

D-Amphetamine enhances skilled reaching after ischemic cortical lesions in rats

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Abstract

Unilateral sensorimotor cortical (SMC) lesions in rats impair reaching and grasping movements of the contralateral forelimb. These impairments can be improved using motor rehabilitative training on a skilled reaching task, but the training may be far from sufficient to return animals to pre-lesion levels of performance. Because D-amphetamine (AMPH) has been found to promote neuroplastic responses to injury and to be very beneficial when combined with some (but not all) types of rehabilitative training, we asked in this experiment whether it could improve the efficacy of rehabilitative training in skilled reaching. Ten to 14 days after unilateral ischemic (endothelin-1 induced) lesions of the SMC, adult rats were given a 3-week regimen of AMPH (1 mg/kg) coupled with daily rehabilitative training on a skilled reaching task, the single pellet retrieval task. AMPH treatment not only dramatically improved reaching performance compared with saline-injected controls, the AMPH treated rats surpassed pre-lesion levels of performance by the end of the rehabilitative training period. The greater performance in AMPH compared to saline-treated rats was still evident at 1 month, but not at 2 and 3 months, after the end of rehabilitative training. Thus, AMPH treatment can greatly enhance the efficacy of rehabilitative training on a skilled reaching task after unilateral SMC lesions, but alternate injection and training regimes may be needed to produce permanent improvements.

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Motor rehabilitative training after brain injury enhances motor recovery and neural plastic changes in affected brain regions [23,28]. Complex “acrobatic” motor skills training after unilateral sensorimotor cortex (SMC) lesions enhances synaptic structural plasticity in the cortex opposite the lesion and reduces tissue loss in peri-lesion cortex of rats [6,21]. In intact rats, training on a skilled forelimb reaching task increases motor cortical dendrites [5,41] and synapses per neuron [22] contralateral to the trained limb. In rats [36] and monkeys [3,29] reach training of the impaired forelimb also spares the loss of distal forelimb motor representation areas adjacent to ischemic infarcts, as assessed with microstimulation mapping. The combination of reach training and exposure to a complex environment after unilateral middle cerebral artery occlusions in rats has been found to improve reaching ability and to enhance dendritic growth in the cortex opposite the lesion [4]. However, motor rehabilitative training alone may

not be sufficient to return animals to pre-lesion levels of performance and a greater efficacy of reach training is likely to be achieved by combining it with other therapies [2,20].

AMPH administration has been found to promote improved behavioral function [7,9–17,19,25,26,32–35,37–39], as well as neurotrophic and neuroplastic responses [27,33] following brain damage. In several animal studies, amphetamine has been found to improve performance when combined with training on beam-walking tasks, which are sensitive to impairments in postural support and coordinated limb use in locomotion [13,14,16]. AMPH also improves visual impairments in cats [17] and forelimb placing behavior in rats [32] with cortical damage. In some (but not all) human studies, AMPH has been found to improve motor function [7,38] and it has also been found to enhance recovery from aphasia [37,39]. Administration of AMPH without concurrent task-specific training may fail to enhance behavioral performance [11,13]. Furthermore, in rats, the efficacy of AMPH has been found to depend on the behavioral requirements of the training. Schmanke et al. [32] found that AMPH

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improved performance on beam-walking and forelimb placing tests, but did not improve performance on measures of coordinated forelimb placing during exploratory locomotion (the Footfault test) or asymmetries in responsiveness to tactile stimulation of the distal forelimb.

In humans, deficits in the upper extremity are a major consequence of stroke that significantly impact functional independence and are in need of much greater focus of rehabilitative training efforts and animals models [30,31]. In rats, impairments in reaching and grasping movements can be sensitively detected using the skilled reaching task, the single pellet retrieval task [40]. In an earlier study, Feeney and Sutton [13] found that a limited amphetamine injection protocol that improved locomotor function after traumatic brain injury in rats was not effective in improving impairments in reaching and grasping. However, Barbay et al. [3] have recently found that, following ischemic lesions to the primary motor cortical hand representation in squirrel monkeys, a single AMPH injection accelerated behavioral improvements in skilled reaching compared with saline-treated animals. The purpose of the present study was to determine if a regimen of repeated AMPH treatment, combined with rehabilitative training on a skilled reaching task, would produce enduring improvements of reaching performance compared with saline-injected rats after unilateral ischemic SMC lesions aimed at the forelimb representation area. Lesions were made by applying endothelin-1, a vasoconstricting peptide [1] to the cortical surface. Ten to 14 days post-lesion, rats received daily rehabilitative training on the single pellet retrieval task. This time point was chosen to determine the efficacy of AMPH in the post-acute stage after ischemic damage and to prevent possible exaggeration of the injury by over-use of the impaired forelimb too early after the lesion [18,24]. Injections of AMPH or saline were given on day 2 and every third day of training for 3 weeks. To determine whether AMPH-induced improvements in reaching performance were enduring, animals were also tested monthly after the last day of rehabilitative training and drug therapy.

Eighteen adult (3–4 months) male Long–Evans hooded rats were housed in pairs and kept on a 12-h light:12-h dark cycle. Rats were moderately food restricted before the onset of training. After matching for pre- and post-operative performance levels on the reaching task, rats were assigned to either receive D-amphetamine (AMPH, $n=10$) or saline (SAL, $n=8$) injections. Animal use was in accordance with a protocol approved by the Animal Care and Use Committee of the University of Texas at Austin and the NIH Guide for the Care and Use of Laboratory Animals (NIH Publication no. 80–23, revised 1996).

Unilateral ischemic lesions of the SMC were made using topical application of endothelin-1 (Peninsula Laboratories, Inc., San Carlos, CA) contralateral to the preferred (for reaching) limb using methods described previously [1]. Rats were anesthetized with ketamine (100 mg/kg) and xylazine (10–13 mg/kg). Skull was removed between 0.5 mm posterior and 2.5 mm anterior to bregma and 3–5 mm lateral to mid-

line. Dura was removed and 3 μ l of endothelin-1 (240 pmol, 0.2 μ g/ml in sterile saline) was applied to the cortical surface at a rate of 1 μ l/3 min. The skull was left undisturbed for 5 min prior to suturing the scalp.

The single pellet retrieval task, adapted from previous studies [5,40,41], was used as the rehabilitative training procedure and as a test of post-lesion forelimb reaching performance. In this task, rats in a training chamber reach through a 1-cm-wide window to retrieve palatable food pieces (45 mg banana-flavored pellets, Bioserve, Inc.) placed on a shelf in a shallow well at a distance of 1 cm from the window. Reaching with the contralesional (impaired) forelimb was effectively enforced by the insertion of an inner chamber wall ipsilateral to this limb and the placement of pellets, one at a time, in the well opposite this limb. For each trial, rats were permitted to reach for a pellet until they successfully retrieved it or made five unsuccessful attempts. A successful reach was defined as one in which the rat grasped the pellet, brought it to its mouth and ate it. Performance was measured as the percentage of successful retrievals per reach attempt and these data were analyzed using SPSS (SPSS, Inc.) repeated-measures analyses of variance (ANOVAs). Scheffe's post hoc test was used to test for group differences at each time point and the α level was set at 0.05.

After pre-operative shaping and determination of endogenous limb preferences, rats were then trained on the preferred forelimb until they reach a criterion of ~40% successful retrievals. Unilateral SMC lesions were then made contralateral to the preferred forelimb. Twenty-two consecutive days of post-lesion rehabilitative training began 10–14 days after the lesion. Each session consisted of 60 trials or 15 min, whichever occurred first. Rats were given an intraperitoneal injection of 1 mg/kg AMPH (10 mg/ml in sterile saline) or 0.9% saline 1–2 h before the onset of training on training days 2, 5, 8, 11, 14, 17, and 20. The dose was chosen based on pilot data indicating that 1 mg/kg of AMPH increases reaching success while not preventing the rats from engaging in the task. Animals were retested in the reaching task on 2 consecutive days for each of the 3 months following the end of the rehabilitative training period.

After completion of the behavioral procedures, animals were transcardially perfused with 0.1 M sodium phosphate buffer followed by 4% paraformaldehyde solution in the same buffer. Two AMPH rats were sacrificed 30 days post-training for inclusion in a pilot study unrelated to the study presented here and one SAL animal died between post-training days 30–60. The brains from these three rats were not included in volume estimates but they were included in behavioral analyses because their removal did not change the effects found in the ANOVA reported below. The volume of remaining cortical tissue in the peri-lesion region and the cortex opposite the lesion (~2.2 to –0.3 mm rostral–caudal to bregma) was determined by measuring cortical area in 50 μ m Toluidine blue stained coronal sections using NeuroLucidaTM software (MicroBrightfield Inc.) at a final magnification of $\times 17$, as described in more detail previously [2]. Volume was

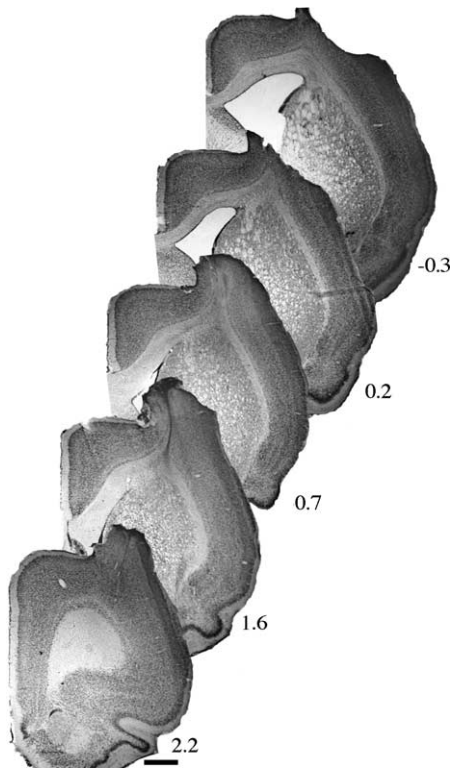


Fig. 1. Representative unilateral endothelin-1 induced SMC lesion as viewed in Nissl stained coronal sections of a saline-injected animal. Numbers are approximate coordinates in mm relative to bregma. Scale bar: 1 mm.

estimated using the Cavalieri method as the product of the summed areas multiplied by the distance between section planes (600 μm).

Fig. 1 shows a representative example of the endothelin-1 induced SMC lesions. Measurements of the volume of the remaining cortex ipsilateral to the lesion revealed a similar lesion size between AMPH and saline-treated animals [ANOVA for Group: $F(1,16) = 0.08$, $p > 0.05$]. The mean \pm S.E.M. volume in mm^3 of the remaining lesion SMC region was 75.06 ± 3.93 in the SAL group and 73.84 ± 2.39 in the AMPH group. There was also no significant difference between groups in cortical tissue lost relative to the contralateral cortex [ANOVA for Group: $F(1,16) = .32$, $p > 0.05$]. The mean difference (contra – ipsi) \pm S.E.M. volume in mm^3 was 15.52 ± 2.92 in the SAL group and 17.76 ± 2.61 in the AMPH group.

As shown in Fig. 2, the unilateral lesions worsened performance in the contralesional forelimb on the single pellet retrieval task. SAL treated rats had modest improvements over days of training. AMPH injected rats had robustly enhanced behavioral performance compared to SAL-injected controls. In repeated-measures ANOVA, there were significant effects of Group [$F(1,16) = 5.36$, $p < 0.05$], Day [$F(25,400) = 5.17$, $p < 0.0001$] and a Group \times Day interaction [$F(25,400) = 2.39$, $p < 0.001$]. In Scheffe's post hoc analyses, the AMPH group had a significantly greater reaching success rate than the SAL group on most therapy days.

Early in the course of rehabilitative training, there was a worsening of performance on the days in which AMPH was administered, especially in the early days of treatment. Compared with each prior day's success rate, the AMPH group performed significantly worse on injection days 5 and 8 (p 's < 0.05). Although the AMPH group showed some decrement in reaching performance on later injection days, these were not significantly different from each preceding day's performance. There was also a reduction in the number of trials completed by the AMPH group in the 15 min training session on the first 3 injection days (mean \pm S.E.M.: 32.30 ± 6.65) compared to SAL on these days (56.83 ± 1.44 , $p < 0.01$) and compared with the preceding non-injection days of the AMPH group in the same period (45.73 ± 4.95 , $p < 0.05$). However, there were no significant differences between AMPH and SAL in the number of trials at any of the later time points. Anecdotal behavioral observations indicated that AMPH increased behavioral reactivity and distractibility on injection days and this was especially evident in the first 3 injection days.

Post hoc analyses also indicated that the behavioral improvements in the AMPH group were not permanent. The AMPH group had a marked decline from the last day of rehabilitation therapy (day 21) compared to days 30–31 and 60–61 after therapy ($p < 0.05$). On day 31 after therapy, the AMPH treated group performed significantly better than the SAL injected animals. This effect was due, in part, to a non-significant decline in the performance level of the SAL group, which was more evident at 1 than at 2 and 3 months post-therapy. There were no significant differences between the groups in the second and third month after the end of the rehabilitation period.

The results indicate that rehabilitative training combined with repeated AMPH treatment can significantly enhance recovery of reaching performance on a skilled reaching task after unilateral SMC lesions relative to saline-injected rats. The behavioral advantage in AMPH treated rats was still evident 1 month after treatment. Two and 3 months after the conclusion of the therapy period, there were no significant differences between the two treatment groups.

The failure to find an enduring enhancement of behavioral recovery in the AMPH treated rats could be due to a need for more frequent practice in reaching and/or a need for occasional sessions of training coupled with AMPH. Other studies have found enduring beneficial effects of AMPH coupled with therapy without additional dosing regimes. For example, behavioral improvements are found 1–2 months post-injury in cats on the beam-walking task [16] and greater than 6 months post-treatment in patients recovering from hemiplegia [7,38] and aphasia [37,39] when therapy is coupled with AMPH. It is possible that this continued benefit is in part due to the opportunity to have ongoing practice in related behaviors after the cessation of treatment. As Feeney et al. suggested, locomotor experience in the home-cage of cats may be a form of practice that maintains beam-walking task performance [13,16]. In contrast, rats in this study may have

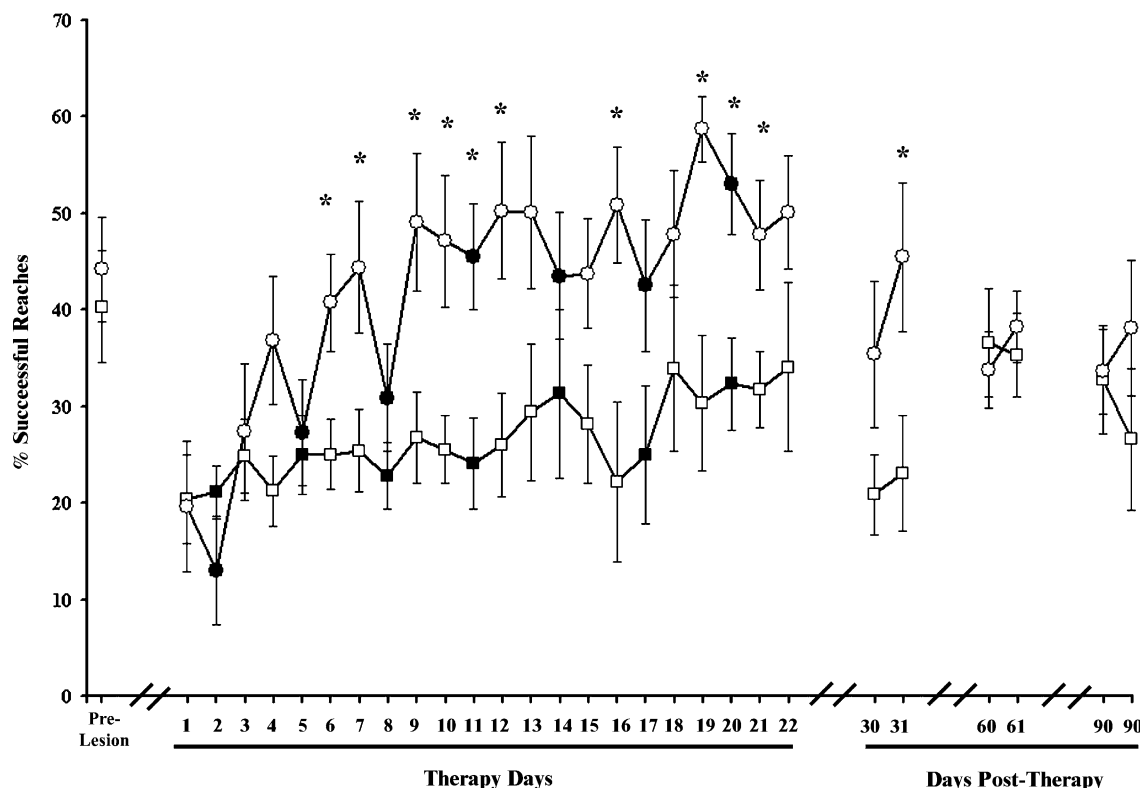


Fig. 2. Percent successful reaches on the single pellet retrieval task over days of training. Rehabilitative training (“therapy”) began 10–14 days after unilateral SMC lesions. All animals had deficits in reaching success as assessed on the first day of post-lesion training. AMPH injected animals performed significantly better over subsequent therapy days compared to saline-injected controls. When animals were retested 1 month after the end of the therapy period, there were decreased success rates in both groups, but the AMPH group nevertheless performed significantly better than SAL. In contrast, there were no significant differences between groups at 2 and 3 months after the end of therapy. Dark symbols represent days in which rats received AMPH or SAL 1–2 h before training onset. The 1–3 month post-therapy period is 2–4 months post-lesion. Data are mean \pm S.E.M. (* p < 0.05).

less opportunity in the home-cage to practice the fine digit and wrist movements required for success on the reaching task. The behavioral effects of amphetamine have been found to be significantly affected by the living environments of rats [8]. Future studies should determine whether more frequent practice is needed to maintain AMPH induced improvements in skilled reaching function. If so, it would be interesting to determine whether recovery on poorly practiced tasks could be reinstated with additional AMPH treatment. It is also possible that longer lasting improvements would have been found if the treatment had been initiated earlier after the lesions rather than 10–14 days post-lesion, as performed in this study. It is also possible that a higher dose of amphetamine (e.g., the more typically used 2 mg/kg) would have produced more enduring effects, although this may have also resulted in greater acute interference with reaching task performance.

Unlike many other amphetamine studies, we found that drug administration 1–2 h before reach training worsened performance on that day’s test (dark circles in Fig. 2). This effect was clearly evident only on the second and third injection days and was coupled with a reduction in the number of trials rats were able to complete per training session and with anecdotal observations of increased behavioral reactivity and activity. Thus, it appears that the psychostimulant

effects of amphetamine may interfere with reaching task performance acutely; nevertheless, performance on the days *between* AMPH injections was dramatically improved relative to SAL treated rats.

This present study supports that repeated AMPH can improve the efficacy of rehabilitative training in skilled forelimb reaching behavior. It seems possible this effect is mediated by an AMPH induced facilitation of the plastic changes in neocortical structure and activity that have previously been found to result from motor rehabilitative training. The conditions needed to make the AMPH-induced behavioral improvements permanent remain to be determined.

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