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Motor-learning Impairment by Amantadine in Healthy Volunteers

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NMDA receptor antagonists impair learning and memory in animal models, presumably by inhibiting long-term potentiation in the motor cortex. Human studies are limited and restricted by the paucity of safe NMDA antagonists. Here, we investigated the contribution of glutamatergic neurotransmission to the capacity of acquiring motor-adaptation learning in humans. In a double-blind design, 200 mg of amantadine (a low-affinity NMDA receptor channel blocker) or a matching placebo were given orally to groups of 14 and 13 human healthy young volunteers, respectively. Blood samples were collected 3 h after treatment to assay plasma concentrations, and the subjects were then tested using a motor-adaptation paradigm consisting of an eight-target-pointing task. To rule out drug-related generalized impairments such sedation, tests measuring motor dexterity and attention were also administered pre- and post-treatment. Comparison of the mean performance levels on the motor-adaptation task revealed that subjects in the amantadine group performed at a lower level than those in the placebo group, but this difference did not reach significance. Interestingly, however, despite plasma amantadine concentrations being relatively low, ranging from 2.09 to 4.74 μM (mean = 3.3 μM), they nevertheless correlated negatively with motor learning. Furthermore, when the amantadine group was divided into low-performance and high-performance subgroups, subjects in the former subgroup displayed mean amantadine concentrations 36% higher than the latter subgroup, and performed significantly worser than the placebo group. No change in performance was found on the motor-dexterity and attention tests. Altogether, our results lend support to the hypothesis that normal NMDA receptor function is necessary for the acquisition of motor adaptation.
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INTRODUCTION

In everyday life, humans use a variety of motor skills, which refer to the process by which movements, either produced alone or in sequence, come to be performed effortlessly through extensive periods of practice (Willingham, 1998). In experimental conditions, these skills often fall into two categories: motor sequence learning and motor adaptation (Doyon *et al*, 2003). While the first measures the incremental acquisition of movements into a well-executed behavior, the second tests our capacity to compensate for environmental changes (Shadmehr and Holcomb, 1997; Doyon *et al*, 2003). Without this type of learning, we would not be able to play a violin, develop controlled artistic movements or drive a car. Several studies, particularly those using brain-imaging techniques, have highlighted the neuroanatomical substrate and, to a certain extent, the neural networks responsible for the acquisition of a new motor skill (for a review, see Doyon and Ungerleider, 2002). However, the physiological mechanisms of this type of procedural learning remain elusive. Learning-related improvements in motor tasks are thought to be related to the plasticity of the motor system (Jackson and Lemon, 2001; Li *et al*, 2001), and may also share common mechanisms with those of functional recovery after stroke (Butefisch *et al*, 1995; Nudo *et al*, 1996).

Using a pharmacological approach, some investigators have recently begun to elucidate the neurobiological bases of motor learning (Butefisch *et al*, 2000; Donchin *et al*, 2002), and have proposed that this type of memory may be mediated by synaptic plasticity such as long-term potentiation (LTP). In fact, LTP is considered by many to be one of the main physiological mechanisms subserving the memory process (Malenka and Nicoll, 1999). Induction of LTP requires the activation of glutamate *N*-methyl-D-aspartate (NMDA) receptors, notably in the hippocampus (Bliss and Collingridge, 1993), but also in several other regions of the brain including the motor cortex (Hess *et al*, 1996; Kitagawa *et al*, 1997) and the striatum (Charpier and Deniau, 1997; Centonze *et al*, 1999, 2001; Spencer and Murphy, 2000).

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Thus, glutamate via NMDA receptors may play a major role in motor learning.

In the present experiment, we attempted to evaluate the impact of NMDA receptor blockade on a new motor-skill-learning paradigm (ie motor adaptation) by using amantadine in healthy human volunteers. Amantadine is a drug administered to patients with Parkinson's disease (Verhagen Metman *et al*, 1998; Blanchet *et al*, 2003), blocking the NMDA receptor ion channel (Kornhuber *et al*, 1991). A version of the eight-target-pointing task was used for the evaluation of this form of motor learning (ie Flament *et al*, 1996; Shadmehr and Holcomb, 1997). We hypothesized that this pharmacological manipulation would interfere with the motor-learning process.

MATERIAL AND METHODS

Subjects and Methodological Considerations

The study protocol was approved by the Ethics Committee of the University of Montreal Hospital Centre (CHU Montreal). Healthy young volunteers were divided into two groups (13 subjects under placebo, 14 subjects under amantadine), and were matched for age, sex, and level of education (Table 1). They were tested after they provided written informed consent. All subjects were right-handed, as tested with the Edinburgh Handedness Inventory (Oldfield, 1971). In an effort to standardize the motor skill in using a joystick, experts in video games were excluded. Participants with experience in playing musical instruments were included because such abilities involve motor-sequence learning rather than motor adaptation. Other habits, such as smoking, coffee intake, drugs (birth control pills), or any psychostimulant agents, were not permitted before and during testing. The subjects were allowed to eat a light lunch during the day of the testing. Timing of the testing during the day was comparable in both groups. The participants usually took 200 mg of amantadine or placebo between 0900 and 1300 h and the motor-adaptation task, administered over a period of 40 min, was performed 3 h later, that is, between 1200 and 1600 h.

Procedure: Experimental Tasks

A motor-adaptation paradigm consisting of an eight-target-pointing task, created on a platform Power-builder 6.0 licensed by Microsoft, was used (Figure 1). In this setup, the subject used a lever-operated pointer to follow an elliptical (nonlinear) path between points appearing on a computer screen. The starting point was indicated by a white circle 0.75 cm in diameter, which appeared in the center of the screen. A cross-hair cursor was superposed over the starting point. A line (0.5 cm thick) elliptical in shape (radius 2.5 cm) indicated the direction of the path to follow. Eight red spots were arranged, equidistant, on a circle with a radius of 10 cm. The subject's task was to attain the targets following a convex-shaped path the most accurately and rapidly possible, and within a time limit of 3 s. The targets could be reached in two ways: (1) a direct mode (DM), in which the direction of movement of the lever and that of the computer cursor were matched. This condition was used as a familiarization condition, and consisted of a brief period of practice allowing for subject selection (inclusion criteria); (2) an indirect mode (IM), in which the directions of the joystick and cursor were opposed, that is the '*x*' and '*y*' co-ordinates of the joystick had been reversed. The latter mode was used as the experimental condition. No practice in the latter condition was allowed before testing began, because we were interested in measuring the subjects' baseline performance levels. The data were collected under an experimental condition that allowed one to measure the capacity of the subject to learn how to adapt to a sensory change (motor adaptation). In this condition, subjects had to reach targets presented at random locations in the IM condition. The subjects were required to perform 12 blocks of 64 trials each (a total of 768 attempts during a period of approximately 40 min) under this experimental condition. The results of a pilot study involving 10 university students (data not shown) have demonstrated that subjects can attain an asymptotic performance level in the number of trials used in the present study protocol.

Neuropsychological Tests

To rule out a drug-induced generalized impairment such as sedation, two neuropsychological tests, a *Purdue Pegboard* test measuring motor dexterity and a D2 test evaluating attention capacities, were administered pre- and post-treatment with placebo or amantadine (Brickenkamp, 1981; Reddon *et al*, 1988).

Table 1 Subjects' Characteristics and Neuropsychological Findings

	Age	Sex	Education level	Neuropsychological tests			
				Purdue Pegboard[a]		D2[b]	
				Pre-	Post-	Pre-	Post-
Placebo group	24.9 ± 0.3	Six F, seven M	17.5 ± 0.1	15.5 ± 1.6	15.8 ± 1.1	93.0 ± 11.8	97.6 ± 4.4
Amantadine group[c]	25.4 ± 0.4	Six F, eight M	17.1 ± 0.1	15.4 ± 2.2	15.9 ± 1.4	91.9 ± 12.8	92.4 ± 15.1

All values are expressed as mean ± SEM, pre- and post- refer to drug administration.
[a]Only data for the preferred hand are shown.
[b]Percentile rank (PR) values are presented.
[c]No difference between amantadine and placebo-treated groups (Student's *t*-test).

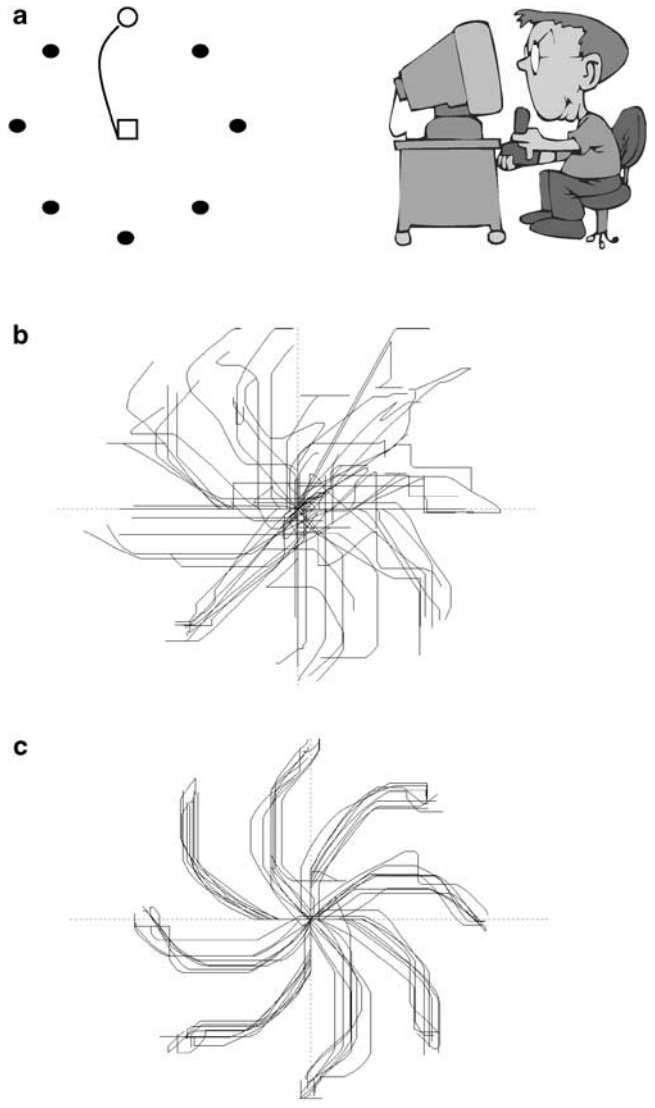

Figure 1 Motor-adaptation learning. (a) Figure illustrating the motor-adaptation task, in which subjects are asked to reach one of the eight targets, following a curved line with a joystick in the inversed mode; that is, the '*x*' and '*y*' coordinates of the joystick had been reversed. (b) Early in training, movements of the curser had significant deviations from the elliptical path. (c) Late in the training, movements of the curser followed essentially a straight elliptical line.

Pharmacological Manipulation

Both amantadine (two capsules of 100 mg each) or matching placebo were given orally in a double-blind design. In both groups, the motor-learning task was initiated 3 h after the drug administration to allow a maximal blood concentration for amantadine to be reached. The amantadine dose used in this experiment is equivalent to the dosage required for the prophylaxis and treatment of uncomplicated influenza A virus illness. In human subjects, maximum plasma amantadine concentrations are directly correlated for doses up to 200 mg/day. At this dosage, amantadine is generally well tolerated, but transient side effects such as nausea, dizziness (lightheadedness), and insomnia may occur. To assay the plasma amantadine concentration, blood samples were taken 3 h after administration and the plasma was stored at -70°C until all subjects had completed the study. Amantadine concentrations were determined using a gas-chromatographic system coupled to a mass-selective detector in the laboratories of Merz Pharmaceuticals (Frankfurt, Germany) (Danysz *et al*, 1994).

Statistical Analysis

A Performance Index (PI) of the participants was calculated for each block using a mathematical formula made up of three indices of measurement: (success rate/(distance $\times$ time)), where (1) success rate refers to the number of correctly completed trials measured by the ratio of the number of targets reached over the number of possible targets per block (denominator is equal to 64: number of trials per block), (2) distance is the length (cm) covered between the starting point and the target, and (3) time represents the time (ms) measured following the first movement of the participant until reaching the target.

A separate analysis using the success rate (accuracy) was also performed. For each subject, the level of accuracy at the end of the training period (Block 12) was compared with the baseline level (Block 1), and an improvement index (the percent of change over baseline) was calculated. A positive percent change indicates that the subject improved on the motor-learning task. For both parameters (performance and accuracy), an Analysis of Variance for repeated measures (ANOVA), followed by *post hoc* analysis (contrast analysis), was used to reveal the statistical significance. A Pearson correlation was employed to measure the possible relation between plasma amantadine concentrations and performance level. $P<0.05$ was regarded as significant.

RESULTS

Motor-learning Performance

Figure 2 illustrates the subjects' levels of performance in both amantadine and placebo groups. When the mean performance levels on the motor-adaptation task for all subjects in the two treatment groups were compared, motor learning improved significantly from Block 2 to Block 12, regardless of the group assignment. Although the performance level in the amantadine group never reached that of the placebo group (Figure 2), the difference was not significant. However, while all subjects in the placebo group were able to make accurate movements to reach targets and all had increased performance level with practice, only a fraction of the subjects in the amantadine group did so. Indeed, almost half of the subjects (six out of 14) in the amantadine group performed at least less than one standard deviation below that of the placebo group. Thus, we divided the amantadine group into high ($n=8$)- and low ($n=6$)-performance subgroups. When comparing these subgroups directly, the amantadine low-performance subgroup showed performance levels significantly worser than that of the amantadine high-performance subgroup ($P<0.01$; data not shown) and the placebo group ($P<0.01$; Figure 3a). To verify that this effect was not related to a selection bias, a comparable group of six subjects from the placebo group with low performance levels (placebo low-performance subgroup) was also chosen. Statistical analysis of the

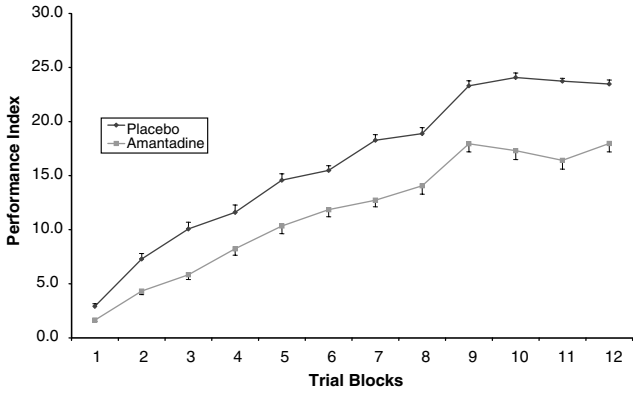

Figure 2 Motor-adaptation learning. The performance index represents the average of performance levels obtained for all participants in each treatment group during a given training block. Each block consisted of 64 consecutive trials. All values are expressed as mean ± SEM. Comparison between amantadine and placebo groups was made using an ANOVA for repeated measures, followed by a contrast analysis (see the text for significance).

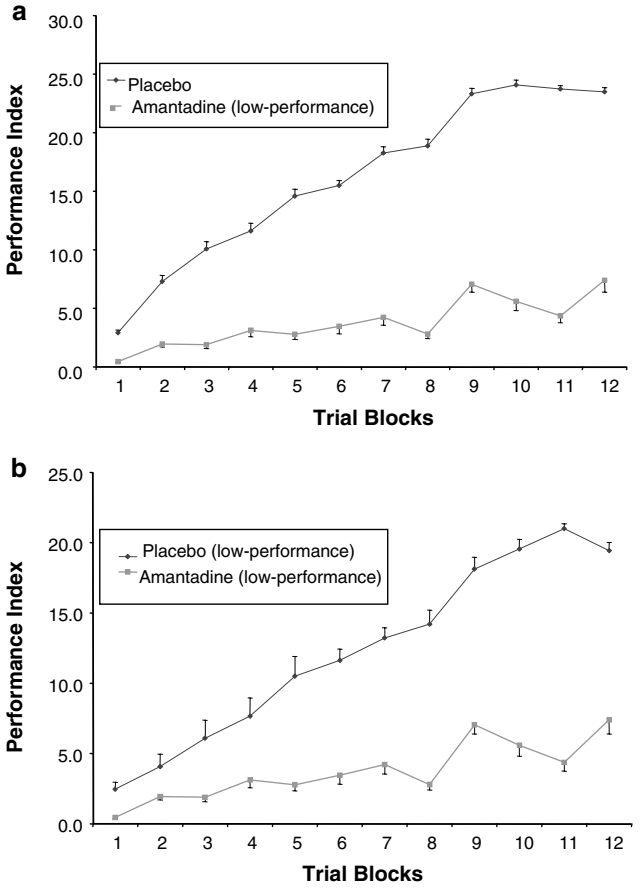

Figure 3 Motor-adaptation learning. The performance index was calculated as in Figure 2. All values are expressed as mean ± SEM. (a) Comparison between the placebo group and the amantadine low-performance subgroup. (b) Comparison between the amantadine low-performance subgroup and the placebo low-performance subgroup.

comparison between the amantadine low-performance subgroup and this subgroup again showed a significant difference in motor learning ($P<0.01$; Figure 3b). In contrast, no difference was found between the placebo group and the amantadine high-performance subgroup (data not shown).

Motor-learning Accuracy

Table 2 shows the subjects' levels of learning accuracy early (Block 1) and late (Block 12) in training. After 12 blocks of trials in the training period, the accuracy to perform the motor-adaptation task improved by 65.5 ± 0.8 and $53.46 \pm 2.1\%$ over baseline for the placebo and amantadine groups, respectively ($P=0.11$). However, motor-learning accuracy was lower in the amantadine low-performance subgroup than in the amantadine high-performance subgroup, the placebo group and the placebo low-performance subgroup ($P<0.01$; Table 2), suggesting decreased ability of the amantadine low-performance subgroup to perform under the influence of the drug. Motor learning in the amantadine high-performance subgroup was comparable to that in the placebo group.

Correlation of Motor Learning with Amantadine Concentrations and Individual Characteristics

Peak plasma amantadine concentrations ranged from 2.09 to 4.74 μM (mean = 3.3 μM) after the acute oral administration of 200 mg of amantadine. The amantadine low-performance subgroup displayed mean amantadine concentrations 36% higher than the high-performance subgroup (mean = 3.8 *vs* 2.8 μM) ($P=0.05$), suggesting that the decreased capacity to learn the motor-adaptation task in the former subgroup could be related to higher amantadine blood levels (Figure 4). Hence, we examined whether the differential rate of learning in the amantadine group was related to their amantadine concentrations, and found a negative correlation between the performance level and the plasma concentration achieved ($r=-57$, $P<0.05$) (Figure 4). Some subjects were impaired even at relatively low amantadine concentrations. Consequently, we examined whether the sensitivity to the drug was related to individual characteristics (age, gender, education level). In both amantadine and placebo groups, women appeared to perform lower than men (amantadine: $P<0.01$; placebo: $P<0.05$). In the amantadine group, a further analysis controlling for sex between performance index and amantadine concentrations was carried out, which revealed that the negative correlation shown in Figure 4 was no longer significant. More importantly, the subjects in the amantadine low-performance subgroup, with a gender bias (5F, 1M) opposite to the amantadine high-performance subgroup (1F, 7M), reached 36% higher amantadine concentrations than the latter, likely on the basis of a higher mg/kg average dose in the former subgroup.

Side Effects

Side effects under amantadine were absent and no subject experienced drowsiness, fatigue, or dizziness. Thus, no drug-induced motor and attention impairments can account for the significant disruption of motor learning recorded in the amantadine low-performance subgroup. The *Purdue Pegboard test* and *D2 test* were administered

Table 2 Motor-Adaptation-Learning Accuracy

Treatment subgroups	(*N*: gender)	Accuracy		
		Block 1	Block 12	Improvement (%)
Placebo (all)	(13: six F, seven M)	6.9 ± 0.5	48.7 ± 0.7[a]	65.5 ± 0.8
Placebo (high performance)	(seven: two F, five M)	7.4 ± 1.0	54.3 ± 0.7[a]	73.2 ± 1.1
Placebo (low performance)	(six: four F, two M)	6.2 ± 1.3	42.3 ± 1.6[a]	56.5 ± 1.1
Amantadine (all)	(14: six F, eight M)	4.0 ± 0.3	38.3 ± 1.5[a]	53.5 ± 2.1
Amantadine (high performance)	(eight: one F, seven M)	6.3 ± 0.5	54.0 ± 0.9[a]	74.6 ± 1.3
Amantadine (low performance)	(six: five F, one M)	1.2 ± 0.2	17.3 ± 2.3[a]	25.3 ± 3.6[b]

All values are expressed as mean ± SEM; accuracy represents the success rate which is the number of correct trials during a given block (one block = 64 trials).
[a]$p < 0.01$ for comparison between pre- (block 1) *vs* post-training (block 12) effect.
[b]$p < 0.01$ for amantadine low-performance subgroup compared with amantadine high-performance subgroup, placebo group, and placebo low-performance subgroup (ANOVA for repeated measures). F: female, M: male.

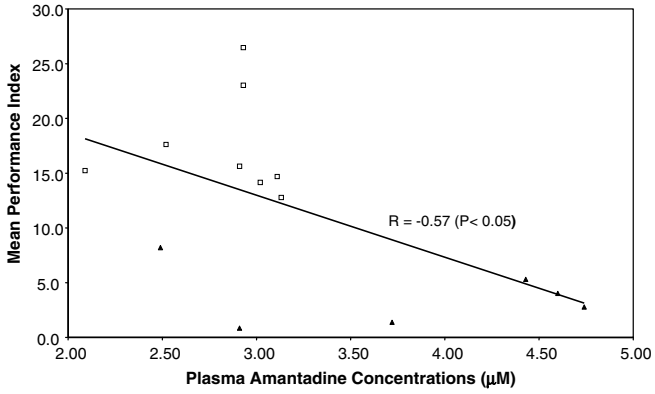

Figure 4 Relationship between motor-learning and plasma amantadine concentrations. The mean performance index, that is, the average of performance levels obtained during the 12 training blocks after a given treatment, of each individual is plotted against the corresponding plasma concentration. Additionally, the regression line of motor learning in relation to plasma level is shown. Participants with high- and low-performance levels are represented, respectively, using the symbols (□) and (▲).

pre- and post-treatment, and showed that attention and motor performance were intact under both placebo and amantadine (Table 1).

DISCUSSION

Amantadine has a plasma half-life of about 12 h (in young adults) and its time to peak concentration is about 3.3 h (Verhagen Metman *et al*, 2002). Therefore, its effect on motor learning should have been stable throughout this experiment. However, in our study, after a single dose of 200 mg, which is considered a strong dose, amantadine blood (and presumably brain) concentrations increased only moderately (mean: 3.3 μM). Thus, it is conceivable that the low concentration of amantadine obtained during the present study was responsible for the lack of an overall amantadine effect on motor learning, and particularly, in the high-performance subgroup. Indeed, *in vitro*, amantadine blocks NMDA receptors with a Ki-value at the PCP-binding site around 10 μM (Kornhuber *et al*, 1991). Such concentrations may be reached after chronic administration in patients with Parkinson's disease, who are much older than our subjects (Kornhuber *et al*, 1995; Verhagen Metman *et al*, 1998).

Although our study sample size does not permit to draw firm conclusions about the role of gender in this type of motor learning, women appeared to perform significantly worser than men in our motor-adaptation task, in accordance with the findings of Sawaki *et al* (2003), who reported gender differences on a simple motor-learning paradigm using flexion–extension thumb movements. Also, it lends support to the hypothesis that female hormones may modulate neural plasticity and motor-skill learning (Maki *et al*, 2002; Smith *et al*, 1999). In our study, however, while gender may have modulated motor learning differently, it cannot explain the significant differences between amantadine low-performance and placebo low-performance subgroups, which are matched for sex distribution. Moreover, the female-predominant amantadine low-performance subgroup achieved higher mean amantadine concentrations than those in the male-predominant amantadine high-performance subgroup, likely because of our fixed, weight-independent dosing schedule, suggesting that the impairment in motor adaptation is more related to amantadine administration rather than to sex differences.

In spite of the low concentrations achieved in this experiment, amantadine still impaired motor-adaptation learning in the amantadine low-performance subgroup, as measured by our target-pointing task. This finding is in agreement with studies showing that dextrometorphan, an NMDA receptor antagonist, has a negative impact on other motor-learning paradigms, including a force-field adaptation task (Butefisch *et al*, 2000; Donchin *et al*, 2002). This effect cannot be explained by a generalized detrimental effect of such drugs on either attention (*D2* test) or motor-dexterity performance (*Purdue Pegboard*), which were not affected during our study. Thus, our findings suggest that glutamatergic neurotransmission is critical for the capacity to acquire motor adaptation in humans.

It is noteworthy that higher amantadine concentrations have been achieved after chronic treatment with amantadine in Parkinson's and Huntington's disease patients (Verhagen Metman *et al*, 1998, 2002), and it is thus possible that such patients might have reduced ability to learn new

motor skills. However, in one study addressing the cognitive decline in Huntington's disease, amantadine failed to alter executive functions and mental flexibility (Verhagen Metman *et al*, 2002). Although the current study was not designed to address the role of amantadine on motor skill learning in such neurological conditions, our data do raise the possibility that amantadine may not have the same detrimental effect on all forms of cognitive and memory functions, at least in a fraction of subjects, and that motor learning may be more sensitive to this pharmacological manipulation.

On the other hand, previous studies have reported that motor learning may not depend merely on NMDA receptor antagonism. Indeed, lorazepam (a GABA-A receptor agonist) also impairs motor learning in humans (Butefisch *et al*, 2000; Donchin *et al*, 2002). The effects of other classes of drugs, such as anticholinergics, on motor learning are not conclusive, however. Scopolamine, a muscarinic receptor antagonist, has been shown to impair use-dependent motor plasticity after repetition of thumb movements (Sawaki *et al*, 2002), but has failed to block motor-adaptation learning (Donchin *et al*, 2002). The latter finding favors the idea that the effect of amantadine is not related to its anticholinergic action exerted either directly (Nastuk *et al*, 1976), or indirectly through inhibition of the NMDA-evoked acetylcholine release (Stoof *et al*, 1992). Finally, as suggested by positron emission tomography studies (Deep *et al*, 1999; Moresco *et al*, 2002), amantadine may exert an indirect dopaminergic effect by stimulating dopa decarboxylase activity or dopamine synthesis in the brain. However, the latter proposal cannot explain our finding because amantadine at therapeutic doses does not substantially increase extracellular brain levels of dopamine or its metabolites (Stoof *et al*, 1992; Quack *et al*, 1995). Furthermore, an increase in dopamine release is likely to improve motor learning rather than dampening it, as suggested by the beneficial effect of D-amphetamine on use-dependent plasticity (Butefisch *et al*, 2002). Thus, the effect of amantadine on motor learning seen in this study appears largely attributable to antagonism of the glutamatergic NMDA receptors.

While the brain is capable of multiple forms of plasticity which are governed, at least in part, by independent mechanisms (Grossman *et al*, 2002), the acquisition of a motor skill is most likely due to LTP-like mechanisms (Hess *et al*, 1996). This view is supported by the fact that drugs inhibiting LTP induction also impair synaptic changes, which occur in response to motor learning such as force-field adaptation (Donchin *et al*, 2002). Interestingly, lamotrigine, a drug that blocks voltage-gated Na^+ and Ca^{2+} channels (Lees and Leach, 1993) without affecting LTP induction (Xiong and Stringer, 1997), failed to reduce motor learning (Butefisch *et al*, 2000; Donchin *et al*, 2002). In our study, it is possible that amantadine interfered with changes in synaptic efficacy, explaining why it blocked motor-adaptation learning. This constitutes supportive evidence for the idea that normal NMDA receptor function is important for the acquisition, not only of explicit, but also of implicit learning both in animals and humans (Martin *et al*, 2000; McGaugh, 2002).

Based on animal and human work, several brain structures, including the striatum, cerebellum, and motor cortical areas of the frontal lobe, are thought to be critical for the acquisition and/or retention of skilled motor behaviors (Doyon and Ungerleider, 2002; Doyon *et al*, 2003). Previous studies have reported possible LTP induction in the primary motor cortex (Hess *et al*, 1996; Butefisch *et al*, 2000) or the cerebellum (Lu *et al*, 1998; Hansel *et al*, 2001; Donchin *et al*, 2002). We cannot rule out that the cerebral plasticity associated with the motor-adaptation task used here has taken place in the striatum. Evidence supporting the role of the striatum in motor-skill learning comes from impairments found in patients with striatal dysfunction, including Parkinson's and Huntington's diseases (Willingham and Koroshetz, 1993; Doyon *et al*, 1997, 1998), as well as from neurophysiological studies (Graybiel, 1995; Charpier and Deniau, 1997), and lesion experiments in rodents (McDonald and White, 1993). Furthermore, the striatum is the point of entry of information into the basal ganglia, and it plays an important role in motor control and habit learning (Graybiel, 2000). The neocortex and thalamus (Parent and Hazrati, 1995) provide the major excitatory inputs to the striatal medium spiny projection neurons, where both glutamate and dopamine terminals converge (Bouyer *et al*, 1984; Freund *et al*, 1984). Finally, in the striatum, repetitive stimulation of corticostriatal fibers causes a massive release of glutamate and produces LTP (Centonze *et al*, 1999; Spencer and Murphy, 2000); a process similar to that seen during learning (Charpier and Deniau, 1997; Mazzucchelli *et al*, 2002). Thus, in our study, amantadine may have blocked striatal NMDA receptors and subsequent LTP induction required for motor learning. However, the precise site of action of amantadine on motor adaptation is not known and further studies combining pharmacological manipulations with modern brain-imaging techniques such as PET or fMRI may be interesting in this regard.

In conclusion, the present results argue for a role of central glutamatergic transmission, particularly NMDA receptors, in the acquisition of motor-adaptation learning in humans. Further studies in patients treated chronically with amantadine or multiple-dose studies in healthy volunteers are needed to confirm these predictions. Moreover, interactions with other neurotransmitters such as dopamine should be investigated in future research.

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