Cutaneous anesthesia of the forearm enhances sensorimotor function of the hand

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Cutaneous anesthesia of the forearm enhances sensorimotor function of the hand. J Neurophysiol 109: 1091–1096, 2013. First published December 5, 2012; doi:10.1152/jn.00813.2012.—Temporary deafferentation of the upper limb, with ischemic or anesthetic nerve block, has rapid effects on sensorimotor cortex. Cutaneous anesthesia of the forearm has recently been found to improve sensory and motor function of the paretic hand in chronic stroke patients. However, the neurophysiological mechanisms are unknown. The aim of this study was to investigate the behavioral and neurophysiological effects of cutaneous forearm anesthesia. Twenty-five healthy right-handed adults participated in this double-blind, randomized study. Participants completed two sessions, with either a topical anesthesia cream (EMLA) or placebo applied to their left forearm in each session. Thresholds for cutaneous sensation and spatial acuity of the left hand were measured before and after the intervention. Transcranial magnetic stimulation was used to measure corticomotor excitability and short-interval intracortical inhibition in the left first dorsal interosseous and abductor digiti minimi muscles before and after the intervention. Manual dexterity was assessed with the grooved pegboard task after the intervention in each session. Left-hand dexterity improved to a greater extent after treatment with EMLA than placebo, and this was related to improved spatial acuity at the fingertips. Corticomotor excitability remained stable, and short-interval intracortical inhibition increased after EMLA treatment. We have confirmed and extended previous reports that cutaneous forearm anesthesia results in improved spatial acuity and manual dexterity of the ipsilateral hand. The neurophysiological mechanisms involved an increase in intracortical inhibition, which may improve the precision of voluntary movement. These results lend support to the therapeutic application of EMLA in movement rehabilitation.

Cutaneous anesthesia; deafferentation; manual dexterity; intracortical inhibition; transcranial magnetic stimulation

RESULTS

Temporary deafferentation produces rapid and reversible effects on the organization and function of primary motor cortex (M1). Most previous studies in humans have used ischemic nerve block (INB) and anesthetic nerve block (ANB) of the upper limb. In general, these studies have shown an increase in the excitability of M1 representations of muscles proximal to the nerve block, which may be due to a decrease in intracortical inhibition (Brasil-Neto et al. 1993; Levy et al. 2002; Ziemann et al. 1998). Remote effects have also been observed, such as an increase in corticomotor excitability and sensorimotor performance measured in the hand contralateral to the deafferented upper limb (Bjorkman et al. 2004; Werhahn et al. 2002a, 2002b). Temporary deafferentation could therefore be a useful adjunct to upper limb rehabilitation, but the use of INB is limited by the associated discomfort and ANB requires that the injection be administered by an experienced anesthetist. These limitations could be overcome by using a topical anesthetic agent, such as EMLA, to produce cutaneous anesthesia. This approach has the advantage of easy application to a specific area of skin without causing motor paresis.

Cutaneous anesthesia of the forearm has shown promise as an adjunct to upper limb rehabilitation, because it enhances sensory function of the ipsilateral hand in healthy adults (Bjorkman et al. 2004, 2009) and sensory and motor function of the ipsilateral paretic hand in chronic stroke patients (Weiss et al. 2011). There is some evidence that cutaneous anesthesia produces a transient reorganization of somatosensory cortex representations (Bjorkman et al. 2009). However, the neurophysiological mechanisms responsible for the observed improvements in motor function are unknown. Cutaneous anesthesia differs from INB in that it blocks cutaneous sensory afferents only, so it cannot be assumed that its effects on cortical function are similar to those produced by INB. Therefore, the aim of this study was to explore the neurophysiological mechanisms by which sensorimotor function of the hand is improved by cutaneous anesthesia of the ipsilateral forearm.

We used transcranial magnetic stimulation (TMS) to measure corticomotor excitability and short-interval intracortical inhibition (SICI) in the hand representation of the right M1 before and after the application of EMLA or placebo to the left forearm. We also measured cutaneous sensation and spatial acuity thresholds in the left hand before and after each intervention, as well as manual dexterity of the left hand. We hypothesized that cutaneous anesthesia of the forearm would enhance manual dexterity and modulate corticomotor excitability and SICI of the hand representation in M1.

MATERIALS AND METHODS

Participants. Twenty-five healthy adults (15 females, 10 males, mean age 24 yr, range 19–42 yr) without history of upper limb injury or neurological disorder participated in this study. Their handedness was assessed using the Edinburgh Handedness Inventory (Oldfield 1971) (mean 74.2, range 0–100). Participants were screened for contraindications to TMS by a neurologist. All participants gave written informed consent, and the institutional ethics committee approved the study in accordance with the Declaration of Helsinki.

Experimental protocol. Figure 1 summarizes the design of the experiment, which required two sessions, one for each treatment. Sessions were separated by at least 7 days, and session order was randomized and counterbalanced between participants.
Baseline sensory and neurophysiological measures (described below) were obtained at the beginning of each session. A treatment of 15 g of local anesthetic cream (EMLA, consisting of 2.5% each of lidocaine and prilocaine; AstraZeneca) or placebo (PLA; aqueous cream BP; Orion) was then applied to the volar side of the left forearm in a 50-mm-wide and 150-mm-long area, starting parallel with and 10 mm proximal to the wrist, as per previous studies (Bjorkman et al. 2004, 2009; Weiss et al. 2011). Immediately following application, the creams were covered with an occlusive bandage for 60 min. Sensory and neurophysiological measurements were repeated following the removal of the bandage and cream, and performance of an additional manual dexterity task was measured. Participants were told that two anesthetic creams of different strengths were being tested. The experimenter responsible for data collection and processing was blinded to treatment allocation until the initial statistical analyses were complete.

**Behavioral measures.** Cutaneous sensory threshold (CST) was determined at four sites on the left upper limb before and after treatment using Semmes-Weinstein monofilaments, following the testing procedure described in their operations manual (Touch-Test 20-piece full kit; Stoelting, Wood Dale, IL). The test sites were the pads of the index and little fingers (D2, D5), the volar surface of the forearm, and the skin overlying the biceps brachii muscle. Participants were blind-folded, told which site was being tested, and asked to respond whenever they perceived a touch. Monofilaments were applied in decreasing order (3 trials per filament) until the participant no longer perceived the stimulus. Monofilaments were then applied in increasing order until the participant was again able to perceive the stimulus reliably, in at least two of three trials. CST was defined as the monofilament rating number that produced a reliable percept.

Spatial acuity threshold (SAT) of the left D2 and D5 was evaluated before and after treatment using the grating orientation task, which is an objective, valid, and reliable test of tactile spatial resolution (Bleyenheuft and Thonnard 2007). Spatial acuity was tested using a set of plastic domes with gratings cut into the surface at equidistant widths ranging from 0.35 to 3.0 mm, following the testing procedure described in their operations manual (JVP Domes; Stoelting, Wood Dale, IL). Domes were pressed on the fingertip for ~1.5 s with the grooves oriented parallel or perpendicular to the long axis of the digit. Participants were blind-folded, told in which side was being tested, and asked to say whether the grooves on the dome were oriented “along” or “across” the fingertip. Each orientation was first demonstrated on the left D2 and D5, to familiarize the participant with the task. Testing began with the widest grooved dome (3.0 mm), and SAT was defined as the minimum groove spacing (in millimeters) for which the participant was able to report the orientation correctly in at least 15 of 20 trials.

Manual dexterity of the left hand was assessed using a grooved pegboard test (GPT; Lafayette Instrument, Lafayette, IN). The GPT is a timed, manipulative dexterity test consisting of placement of pegs into 25 holes. Pegs have a square key edge on one side such that the pegs must be manipulated in the hand precisely to align with each hole (with key slots of varying orientation). Participants placed five pegs to familiarize themselves with the GPT immediately after the baseline spatial acuity assessment. Four timed GPT attempts took place after the posttreatment spatial acuity assessment. On each attempt participants were instructed to complete the pegboard test as quickly as possible and were timed with a stopwatch. The time between the start of each attempt was 2.5 min. GPT scores were calculated as the total time (in seconds) to place 25 pegs plus a 1-s penalty for each dropped peg. The scores for attempts 2–4 were normalized to the score for attempt 1 in each session. Normalized scores <1 indicate an improvement in GPT performance (whether by a faster trial time or fewer dropped pegs).

**Neurophysiological measures.** Surface electromyography (EMG) of left and right first dorsal interosseous (FDI) and abductor digitii minimi (ADM) muscles was recorded using 10-mm-diameter Ag–AgCl electrodes (Ambu, Ballerup, Denmark) placed in a tendon-belly montage, following standard skin preparation techniques. A common ground surface electrode (3M Canada Health Care) was placed over the lateral epicondyle of each humerus. EMG signals were amplified (CED 1902; Cambridge Electronic Design, Cambridge, UK), bandpass filtered (20–1,000 Hz), sampled at 2 kHz (CED 1401), and stored for off-line analysis (Signal V4.09). Single- and paired-pulse TMS of right M1 was delivered using two Magstim 200 stimulators connected to a BiStim unit (Magstim, Dyfed, UK). A figure-of-eight coil (70-mm wing diameter) was held tangentially to the scalp with the handle pointing backwards and laterally at an angle of ~45° in the sagittal plane. The induced current flow was in a posterior-to-anterior direction across the precentral gyrus. The coil was positioned at the optimal site for producing maximal motor evoked potentials (MEPs) in the resting left FDI muscle, and this spot was marked on the scalp to ensure consistent coil placement throughout the experiment.

During TMS the participant sat comfortably with the hands resting on a pillow. Resting motor threshold (RMT) was defined as the minimum intensity for eliciting MEPs of at least 50 μV peak-to-peak amplitude in four of eight trials in the relaxed FDI muscle. Active motor threshold (AMT) was defined as the minimum intensity for eliciting MEPs in four of eight trials when the left FDI muscle was preactivated by performing a key-grip pinch. Neurophysiological measures were made immediately before the application of each treatment and immediately after completion of the posttreatment GPT attempts. The test stimulus intensity was set to produce nonconditioned (NC) MEP amplitudes that were 50% of the maximal MEP obtainable in FDI, to ensure MEP amplitude was on the linear part of the stimulus-response curve (Devanne et al. 1997). The conditioning stimulus intensity was set to 100% AMT of FDI and preceded the test stimulus by 2 ms (Peurala et al. 2008) to produce conditioned (C) MEPs in both FDI and ADM. The root mean square of the pretrigger EMG (rmsEMG; in μV) was determined over the period 30–100 ms before the test stimulus. Trials with pretrigger rmsEMG activity >10 μV in any muscle were discarded from analysis in compliance with international recommendations (Chippaux et al. 2012). Twenty single and 20 paired stimuli were delivered in a pseudorandomized order. Peak-to-peak left FDI and left ADM MEP amplitudes were determined for each trial. C and NC MEP amplitudes were separately rank ordered and trimmed before calculation of the means, to obtain an accurate measure of central tendency when the data are skewed (Wilcoxon 2001). SICI was calculated for FDI and ADM as a percentage; %SICI = 100 – (C/NC × 100), where C and NC correspond to mean conditioned and nonconditioned MEP amplitudes, respectively. SICI data from participants where the protocol failed to produce SICI at baseline were excluded from subsequent analyses. SICI data from participants where posttreatment NC MEPs were <50% or >200% of the participant’s pretreatment mean were also excluded from subsequent analyses.

**Statistical analysis.** A manipulation check of the effect of treatment on forearm CST was conducted using a repeated-measures analysis of variance (RM ANOVA), with factors of treatment (EMLA, PLA) and...
crease at the treatment site, decreased at a proximal site, and the analyses.

Three participants completed only the EMLA session, and the placebo treatment. Error bars represent SD. *\( P < 0.05 \); **\( P < 0.01 \).

RESULTS

Of the 25 participants, 14 received the EMLA treatment first. Three participants completed only the EMLA session, and missing placebo session data were replaced with series means in the analyses.

Behavioral measures. After EMLA treatment, CST increased at the treatment site, decreased at a proximal site, and was unchanged at distal sites. Spatial acuity at the fingertips and manual dexterity increased after EMLA treatment. There was a positive relationship between improved spatial acuity at the fingertips and improved GPT performance after EMLA treatment.

As expected, there was an interaction between treatment and time for forearm CST (\( F_{1,24} = 36.27, P < 0.001 \)). Forearm CST increased after EMLA treatment (Pre: mean 2.74, SD 0.75; Post: mean 4.20, SD 0.99; \( t_{24} = -6.20, P < 0.001 \)) but was unaffected by PLA treatment (Pre: mean 2.87, SD 0.52; Post: mean 2.83, SD 0.52; \( t_{24} = 0.37, P = 0.717 \)). There were no between-session differences in pretreatment thresholds (paired \( t \)-test, \( P > 0.5 \)).

Similarly, there was an interaction between treatment and time for proximal CST, overlying biceps brachii (\( F_{1,24} = 7.41, P = 0.012 \)). Proximal CST decreased after EMLA treatment (Pre: mean 2.91, SD 0.73; post: mean 2.34, SD 0.70; \( t_{24} = 4.33, P < 0.001 \)) but was unaffected by PLA treatment (Pre: mean 2.93, SD 0.68; Post: mean 2.77, SD 0.69; \( t_{24} = 1.60, P = 0.124 \)). There were no between-session differences in pretreatment thresholds (paired \( t \)-test, \( P > 0.9 \)).

There were no effects or interactions with treatment on distal CSTs at D2 and D5 (all \( P > 0.175 \)). There was a main effect of digit (\( F_{1,24} = 4.80, P = 0.038 \)), with thresholds being slightly higher at D2 (mean 2.22, SD 0.59) than at D5 (mean 2.11, SD 0.42) over both sessions. There were no between-session differences in pretreatment CSTs for the D2 or D5 (paired \( t \)-tests, both \( P > 0.2 \)).

There was an interaction between treatment and time for SATs at D2 and D5 (\( F_{1,24} = 6.10, P = 0.021 \)) (Fig. 2). Spatial acuity improved after EMLA treatment (Pre: mean 2.54 mm, SD 0.68 mm; Post: mean 2.05 mm, SD 0.65 mm; \( t_{24} = 2.96, P = 0.007 \)) but was unaffected by PLA treatment (Pre: mean 2.21 mm, SD 0.80 mm; Post: 2.23 mm, SD 0.62 mm; \( t_{24} = -0.21, P = 0.834 \)). There was also a main effect of digit (\( F_{1,24} = 93.87, P < 0.001 \)), with spatial acuity being better at D2 (mean 1.77 mm, SD 0.84 mm) than D5 (mean 2.75 mm, SD 0.89 mm). There were no between-session differences in pretreatment SATs (paired \( t \)-tests, both \( P > 0.05 \)).

There was a main effect of treatment (\( F_{1,24} = 7.17, P = 0.013 \)) and a main effect of attempt (\( F_{2,48} = 17.31, P < 0.001 \)) on normalized GPT scores (Fig. 3). Normalized scores were
There were no between-session differences in pretreatment NC MEP amplitude for FDI or ADM (paired t-tests, both \( P > 0.2 \)). Mean pretreatment NC FDI MEP amplitude was 1.94 mV (SE 0.28 mV) for the EMLA session and 1.60 mV (SE 0.24 mV) for the PLA session. Mean pretreatment NC ADM MEP amplitude was 0.89 mV (SE 0.26 mV) for the EMLA session and 0.82 mV (SE 0.17 mV) for the PLA session. There were no main effects or interactions with treatment on pretrigger rms-EMG in the NC trials (\( F_{1,24} = 0.53, P = 0.475 \)). Grand average rms-EMG means were 3.7 \( \mu \)V (SE 0.3 \( \mu \)V) for the left hand and 3.3 \( \mu \)V (SE 0.5 \( \mu \)V) for the right hand, confirming that both hands were at rest during the acquisition of NC MEPS.

Data from 20 participants were retained for analysis of SICI. Representative MEP traces are provided in Fig. 5. Data from three participants were excluded because their posttreatment mean NC MEP amplitude was either <50% or >200% of their pretreatment mean. Data from a further two participants were excluded because the SICI protocol was ineffective, with facilitation produced instead of the required inhibition.

The SICI protocol was successful and produced around 50% inhibition in both FDI and ADM pretreatment (Fig. 6). There were no main effects or interactions with muscle, so all %SICI results are collapsed across FDI and ADM. There was an interaction between treatment and time on %SICI (\( F_{1,19} = 6.05, P = 0.024 \) (Fig. 6), because %SICI increased after EMLA treatment (Pre: 53.3%, SE 5.8%; Post: 67.2%, SE 3.4%; \( t_{19} = -3.64, P = 0.002 \) but not after PLA treatment (Pre: 59.7%, SE 4.7%; Post: 63.9%, SE 4.6%; \( t_{19} = -1.605, P = 0.125 \). There were no between-session differences in pretreatment %SICI, collapsed across muscle (paired \( t \)-test, \( P > 0.2 \)). There was no correlation between treatment effects on %SICI and mean normalized GPT scores (both \( P > 0.2 \)).

There were no main effects or interactions with treatment on optimized for FDI. There was also an interaction between treatment and time (\( F_{1,24} = 4.43, P = 0.046 \)). This interaction arose because NC MEP amplitude was facilitated after PLA treatment (Pre: 1.21 mV, SE 0.14 mV; Post: 1.49 mV, SE 0.20 mV; \( t_{24} = -2.50, P = 0.019 \) but not after EMLA treatment (Pre: 1.42 mV, SE 0.24 mV; Post: 1.24 mV, SE 0.18 mV; \( t_{24} = 1.06, P = 0.3 \)).
pretrigger rmsEMG in the SICI trials (all $P > 0.05$). Grand average rmsEMG means were 3.8 $\mu$V (SE 0.36 $\mu$V) for the left hand and 3.5 $\mu$V (SE 0.87 $\mu$V) for the right hand, confirming that both hands were at rest during the acquisition of C MEPs.

**DISCUSSION**

Cutaneous anesthesia of the forearm improved sensory and motor performance of the ipsilateral hand and increased short-interval intracortical inhibition in the contralateral M1. Increased intracortical inhibition may enhance surround inhibition in M1, increasing the precision of motor output. These novel results are in contrast to the neurophysiological effects of ischemic nerve block, which include a decrease in GABAergic intracortical inhibition (Levy et al. 2002; Werhahn et al. 2002a; Ziemann et al. 1998).

Cutaneous sensibility of the forearm decreased after EMLA cream application, as expected, and spatial acuity at the fingertips improved. This is in agreement with previous studies of the effects of forearm cutaneous anesthesia on fingertip spatial acuity thresholds (Weiss et al. 2011) and two-point discrimination thresholds (Bjorkman et al. 2004, 2009). Cutaneous sensibility improved proximal to the site of forearm anesthesia, possibly due to rapid reorganization of the cortical representations of the upper limb. Functional MRI during cutaneous anesthesia has revealed expansion of adjacent areas in the primary somatosensory cortex into the "vacant" anaesthetized forearm area (Bjorkman et al. 2009). The reported effects of cutaneous anesthesia on sensory function at distal sites are variable (Bjorkman et al. 2004, 2009), possibly due to a ceiling effect on sensory thresholds. In the present study we also found that cutaneous sensory threshold at the fingertips was unaffected by forearm anesthesia, and this result was unbiased by ceiling effects, because no participant could perceive the finest monofilament. Together, these results indicate that forearm cutaneous anesthesia improves spatial acuity, but not cutaneous sensation, at the fingertips. Expansion of cortical representations may enhance spatial resolution, without necessarily increasing sensitivity to light touch. Improved spatial acuity may result from expansion of the fingertip representations in primary sensory cortex into the deafferented forearm representations, as observed with fMRI (Bjorkman et al. 2009).

A positive correlation was observed between improvement in spatial acuity and performance on the grooved pegboard task after EMLA treatment. This is in line with the positive relationship previously reported between spatial acuity and GPT scores in older adults (Tremblay et al. 2003). Of the four types of cutaneous mechanoreceptors in the fingertips, Merkel cells are thought to be most important for spatial acuity and performance on the GPT, because only this population of receptors provides a neural image of the stimulus and its orientation, independent of contact force (Johnson 2001). We found no relationship between depth of anesthesia and performance on the GPT, and cutaneous sensory thresholds at the fingertips were unaltered. Therefore, the beneficial effects of EMLA treatment on GPT performance are most likely mediated, at least in part, by improved spatial acuity at the fingertips.

Corticomotor excitability was stable after EMLA treatment. Although there was a small but significant facilitation of corticomotor excitability after placebo treatment, possibly related to postexercise facilitation (Garry et al. 2004), NC MEP amplitudes remained within a range that allows interpretation of the effects of treatment on SICI (Roshan et al. 2003). There was an increase in SICI acting on resting FDI and ADM M1 representations after EMLA treatment, but not after placebo. This increase in basal SICI after EMLA may have prevented the facilitation of corticomotor excitability observed after placebo treatment and supported the recruitment of surround inhibition within M1 during GPT performance. Surround inhibition suppresses corticomotor excitability to focus neuronal activity and improve the precision of motor output (Beck and Hallett 2011). Surround inhibition is mediated through GABAergic intracortical interneurons and serves to fractionally inhibit competing motor representations to prevent them from interfering with voluntary movements (Mink 1996). During performance of a precise manual task, such as the GPT, SICI is modulated such that intracortical inhibition of the desired movement is reduced and simultaneously increased for undesired movements (Beck and Hallett 2011; Stinear and Byblow 2004, 2003). The observed increase in SICI acting on the M1 hand representation following EMLA treatment may have supported the recruitment of surround inhibition and enhanced the selectivity of motor output during the grooved pegboard task. However, surround inhibition was not directly evaluated, because SICI was measured with both hands at rest. This may explain why there was no relationship between the increase in SICI at rest and the improvement in GPT performance after EMLA treatment. Future studies could further explore the effects of EMLA treatment on SICI by evaluating the effects of forearm cutaneous anesthesia on surround inhibition during precise finger movement.

The present results indicate that noninvasive topical anesthesia can modulate intracortical function and improve manual dexterity. One of the limitations of this study is that SICI was only measured in hand muscles. It remains unknown whether EMLA treatment also affects SICI acting on M1 representations of forearm or arm muscles. Previous studies using INB have found some evidence of decreased SICI acting on proximal muscle representations (Ziemann et al. 1998), which may permit the expansion of these representations into the deafferented cortex. Future studies could examine whether disinhibition of proximal representations also occurs following cutaneous anesthesia.

**Conclusion.** We have confirmed and extended previous reports that cutaneous anesthesia of the forearm results in
improved sensory function and manual dexterity of the ipsilateral hand. Unlike other forms of deafferentation, such as ischemic or anesthetic nerve block, EMLA is painless and easily administered. Our finding that cutaneous anesthesia can modulate intracortical function and improve manual dexterity may hold clinical potential, especially in disorders that impair fractionated hand movement, such as in focal hand dystonia or following stroke.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.A.P., W.D.B., and C.M.S. conception and design of research; M.A.P. and F.A.M.J. performed experiments; M.A.P., F.A.M.J., and C.M.S. analyzed data; M.A.P. and C.M.S. prepared figures; M.A.P. and C.M.S. drafted manuscript; F.A.M.J. performed experiments; M.A.P., F.A.M.J., and C.M.S. analyzed data; M.A.P., W.D.B., and C.M.S. conceived and designed research; M.A.P. and W.D.B. and C.M.S. interpreted results of experiments.

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