three hours later a second TMS mapping was performed without any previous motor training to investigate the pure amphetamine effect on the motor maps, without motor training. Additionally, in three healthy subjects two TMS mappings were performed at an interval of 2 h, without intake of any drug and without performing any motor task, in order to show the reproducibility of motor maps.

Attentional changes

To investigate the influence of amphetamine on the subjects' attention, we applied a conventional computer-based attention test (DAUF, Wiener-Testsystem, Version 3.00; Schuhfried, Mödling, Austria) before and about 4 h after the intake of amphetamine in a subgroup of four healthy subjects. Rows of seven triangles are displayed on the screen in quick succession over 20 min. These triangles pointed either upwards or downwards. Whenever three triangles pointed downwards the subject had to press a reaction button. We evaluated the number of correct and incorrect answers as well as the reaction time.

Statistical analysis

Student's paired *t*-test was used to compare the electrophysiological parameters obtained by TMS mapping before and after performing the motor task within each session, as well as the pre- and

post-differences of these parameters between both sessions. Additionally, the electrophysiological parameters of the initial maps of both sessions were compared in order to test the reproducibility of the maps. To evaluate the effect of repetitive training and amphetamine intake on motor performance, the mean latency difference of contraction onset for the intervals 0–10, 10–20, 20–30, 30–40, 40–50 and 50–60 min was calculated in each subject for each session, and an ANOVA for repeated measurements (main factors: time interval, drug intake and order of sessions) with *post hoc t*-test analysis (Bonferroni-corrected for multiple comparisons) was performed. Pearson's correlation coefficient *r* was calculated in order to detect a possible relationship between the pre- and post-differences of the mapping parameters and the improvement of motor task performance, defined as the difference between the mean onset latency difference in the 0–10-min and the 50–60-min interval. Significance of the correlation coefficient was tested using a *t*-test. For all tests, significance was assumed at the 5% level.

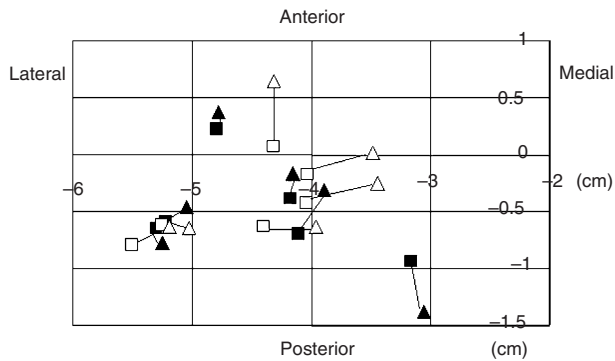
Results

TMS mapping (Table 1)

*Centre of gravity* (Fig. 1) – In the amphetamine-free session, a significant medial shift of the *y* co-ordinate of the COG was observed after the performance of the motor task ( $-44.6 \pm 8.1$  mm pre vs  $-43.6 \pm 8.2$  mm post,  $P = 0.041$ ). This medial shift was even more pronounced in the amphetamine session ( $-45.9 \pm 6.3$  mm pre vs  $-42.4 \pm 7.5$  mm post,  $P = 0.012$ ), which was revealed by a comparison between the shifts of the *y* co-ordinate in both sessions ( $1 \pm 0.9$  mm without amphetamine vs  $3.5 \pm 2.2$  mm with amphetamine,  $P = 0.039$ ). For the *x* co-ordinate of the COG no significant differences were observed, neither between the pre- and post-conditions of a single session, nor in the comparison of both sessions.

**Table 1** Mean  $\pm$  SD for the different MEP parameters assessed before and after 1 h of synchronized movements of the right thumb and shoulder with and without amphetamine. Student's paired *t*-test was used to compare the parameters before and after training: *P*-values are reported, bold type indicates significant changes. COG = centre of gravity

	No drug			Amphetamine		
	Before training	After training	<i>P</i> -value	Before training	After training	<i>P</i> -value
<i>x</i> co-ordinate COG (cm)	$-0.508 \pm 0.399$	$-0.453 \pm 0.588$	0.663	$-0.433 \pm 0.321$	$-0.248 \pm 0.511$	0.090
<i>y</i> co-ordinate COG (cm)	<b><math>-4.458 \pm 0.811</math></b>	<b><math>-4.363 \pm 0.825</math></b>	<b>0.041</b>	<b><math>-4.589 \pm 0.631</math></b>	<b><math>-4.238 \pm 0.750</math></b>	<b>0.012</b>
Motor threshold (%)	<b><math>36.7 \pm 5.7</math></b>	<b><math>35.3 \pm 6.0</math></b>	<b>0.043</b>	$36.0 \pm 5.9$	$35.2 \pm 5.6$	0.093
Area (cm <sup>2</sup> )	$15.3 \pm 3.6$	$13.7 \pm 3.6$	0.175	$13.7 \pm 4.0$	$14.8 \pm 4.2$	0.435
Sum of amplitudes (μV)	$1329.5 \pm 310.1$	$1345.7 \pm 400.4$	0.946	$1317.7 \pm 612.0$	$1571.5 \pm 574.2$	0.271



**Figure 1.** Centres of gravity (COG) of both sessions (with and without amphetamine intake) before and after training in the six subjects who underwent TMS mapping. COGs of the same session are linked. The COGs of the APB muscle are shown over the left hemisphere in a two-dimensional co-ordinate system, with the  $y$  co-ordinates giving the latitude in medio-lateral direction, and the  $x$  co-ordinate giving the longitude in anterior–posterior direction. (□) Session without drug intake before training, (▲) amphetamine session before training, (▲) session without drug intake after training, (Δ) amphetamine session after training.

**Motor threshold (MT)** – In both sessions, a decrease of the motor threshold was observed after the repetitive motor performance. This decrease was statistically significant in the amphetamine-free session ( $36.7 \pm 5.7\%$  pre vs  $35.3 \pm 6.0\%$  post,  $P = 0.043$ ), but failed to reach statistical significance in the amphetamine session ( $36.0 \pm 5.9\%$  pre vs  $35.2 \pm 5.6\%$  post,  $P = 0.093$ ). However, the difference between the shifts in both groups was not statistically significant ( $-1.3 \pm 1.2\%$  without amphetamine vs  $-0.8 \pm 1.0\%$  with amphetamine,  $P = 0.363$ ).

**Area** – Without drug intake, there was a tendency towards a reduction in the area ( $15.3 \pm 3.6 \text{ cm}^2$  pre vs  $13.7 \pm 3.6 \text{ cm}^2$  post,  $P = 0.089$ ), whereas no significant changes were seen after amphetamine intake ( $13.7 \pm 4.0 \text{ cm}^2$  pre vs  $14.8 \pm 4.2 \text{ cm}^2$  post,  $P = 0.435$ ). When the changes in both sessions were compared, a significant difference was observed ( $-1.7 \pm 2.6 \text{ cm}^2$  without amphetamine vs  $+1.2 \pm 3.4 \text{ cm}^2$  with amphetamine,  $P = 0.003$ ).

**Sum of amplitudes (SOA)** – No significant differences were observed in the SOA, neither between the pre- and post-conditions in one of the sessions, nor in comparison of both sessions.

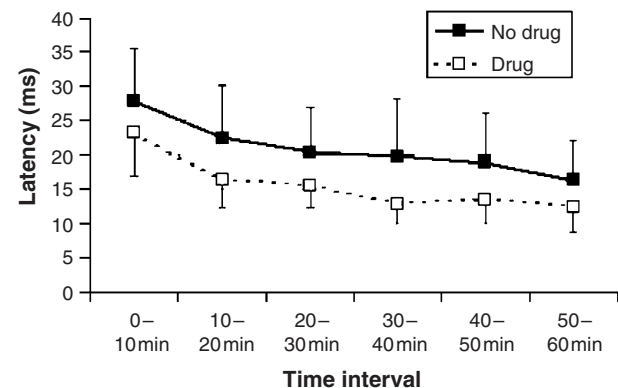
#### Control experiments

Comparing the TMS mapping before and after amphetamine administration alone, without motor training, there were no significant changes in one

of the mapping parameters. The  $y$  co-ordinate of the COG was  $-40.4 \pm 4.1 \text{ mm}$  before vs  $-40.7 \pm 5.0 \text{ mm}$  after drug intake ( $P > 0.05$ ). Regarding the reproducibility of TMS mapping without drug administration, no significant changes could be observed in one of the mapping parameters either.

#### Motor performance

There was a significant shortening of the latency between the onset of contraction of the APB and deltoid muscle during training in both sessions. In the amphetamine-free session, the mean latency during the first 10 min was  $27.8 \pm 7.6 \text{ ms}$  (mean  $\pm$  SD), and during the last 10 min  $16.4 \pm 5.8 \text{ ms}$  ( $P = 0.008$ ), indicating a significant improvement of the motor performance in the course of training. This effect was also found in the session where amphetamine was administered, with the reduction in latency from  $23.3 \pm 6.5$  to  $12.4 \pm 3.6 \text{ ms}$  ( $P < 0.001$ ). However, the difference between both groups was not statistically significant. Considering all time intervals, an ANOVA for repeated measurements was performed. It revealed a significant influence of the factors time interval ( $P = 0.003$ ) and drug intake ( $P = 0.012$ ), but not of the order of sessions factor ( $P = 0.684$ ) on the latency between the onset of contraction. There was no significant interaction between the different factors. However, *post hoc*  $t$ -tests (Bonferroni-corrected) showed no significant differences between the amphetamine session and the control session for the latencies at any of the time intervals 0–10, 10–20, 20–30, 30–40, 40–50 or 50–60 min (Fig. 2). The drug was well tolerated; none of the subjects reported any side-effects.



**Figure 2.** Comparison of motor performance with and without amphetamine intake. The mean latency difference between the onset of muscle contractions (abductor pollicis brevis and deltoid muscle) is shown at different time intervals during motor training.

Relationship between motor performance and TMS mapping

Neither for the changes in the  $x$  co-ordinate ( $r = 0.315$ ) nor for the changes in the  $y$  co-ordinate ( $r = 0.130$ ), could a significant correlation to the improvement of the motor performance be observed. The improvement of the motor performance did not correlate with the changes in the MT ( $r = 0.441$ ), area ( $r = 0.388$ ) or SOA ( $r = 0.505$ ) either.

Attentional changes

In the computer-based attention test we found no significant differences in right answers, wrong answers and reaction time (Student's paired  $t$ -test:  $P > 0.05$ ) before and after administration of amphetamine.

Amphetamine serum level

Amphetamine serum levels increased during the first 3 h and reached a peak between 3 and 4 h after drug ingestion, with a slight decrease after 5 h. The mean serum level at the beginning of the motor performance was  $30.4 \pm 7.8$ , and  $26.1 \pm 5.9$  ng/ml at the end of the session. There was no correlation between the improvement of motor performance or the changes in one of the neurophysiological parameters and the amphetamine serum level in the amphetamine session.

## Discussion

The main finding of this study is that the repetitive performance of a motor task consisting of a synchronized contraction of the APB and deltoid muscle leads to a directional shift of the motor output map of the APB muscle towards the more medial representation of the co-contracted muscle, and that this directional shift can be enhanced by the administration of amphetamine before training. The same directional shift has already been demonstrated by means of TMS mapping in previous studies using similar paradigms (1–3). Whereas changes in motor threshold and area may be simply due to changes in local motor excitability and not necessarily linked to cortical plastic changes (26), the shift of the motor output map must be considered as change in the representation of movements in the primary motor cortex, and therefore as a correlate of motor cortex plasticity (27). An unspecific effect of amphetamine on TMS mapping parameters was ruled out by an appropriate control experiment. The results therefore suggest that amphetamine is able to enhance training-induced

motor cortex plasticity, a finding which is also supported by recent studies using a different TMS and motor-training paradigm (19, 20).

Similar use-dependent alterations of movement representations could be observed in the primary motor cortex of adult squirrel monkeys by Nudo et al. (6). They discovered that after training there was an area expansion of dual-response representations, i.e. cortical sectors over which stimulation produced movements over two or more joints. This may explain the shift of the APB motor output map towards the representation of the co-contracted deltoid muscle in our study. This representational shift can be referred to a principle presented by Hebb, who suggested that individual neurones could participate in different cell assemblies and be involved in multiple functions and representations (28). The synchronization or pairing of impulses would then lead to an increase in the excitability of specific neuronal populations, and to a strengthening of the efficacy of their synaptic pathways (3).

Amphetamine is an indirect agonist of the catecholaminergic system, which mediates the release of dopamine and noradrenaline (29). Amphetamine is also able to decrease extracellular GABA concentrations (30), as well as stimulating the glutamatergic system (31, 32). When tested in healthy humans using a paired pulses TMS paradigm (33), it was able to enhance intracortical facilitation (18), which is decreased after the administration of GABA agonists (10) and NMDA antagonists (15, 34). As possible mechanisms of cortical plasticity which are likely to occur within the time period of 1 h observed in our study, an unmasking of pre-existing synaptic connections by removal of GABAergic inhibition (8, 9), and LTP-like changes in synaptic efficacy which are mediated through NMDA receptor activation (12–14) have been identified. There has been additional experimental evidence that these mechanisms may be responsible for the directional shift of the motor output map in our study, because this shift can be blocked by administration of the GABA agonist lorazepam and the NMDA antagonist amantadine (2). It can therefore be assumed that the amphetamine-mediated enhancement of short-term cortical plastic changes observed in our study might be mainly due to the drug's influence on the GABAergic and glutamatergic system. However, a contribution of the catecholaminergic system to the facilitation of the cortical plastic changes cannot be ruled out.

When comparing the first and the last 10 min of the training sessions, in both sessions a significant improvement was observed in motor performance, which did not differ with or without amphetamine intake. There was also no significant correlation

between the performance improvement and the changes in one of the mapping parameters. This lack of correlation also corresponds to the results reported by Liepert et al. (3), who did not find a correlation between the improvement of motor performance and the shift of the motor output map. It supports their view that the repetition of a synchronized movement is more important for the induction of cortical plasticity than the improvement of the motor performance, and that pairing of pre- and post-synaptic activation with intervals of up to 200 ms is still able to produce synaptic plasticity (35). Therefore the repetitive motor training must be considered as a model to induce cortical plasticity, allowing the study of its underlying mechanisms on a synaptic level by pharmacological modulation. As shown by the lack of correlation to the TMS mapping parameters, this paradigm may not be suitable to assess clinical effects of amphetamine related to the plastic changes in the motor cortex. This might be due to the fact that the improved performance of the trained task does not only depend on plastic changes in the primary motor cortex, but might be a complex phenomenon requiring the contribution of higher cortical functions and factors such as attention or motivation. The lack of attentional changes after amphetamine administration is in line with this hypothesis.

Nevertheless, the finding of an enhanced training-induced motor cortex plasticity after amphetamine administration may have therapeutical implications: it could be shown that rehabilitative training in stroke patients leads to significant motor improvement accompanied by extensive cortical plastic changes in the motor cortex (36–38), and there have been first reports that amphetamine paired with physical therapy may accelerate motor recovery from a stroke (21, 22). Our results may provide insight into the role of amphetamine in cortical plasticity, and therefore encourage further clinical research aimed at the combined use of amphetamine and physical therapy in patients with brain lesions.

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