Development of motor maps in rats and their modulation by experience

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Young NA, Vuong J, Teskey GC. Development of motor maps in rats and their modulation by experience. J Neurophysiol 108: 1309–1317, 2012. First published June 20, 2012; doi:10.1152/jn.01045.2011.—While a substantial literature demonstrates the effect of differential experience on development of mammalian sensory cortices and plasticity of adult motor cortex, characterization of differential experience on the functional development of motor cortex is meager. We first determined when forelimb movement representations (motor maps) could be detected in rats during postnatal development and then whether their motor map expression could be altered with rearing in an enriched environment consisting of group housing and novel toys or skilled learning by training on the single pellet reaching task. All offspring had high-resolution intracortical microstimulation (ICMS)-derived motor maps using methodologies previously optimized for the adult rat. First, cortical GABA-mediated inhibition was depressed by bicuculline infusion directly into layer V of motor cortex and ICMS-responsive points were first reliably detected on postnatal day (PND) 13. Without relying on bicuculline disinhibition of cortex, motor maps emerged on PND 35 and then increased in size until PND 60 and had progressively lower movement thresholds. Second, environmental enrichment did not affect initial detection of responsive points and motor maps in non-bicuculline-treated pups on PND 35. However, motor maps were larger on PND 45 in enriched rat pups relative to pups in the standard housing condition. Rats in both conditions had similar map sizes on PNDs 60, 75, and 90. Third, reach training in rat pups resulted in an internal reorganization of the map in the hemisphere contralateral, but not ipsilateral, to the trained forelimb. The map reorganization was expressed as proportionately more distal (digit and wrist) representations on PND 45. Our data indicate that both environmental enrichment and skilled reach training experience can differentially modify expression of motor maps during development.

Highly organized movement representations (motor maps) in the frontal cortex have been well described in microstimulation studies of adult animals, particularly in cats (e.g., Asanuma and Sakata 1967; Asanuma and Ward 1971), a variety of primate species (e.g., Asanuma and Rosen 1972; Nudo et al. 1996; Rosen and Asanuma 1972; Sherrington 1906), humans (see Penfield and Rasmussen 1968), and rodents (Kleim et al. 1998; Neafsey and Sievert 1992; Nudo et al. 1990; Tennant et al. 2011; Young et al. 2011). The ability to evoke movements from motor areas requires that there is a sufficient level of synaptic connectivity within layer V, which is present at some point during development and is further modified throughout life in response to differential motor experience (Monfils et al. 2005). In the cat, forelimb motor maps are not detectable with standard intracortical microstimulation (ICMS) techniques until after postnatal day (PND) 45, with adult emergence at PND 81. Furthermore, the developmental emergence of the map into adulthood is characterized by lowering of the movement threshold and a progressive increase in distal movement representations (Chakrabarty and Martin 2000). Transcranial magnetic stimulation studies in humans have shown a similar lowering of the stimulation intensity required to elicit motor-evoked potentials until adolescence (Eyre et al. 2000). The roles of experience and skilled learning have not yet been considered in the emergence of motor maps during development.

The present study was undertaken to construct a developmental profile of the rat forelimb motor map and associated movement thresholds, and to determine whether it can be shifted by differential enrichment experience and/or skilled learning. The forelimb motor area was chosen for this study because of its clearly defined borders, ease of accessibility for microstimulation, uncomplicated identification of elicited movements, direct relationship to reorganization in response to motor learning (Kleim et al. 1998), and previous forelimb motor development characterization in the cat (Chakrabarty and Martin 2000). Given that the expression of motor maps is highly influenced by the relative contributions of excitation and inhibition (Young et al. 2011), we first disinhibited the cortex with local infusions of bicuculline in anesthetized rat pups between PNDs 11 and 15 in order to determine the earliest emergence of the map using standard ICMS parameters routinely employed in the adult rat (Castro-Alamancos and Borrel 1995; Kleim et al. 1998; Nudo et al. 1990; Young et al. 2011). Second, we exposed a different set of rats to either lifelong environmental enrichment (novel toys, group housing in large cage) or deprived laboratory housing (paired housing in standard shoebox cage) and then derived forelimb motor maps on PNDs 30, 35, 45, 60, 75, and 90 to determine the emerging developmental profile of the rat...
motor map and how it may be altered with enriched rearing. A final, separate group of rats raised in deprived laboratory housing conditions (paired housing in standard shoebox cage) underwent daily reach training from PND 35 to PND 44 to determine the effect of skilled motor learning on the functional expression of juvenile motor maps relative to unskilled control rats.

MATERIALS AND METHODS

Rats

Female Long-Evans hooded rats were obtained from the University of Calgary Breeding Colonies for breeding purposes, and the resulting male offspring were used in the deprived/enriched experiment. Male Long-Evans hooded rats from Charles River were used in the bicuculline and reach training experiments. The colony room was kept at 21°C under a 12:12-h light-dark cycle (lights on at 0500). Rats received Lab Diet 5001 (PMI Nutrition International, Brentwood, MO) and water ad libitum. The rats were housed and handled according to Canadian Council on Animal Care guidelines, and experimentation was approved by the Life and Environmental Science Animal Care Committee.

Bicuculline Infusion

Between PND 11 and PND 15 rats received 1(S),9(R)-(−) -bicuculline methidide (Sigma-Aldrich, Oakville, ON, Canada) dissolved in 27°C physiological saline and infused into layer V of sensorimotor cortex after an initial ICMS mapping attempt (see below). Bicuculline (50 μg/ml; 0.1 μmol/ml) was delivered in the sensorimotor cortex at a neocortical depth of 1,550 μm with a manual microinjection unit (model 5000, Kopf Instruments, Tujunga, CA) via three separate 5-μl injections, over a 5-min period, each. This volume was chosen to ensure that the drug diffused over a distance of several millimeters. Forelimb motor maps were derived 30 min after the last infusion and also at 120 min after the infusion when bicuculline was no longer active (Jacobs and Donoghue 1991; Kim et al. 2012). Anesthetic was maintained at typical ICMS levels (see below) during bicuculline infusion in all rats.

A separate group of five rat pups, of age and weight (PND 15–19 and between 33 and 46 g) that would not normally express responsive points without the aid of bicuculline, were treated in the same way as described above except that they received physiological saline infusions rather than bicuculline.

Intracortical Microstimulation

Rats initially received intraperitoneal injections of ketamine (100 mg/kg) and xylazine (5 mg/kg). Supplemental injections of ketamine alone (25 mg/kg), or a cocktail of both ketamine (17 mg/kg) and xylazine (2 mg/kg), were delivered intraperitoneally as required throughout the surgical procedure to maintain a constant level of anesthesia as indicated by breathing rate, vibrissa whisking, and a foot reflex in response to a gentle pinch (see Tandon et al. 2008).

A craniotomy exposed the sensorimotor neocortex of the left hemisphere. An 18-gauge needle, a small puncture was made in the cisterna magna to reduce pressure due to edema. Dura was carefully removed, and 37.4°C silicone fluid (Factor II, Lakeside, AZ) was used to cover the neocortical surface. A X41.5 digital image of the exposed portion of the brain was captured using a Stemi 2000-C stereomicroscope (Carl Zeiss, Thornwood, NY) and a digital camera (Canon Canada, Mississauga, ON, Canada) and displayed on a computer. A grid composed of 500-μm squares was overlaid on the digital image. Penetration points were chosen at the intersections of the grid lines and at a central point in the middle of each square (interpenetration distance of 353 μm), except when located over a blood vessel. Microelectrodes made from borosilicate glass capillaries (World Precision Instruments, Sarasota, FL) on a micropipette puller (Kopf Instruments) were filled with 3.5 M NaCl and beveled at a 30° angle to yield a 3-μm tip diameter with impedance values between 1.0 and 1.5 MΩ. Penetrations of the neocortex by the glass electrode were guided by a microdrive (Narishige, Tokyo, Japan). The optimal stimulation depth was determined for each age group by conducting a depth profile of the first electrode penetration site (see Young et al. 2011). Electrical stimulation was delivered via an isolated stimulator (A-M Systems, Carlsborg, WA) and consisted of 13 monophasic cathodal pulses, each 200 μs in duration, delivered at a frequency of 333 Hz and repeated every second. Rats were maintained in a prone position, with the limb contralateral to the stimulation side being supported by placing one finger below the elbow joint and elevating the forelimb. This allowed visual detection of all possible forelimb (digit, wrist, elbow, or shoulder) movements. At each penetration site the minimal threshold required to elicit a movement was recorded, and a color-coded dot was placed on the digital image. Penetration sites that failed to elicit a movement at any current intensity, up to the maximum of 60 μA, were defined as nonresponsive. To determine movement threshold, current intensity began at 0 μA and was increased until a movement was detected and then decreased until the movement was no longer present (Kleim et al. 1998; Young et al. 2011). No more than 10 trains of pulses were delivered to a single site to determine movement because excess stimulation can alter the integrity of the map border (Nudo et al. 1990). The border of the forelimb motor map was defined first and was characterized by any nonforelimb movement that included head and neck, jaw, vibrissae, trunk, tail, hindlimb, or nonresponsive sites. The more central map points were then determined in an effort to reduce the likelihood of the ICMS affecting the border points of the map (Nudo et al. 1990). The level of anesthesia was also assessed by revisiting positive-response sites to check for changes in movement thresholds as mapping progressed. Manipulation of stimulation parameters was then assessed in selected areas of the map as described in the appropriate sections below. After mapping sessions, rats were humanely euthanized with injection of 1 ml of 240 mg/ml pentobarbital sodium, Canvas (version 9.0.1) imaging software (ACD Systems, Miami, FL) was used to calculate the areal extent of all forelimb areas. The proportion of distal (digits and wrist) and proximal (elbow and shoulder) movements that occurred during mapping was calculated. Distal movements were determined as the average of the distal and proximal proportion of all forelimb areas. The mean stimulation threshold for each movement category was also calculated.

Deprived/Enriched Experiment

Female rats were mated, and pregnancy was verified by the presence of a solid yellow vaginal plug at the bottom of the cage. The presence of a vaginal plug indicated gestational day 1. The inseminated female rats were individually placed either in a standard Plexiglas shoebox cage (45 cm × 25 cm × 20 cm; n = 20) or a large Plexiglas cage (61 cm × 47 cm × 64 cm; n = 10). The small cage served as the deprived condition, while the large cage served as the enriched environment and included plastic tubes, cardboard tubes, running wheels, balls, and other toys (Bio-Serv, Frenchtown, NJ) that were changed five times a week. Female rats that were housed in standard shoebox cages were not provided with any toys or additional items other than their standard food pellets, water bottle, and bedding. All female rats remained in their respective housing conditions until weaning.

All litters were culled to six males on PND 1. These offspring resided in their respective housing conditions with the dam until weaning and were weaned from the dam on PND 21. In the enriched environment condition, the dam was removed from the large cage on PND 21 while all offspring remained. Enriched offspring had continuous enrichment, both before weaning and after weaning, for the
duration of the experiment to ensure lifelong enrichment opportunities, as this has been shown to be an important variable (Simonetti et al. 2009). In the deprived condition, offspring were separated from the dam and housed in pairs in standard shoebox cages and were not provided with any toys or additional items other than their standard food pellets, water bottle, and bedding. Deprived offspring remained in this housing condition for the duration of the experiment.

All rats had high-resolution forelimb motor maps derived by ICMS at PND 30, 35, 45, 60, 75, or 90. No more than two rat pups per litter were used per postnatal age. This resulted in 12 groups in total that had forelimb motor maps derived, which included PND 30 enriched (n = 4) and deprived (n = 4); PND 35 enriched (n = 9) and deprived (n = 7); PND 45 enriched (n = 7) and deprived (n = 12); PND 60 enriched (n = 8) and deprived (n = 7); PND 75 enriched (n = 10) and deprived (n = 8); and PND 90 enriched (n = 12) and deprived (n = 9).

Skilled Reach Training Experiment

Reach training began on PND 35. Rats were trained in a Plexiglas chamber (13 cm wide, 35 cm long, and 35 cm high) with an open slot (13 mm) in the center of the front wall that was modified from apparatus previously described by others (Bury and Jones 2002; Whishaw et al. 1991). A 7.5-cm-long by 3.5-cm-wide Plexiglas shelf was attached to the outer front wall at a height of 5.5 cm above the floor of the chamber. Forty-five-milligram banana-flavored Dustless precision pellets (no. F0059; Bio-Serv) were singly placed, on their side, in shallow wells in the shelf that were aligned with the vertical edges of the window at a distance of 1.5 cm from the outside of the front wall.

Rats were placed in the chamber once a day for a 15-min period for a total of 15 consecutive days. In this unimanual task, rats were trained to reach with their preferred forelimb (Whishaw 1992). A single pellet was placed in a well, and rats were permitted a single reach attempt. After a failed reach attempt, the pellet was removed from the well. After either a failed or successful reach attempt, a pellet was put into the back of the reach training chamber to ensure that the rats moved away from the front of the box, obligating them to reset their reaching position. This procedure increased the chances of a successful reach because it prevented multiple frantic reach attempts and reduced the number of reaches from an inappropriate initial location and posture (Whishaw 2000; Monfils and Teskey 2004; Henderson et al. 2012). A fresh pellet was placed in the well as the rat moved to the back of the chamber. In the early trials, on training days 1–3, the rats were rewarded at the back of the reaching cage for each attempt. As training progressed, the rats were rewarded at the back of the reaching apparatus only for successful reaches. Rats were required to move to the back of the chamber between each attempt, regardless of whether or not they had reached successfully, to ensure a postural reset. This is important because poor posture can lead to repeated unsuccessful reach attempts. A successful reach consisted of the rat making a single reach and grasp of the pellet from the well, bringing it to its mouth, and eating the pellet. The reaching performance was assessed daily by calculating the percentage of success (number of successful attempts/total number of attempts × 100).

As in the skilled-reaching condition, yoked control rats in the unskilled condition were trained to reach through the slot at the front of the reach training chamber (Monfils and Teskey 2004). Moreover, in the unskilled condition the pellet was removed from the well by the experimenter immediately prior to a reach attempt to ensure that rats were never allowed to successfully retrieve the pellet. In the unskilled condition the rats do not have to correctly gauge the distance from their fingers to the pellet, they do not contact, grasp, hold, or translate the pellet to their mouth, and thus the condition does not require skill but does control for the rotary movements of the forelimb. After a failed reach attempt, rats received a pellet at the back of the reach training chamber. After 15 days of unskilled reaching, the rats underwent a probe trial in which they were allowed to retrieve the pellets that were presented to them at the front of the reach training chamber.

On PND 45 or 46 rats in the unskilled and skilled reach-trained groups first had their motor maps derived in the hemisphere contralateral to their preferred forelimb as described above and then in their ipsilateral hemisphere.

Statistical Analysis

All data are reported as means ± SE, and statistical significance was set at P < 0.05. The statistical analysis was completed with SPSS software (SPSS, Chicago, IL). Rats required less ketamine with age, and ketamine has an unknown relationship with cortical circuits; therefore, the analyses of total forelimb area, mean movement threshold, and percentage of distal and proximal movements within deprived and enriched conditions were compared with each preceding age group in effort to control for potential anesthetic effects. The hemispheric analysis on map size was performed with an independent t-test. A priori analysis of total forelimb area, mean movement threshold, and percentage of distal and proximal movements to the total forelimb area were also conducted between the conditions at different postnatal ages with independent t-tests.
Development of motor maps with enrichment. Mean movement threshold declined with age $[R^2 = 0.199, F(1,45) = 11.16, P = 0.0017]$ (Fig. 3A). PND 35 and 45 rats had similar movement thresholds. PND 45, 60, 75, and 90 rats also had movement thresholds that were not statistically different from each other. PND 35 rats had higher movement thresholds than PND 60 [$t(16) = 2.82, P = 0.017$] and PND 75 [$t(17) = 3.22, P = 0.001$] rats.

Total rostral and caudal forelimb areas increased with age in the enriched condition (Figs. 2 and 3). PND 35 rats had smaller map area than PND 45 rats [$t(14) = 4.58, P = 0.05$]. There was no difference in map areas in PND 45, 60, 75, and 90 rats. This indicates that size of forelimb motor maps of enriched rats reaches a plateau at PND 45. There was no difference in the proportion of distal or proximal forelimb movements in the total forelimb map area at any postnatal age.

Reach Training

Rats between 35 and 44 days of age in the skilled reach-trained group ($n = 6$) showed improvement in reaching success over time and achieved a mean success of 76.35% on the last day of training, while unskilled control rats ($n = 6$) achieved 3.77% success on the probe trial.

During the ICMS procedure skilled reach-trained rats, compared with unskilled control rats, did not significantly differ in their ketamine (unskilled 1.6 ± 0.3; skilled 1.8 ± 0.2) or xylazine (unskilled 0.0105 ± 0.0015; skilled 0.0090 ± 0.0002) levels (expressed in mg·kg$^{-1}$·min$^{-1}$), forelimb movement thresholds (unskilled 31.27 ± 21.5 µA; skilled 29.97 ± 26.8 µA), or total motor map size (unskilled 2.57 ± 0.51 mm$^2$; skilled 2.84 ± 0.46 mm$^2$).

Skilled reach-trained rats had significantly [$t(5) = 4.37, P < 0.01$] proportionately more distal (wrist and digit) movements relative to proximal (elbow and shoulder) in the hemisphere contralateral to the trained forelimb compared with the ipsilateral hemisphere.

Table 1. Number of ICMS-positive responsive sites after bicuculline within each age

<table>
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<tr>
<th>Rat</th>
<th>Postnatal Age, days</th>
<th>ICMS+ Responses Prior to Bicuculline Infusion</th>
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ICMS, intracortical microstimulation.
eral hemisphere (Fig. 4). There were no significant differences between the mean map area in the contralateral and ipsilateral hemispheres of unskilled control rats. Moreover, there was no significant difference in map area between ipsilateral hemisphere in skilled rats and ipsilateral hemisphere in unskilled rats (Fig. 4).

DISCUSSION

This is the first study to show in developing rats that 1) forelimb motor maps are first detectable at the end of the second postnatal week with low ICMS current levels and concurrent pharmacological reduction of inhibition, 2) enrichment can transiently advance the development of larger forelimb motor maps, and 3) skilled learning results in an internal reorganization of the forelimb map in juvenile rats that is specific to the contralateral hemisphere.

The size and movement thresholds of motor maps can be affected by various electrical stimulation parameters such as current intensity, the number of pulses in a train, and stimulation frequency, as well as pharmacological manipulations that can include ICMS anesthetics (Donoghue and Wise 1982; Tandon et al. 2008; Young et al. 2011), and therefore map expression reported in any experiment is dependent on the methods used. Anesthetics used in microstimulation of rodents can affect map size and increase movement thresholds in motor cortex (Gioanni and Lamarche 1985; Sapienza et al. 1981; Tandon et al. 2008; Young et al. 2011), and while anesthesia can affect the degree of responsiveness of neurons, it does not seem to result in any significant changes in cortical topography (Tandon et al. 2008). In the present study, we tracked ketamine use and statistically compared each group to detect differences in its use. Our analysis showed a difference in ketamine use to maintain a consistent level anesthesia only in PND 35 and PND 90 rats. From this we can conclude that ketamine anesthesia contributes minimally to our overall findings, and we have avoided making direct comparisons of the PND 35 and PND 90 groups as a result. In this study, we chose to use a maximum current intensity of 60 μA and an electrode interpenetration distance of 353 μm to reduce the likelihood of current spread to adjacent sites that could result in overlapping areas of activation and thus bias forelimb motor maps to be larger (Stoney et al. 1968; Young et al. 2011). When using this technique, we reliably detected forelimb motor maps on PND 35 but not on PND 30 (data not shown). However, we suspected that ICMS-induced movements could be elicited much earlier given the nature of forelimb usage in younger rats. We chose to use normal adult ICMS intensity levels concurrent with pharmacological blockade of inhibition rather than raising the intensity of ICMS to levels that would result in widespread activation and thus bias forelimb motor maps to be larger (Stoney et al. 1968). When bicuculline was infused into layer V of motor cortex to depress GABAergic function (Curtis et al. 1970) and suppress Ca2+-activated potassium channels (Khawaled et al. 1999), it revealed that the forelimb motor map is present and can support ICMS-driven forelimb movements on PND 13 in Long-Evans rat pups weighing >33 g. Volnova and Ivanova (2002) carried out experiments in an unspecified strain of “white rats,” used unspecified train durations and current intensities as high as 150 μA, and reported that ICMS was not effective before PND 10. In the rat, the end of the second...
The rapid unmasking of inhibitory intracortical connections with age, related decrease in the minimum ICMS current to induce a response in the motor cortex, could, in part, account for the lowering of movement thresholds and increase in the size of motor maps. In the neocortex, this decrease with age as map area increased, and this inverse relationship between threshold and map area is consistent with previous descriptions (Young et al. 2011). Seizures, which alter the balance of excitation and inhibition, have been shown to both lower movement thresholds and result in larger motor maps (Henderson et al. 2011; Teskey et al. 2002; Young et al. 2009). We suggest that this increases in map area throughout development rely, in part, on a reduction of GABAergic-mediated inhibition resulting in an unmasking of intracortical connections with age as well as with progressive growth-related changes.

GABAergic inhibition of cortical modalities decreases with age. Primate and feline visual neocortex show downregulation of GABAergic inhibition with age, which is related to a loss of neuronal response to orientation and directional selectivity (Hua et al. 2006; Schmolesky et al. 2000) that can be reversed with GABA agonists (Leventhal et al. 2003). Age-related downregulation of GABAergic inhibition has also been found in auditory neocortex (Caspar et al. 2008). GABA receptor mRNA levels in the neocortex reach their peak at PND 30 in the rat (Carpenter et al. 1988) and then progressively decline. Specifically, expression of the α1 GABAA subunit, which has been shown to upregulate inhibition (Raol et al. 2006), is increased and peaks in rat motor cortex at PND 30 and then proceeds to decline until PND 60 (Yu et al. 2006). This description of GABA neocortical maturation in the rat coincides with our developmental profile of forelimb motor maps.

Our data show that maps are expressed at PND 35 and reach “adult” size at PND 60 in nonenriched rats, which fits nicely with GABA subunit regulation characterized by Yu et al. (2006). Our enriched rats begin to express motor maps at PND 35 and reach “adult” size at PND 45, which suggests that GABAergic development is accelerated in enriched rats. It is reasonable to suspect that GABAergic modulation of neocortical activity is necessary during development, as it has been shown that GABA agonist infused to the motor map in kittens later impairs map expression (Chakraborty and Martin 2005). The normal development of somatosensory maps also relies on experience-dependent GABAergic modulation of neocortical connections (Micheva and Beaulieu 1997).

Enrichment can modulate GABAergic function in the cortex, as visual enrichment has been shown to decrease GABAergic inhibition in the visual cortex and restore visual acuity after amblyopia (Sale et al. 2007) and dark-rearing (Bartoletti et al. 2004). With these descriptions of GABAergic modulation of the visual cortex with enrichment, and the findings of the present study, it is not unreasonable to suspect that enrichment may have altered GABAergic function of motor cortex in such a way that it accelerated adult expression of the motor map; however, the specific relationship of motor enrichment to neocortical GABA function remains to be fully characterized. In the present experiment, environmental enrichment was successful in promoting larger map areas at PND 45. We hypothesize that this is because our enriched environment provided motor activity that was sufficient in generating activity-dependent patterns necessary to support the development of cortical motor maps. In the adult rat, reorganization of the neocortical forelimb motor map requires a pattern of neural development that is responsible for the switch from excitatory to inhibitory GABAergic responses (Miles 1999; Rivera et al. 1999) nears completion at PND 14 (Dzhala et al. 2005).

The development of some primary sensory systems also occurs around this age as well. The map of layer 2/3 barrel receptive fields for vibrissa stimulation is formed at 2 wk postnatally (Stern et al. 2001). The tonotopic organization of auditory cortex matures rapidly during the second and into the third postnatal week with broadly responsive neurons becoming tuned to specific frequencies (de Villers-Sidani et al. 2007) and the emergence of an adultlike tonotopic map (Zhang et al. 1999) nears completion at PND 14 (Dzhala et al. 2005).

In the present study, motor maps were reliably detected without local pharmacological reduction of inhibition in all rats at PND 35. Thereafter, in the deprived condition the forelimb motor map sizes increased in area with age until PND 60, when they reached adult sizes, indicating a long maturation time course. We report that movement thresholds were found to decrease with age as map area increased, and this inverse relationship between threshold and map area is consistent with previous descriptions (Young et al. 2011). A similar age-related decrease in the minimum ICMS current to induce a movement has been reported in the cat (Chakraborty and Martin 2000), and similarly there is lowering of the stimulation intensity required to elicit motor-evoked potentials with transcranial magnetic stimulation in children as they develop (Eyre et al. 2000).

An age-related shift in the balance of excitation/inhibition in the neocortex could, in part, account for the lowering of movement thresholds and increase in the size of motor maps. The rapid unmasking of inhibitory intracortical connections

![Graph](http://jnn.physiology.org/figure/1314/JN.01045.2011.F04)

**Fig. 4.** Mean (±SE) proportion of distal (digit and wrist) representations in hemispheres ipsilateral and contralateral to the reaching forelimb in both skilled and unskilled rats. *Statistical significance between ipsilateral and contralateral groups at P < 0.05.
activation that is provided by training in skilled, complex forelimb movements, while nonspecific motor activity, like exercise, has been shown to be ineffective (Adkins et al. 2006; Kleim et al. 2002; Remple et al. 2001). We have shown that motor learning in a skilled reaching task increases the proportion of distal area in the forelimb motor map of the trained hemisphere in juvenile rats, as it does in adults (Kleim et al. 1998). The skill-trained contralateral hemisphere of juvenile rats showed distal expansion within the forelimb map area relative to the unskilled ipsilateral hemisphere. There were no differences in forelimb map areas between hemispheres in untrained rats, indicating that handedness preference is not revealed by forelimb map size in this species as it can be in primates (Nudo et al. 1992). Skilled motor learning in juvenile rats between PND 35 and PND 44 did not result in larger motor map areas relative to yoked control rats, only internal reorganization of distal movements (digits, wrist) with motor learning. Skilled forelimb movements are evident prior to the adult expression of the motor map. The emergence of skilled motor dexterity in cats at PND 45 (Armand and Kably 1993) corresponds with the detection of high-threshold movements in the motor cortex (Chakrabarty and Martin 2000). Rats naturally begin to make reach attempts for food at PND 19, with precise reaches consistently occurring at PND 26 (Brown 2005), well before motor maps can be detected without pharmacological intervention. Lifelong environmental enrichment was effective in accelerating development after initial emergence, but brief (15 min/day for 15 days) dexterous forelimb motor training around the time when the forelimb motor map begins to emerge does not result in expanded cortical area of forelimb motor maps. In light of these findings, we suspect that motor activity patterns necessary to accelerate development of motor maps cannot be detected without pharmacological stimulation. Accelerated development following emergence of forelimb motor maps in enriched rats suggests that hard-wired primary motor maps can, in fact, be modified by early environmental experience.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: N.A.Y. and G.C.T. conception and design of research; N.A.Y. and J.V. performed experiments; N.A.Y., J.V., and G.C.T. analyzed data; N.A.Y., J.V., and G.C.T. interpreted results of experiments; N.A.Y. and G.C.T. prepared figures; N.A.Y. drafted manuscript; N.A.Y., J.V., and G.C.T. approved final version of manuscript; G.C.T. edited and revised manuscript.

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