# Report

# The Involvement of the Left Motor Cortex in Learning of a Novel Action Word Lexicon

Gianpiero Liuzzi,[1,3] Nils Freundlieb,[1] Volker Ridder,[1]
Julia Hoppe,[1] Kirstin Heise,[1] Maximo Zimerman,[1]
Christian Dobel,[2] Stefanie Enriquez-Geppert,[2]
Christian Gerloff,[1] Pienie Zwitserlood,[3]
and Friedhelm C. Hummel[1,*]
[1]University Hospital Hamburg-Eppendorf, Department
of Neurology, 20246 Hamburg, Germany
[2]Institute for Biomagnetism and Biosignalanalysis
[3]Psychological Institute II
University of Münster, 48149 Münster, Germany

## Summary

**Current theoretical positions assume that action-related word meanings are established by functional connections between perisylvian language areas and the motor cortex (MC) [1–4] according to Hebb's associative learning principle [5]. To test this assumption, we probed the functional relevance of the left MC for learning of a novel action word vocabulary by disturbing neural plasticity in the MC with transcranial direct current stimulation (tDCS) [6–9]. In combination with tDCS, subjects learned a novel vocabulary of 76 concrete, body-related actions by means of an associative learning paradigm. Compared with a control condition with "sham" stimulation, cathodal tDCS reduced success rates in vocabulary acquisition, as shown by tests of novel action word translation into the native language. The analysis of learning behavior revealed a specific effect of cathodal tDCS on the ability to associatively couple actions with novel words. In contrast, we did not find these effects in control experiments, when tDCS was applied to the prefrontal cortex or when subjects learned object-related words. The present study lends direct evidence to the proposition that the left MC is causally involved in the acquisition of novel action-related words.**

## Results

Current neurobiological and cognitive "embodied semantics" theories postulate that semantic knowledge is distributed over widespread, functionally connected cortical regions and includes brain areas that process sensory and action-related information [1, 2, 4, 10–14]. In line with these theories, neuroscientific evidence underscores the engagement of motor cortical areas not only in action execution and perception [15] but, critically, also in action word comprehension [2, 16, 17]. Lesion and neuroimaging studies have suggested that linguistic functions such as phonetic discriminations and semantic processing are highly dependent on motor cortical activity, particularly on left primary and premotor areas [11, 18–22]. It has been frequently described that functional connections between the motor cortex (MC) and language areas might represent the final state of Hebbian learning rules [2, 3, 5]. Some previous studies have suggested that

sensorimotor experience affects the acquisition of verbal knowledge, in line with "embodied semantics" theories [23, 24]. However, to the best of our knowledge, there are no studies that have investigated the effect of noninvasive brain stimulation on associative learning of novel action-related words. We thus tested whether interference with plasticity-related motor cortical mechanisms influences the acquisition of novel action words in an associative learning paradigm.

We studied the effect of cathodal, anodal, and sham transcranial direct current stimulation (tDCS) applied to the left MC on learning of a novel action-word vocabulary in a double-blind, sham-controlled, randomized, matched-samples design in 30 young, healthy, right-handed volunteers. tDCS to the MC has proven a powerful method in modulating excitability (anodal: upregulation; cathodal: downregulation) and influencing associative learning, suggested to be related to long-term potentiation (LTP-like: anodal tDCS) and long-term depression (LTD-like: cathodal tDCS) [7, 25]. After administration of tDCS, subjects engaged in an intense language learning paradigm (Figure 1A). During training, subjects learned the action-related meaning for 76 four-letter pseudo-words, e.g., "apef," by means of associative couplings with photos of concrete, body-related actions (Figure 1B). Photos were taken from different perspectives and with different actors so that, across repetition of pictures, only the depicted action remained constant (Figures 1C and 1D). We chose only actions that yielded consistent naming agreement in a separate rating study (Table S1, available online). The primary outcome measure was the percentage of novel action words correctly translated into German at the end of the training session on day 4 (translation test; Figure 1A). The translation test was chosen to assess whether subjects had established robust semantic associations of the action concepts with the novel words independent of the action photos used during training. Note that translation itself was not trained in the acquisition phase.

MC stimulation had a significant effect on translations ($F_{2,27}$ = 3.74, p = 0.037). The number of novel action words correctly translated into German was significantly reduced after cathodal tDCS to the left MC as compared with sham stimulation (Scheffé p = 0.05; Figure 2). No such effect was observed after anodal stimulation (Scheffé p = 0.13). We then tested the topographic and semantic specificity of the effect observed after tDCS to the MC. To this end, we designed two control experiments:

1) To rule out an influence of tDCS on prefrontal regions adjacent to the MC and on right frontopolar regions beneath the reference electrode, we applied tDCS to the left dorsolateral prefrontal cortex (DLPFC), which might play a role in learning of verbal material [26, 27]. We used identical stimulation parameters and the same action-word lexicon as in the MC experiment. However, tDCS to the DLPFC did not have an effect on translations after language training ($F_{2,24}$ = 1.33, p = 0.29).

2) To test the semantic specificity of MC stimulation on action-related words, we developed a learning paradigm
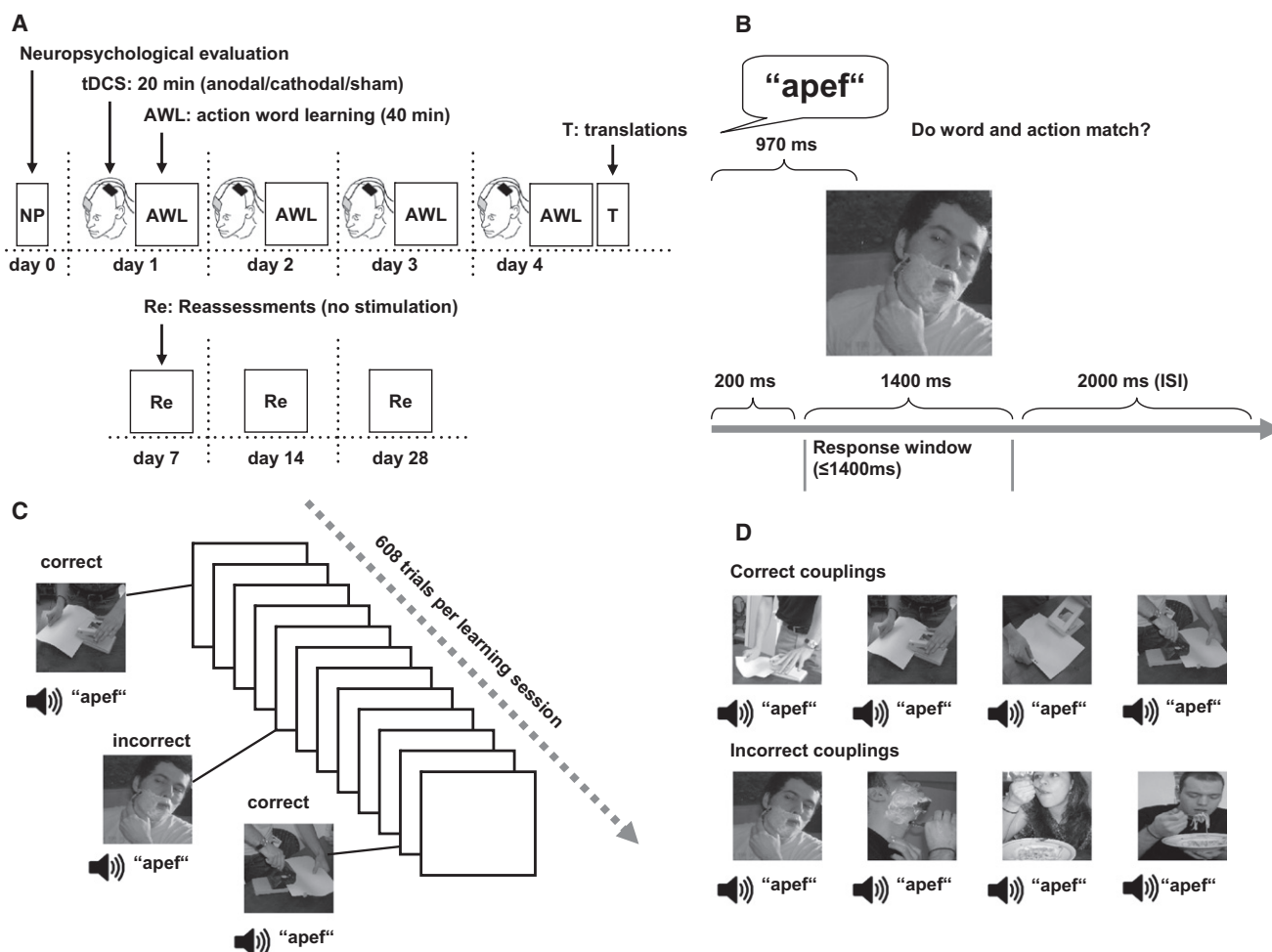
*Correspondence: f.hummel@uke.uni-hamburg.de

Figure 1. Learning Paradigm

(A) The training of novel action-word learning was spread over four single learning sessions (40 min each), separated by 24 hr (days 1–4). Prior to each learning session, subjects received tDCS. At days 7, 14, and 28, session 1 was repeated for reassessments without stimulation.

(B) The learning paradigm is based on an associative and statistical principle [28]. Correct and incorrect couplings of spoken pseudowords and photographic illustrations of concrete, body-related actions were presented. In the learning sessions, subjects were instructed to decide intuitively whether action and pseudoword matched or not. Only responses during photo presentation (1.4 s) were accepted. No feedback regarding the correctness of responses was provided. The intertrial interval was fixed at 2 s.

(C) Each learning session consisted of 608 trials and was subdivided into two blocks. Over the course of the learning session, correct couplings occurred more frequently than incorrect couplings.

(D) Each pseudoword was coupled four times with the correct action and twice with two different incorrect actions (ratio 4:2). Photos of actions were taken from different perspectives and with different actors. Each single photo was coupled once with a correct pseudoword and once with an incorrect pseudoword. The respective action, for example "to hole," remained constant across four correct couplings. Thus, to learn the correct meanings of the pseudowords, subjects had to extract the correct action-related information from four different photos. From one learning session to the next, the correct couplings were kept identical, but one incorrect coupling, for example "to eat" and "apef," was exchanged. The ratio of 4:2 between correct and incorrect couplings was preserved in each learning session. Subjects were not informed about the underlying statistical principle of the learning paradigm and did not receive any feedback regarding their performance until completion of the study protocol. At the end of day 4, subjects were required to translate the 76 novel action words into German ("translations"). Synonyms of the action words as defined by the German database "Deutscher Wortschatz – Universität Leipzig" (http://wortschatz.uni-leipzig.de) counted as correct answers.

for novel object-related words (control experiment "object word learning" [OWL]). Only photos of still, non-action related objects like "tree" or "candle" that were evaluated in a rating study (see Supplemental Experimental Procedures and Table S2) were used. In this control experiment, we did not find any effect on translating object-related words (Mann-Whitney U test: p = 0.83; Figure S2).

We then tested whether the results of the translation measure could be explained by a specific effect of MC

stimulation on associative learning behavior. In the theoretical framework of the Hebbian learning principle, it has been proposed that synchronized firing of two neuronal populations leads to synaptic strengthening between these populations [5]. Accordingly, if coactivation of motor cortical and phonological input is the basis for successful learning of novel words associated with action-related meanings [3], we would expect the correct couplings of novel words and action to be particularly inhibited by LTD-like effects in the MC. To test this assumption, responses during training were stratified into "hits" of correct couplings (correct identification of

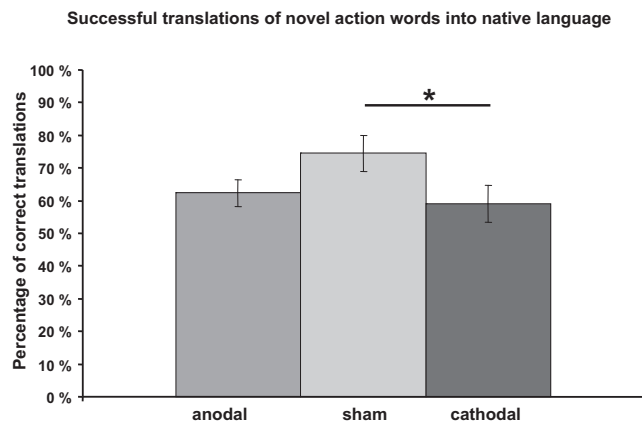**Successful translations of novel action words into native language**

Figure 2. Effect of tDCS over the Left Motor Cortex on Translations of Learned Novel Action Words into Native Language

tDCS had a significant effect on the translation test. The posthoc Scheffé test showed that the percentage of correctly translated novel action-related words into native language was significantly reduced after cathodal tDCS to the left motor cortex (star above line: p < 0.05). Data are represented as mean ± standard error.

correct couplings), "misses" of correct couplings (false rejections of correct couplings), "correct rejections" of incorrect couplings, and "false alarms" (incorrect coupling accepted as correct). The responses were then fed into a three-factorial

analysis of variance (factors: response types [hits, misses, correct rejections, false alarms], time [day 1–28], MC stimulation [anodal, cathodal, sham]; please see "Data Analysis" in Supplemental Experimental Procedures). Over the course of training, subjects learned to distinguish between correct and incorrect couplings (time × response type: $F_{18,486} = 112.22$, $\varepsilon = 0.14$, p < 0.001; Figure S1). Results involving the factor MC stimulation revealed that <u>cathodal</u> stimulation had a significant effect on identifying <u>correct</u> couplings, but not on incorrect couplings. The significant stimulation × response type interaction ($F_{6,81} = 4.45$, $\varepsilon = 0.56$, p = 0.006; Figure 3) was explained by <u>fewer</u> hits and <u>more</u> misses after cathodal stimulation (hits: $F_{2,27} = 5.07$, p = 0.014, cathodal < sham p = 0.017; misses: $F_{2,27} = 5.70$, p = 0.009, cathodal > sham p = 0.009). We found no stimulation effect on "hits" and "misses" after anodal stimulation compared with sham (both Scheffé tests p > 0.1). Responses to incorrect couplings were not affected by any type of stimulation (correct rejections: $F_{2,27} = 2.01$, p = 0.15; false alarms: $F_{2,27} = 1.0$, p = 0.38). The three-way interaction time × response type × stimulation was not significant ($F_{36, 486} = $ , $\varepsilon = 0.14$, p = 0.33), because the stimulation effect was already present from the first training session on. Moreover, the number of no responses or delayed responses decreased over time ($F_{6,162} = 27.34$, $\varepsilon = 0.27$, p < 0.001) but was not different between the stimulation groups, thus minimizing the probability of stimulation effects on attention (main effect and interactions including the factor "stimulation" not significant). The effect of tDCS on correct couplings
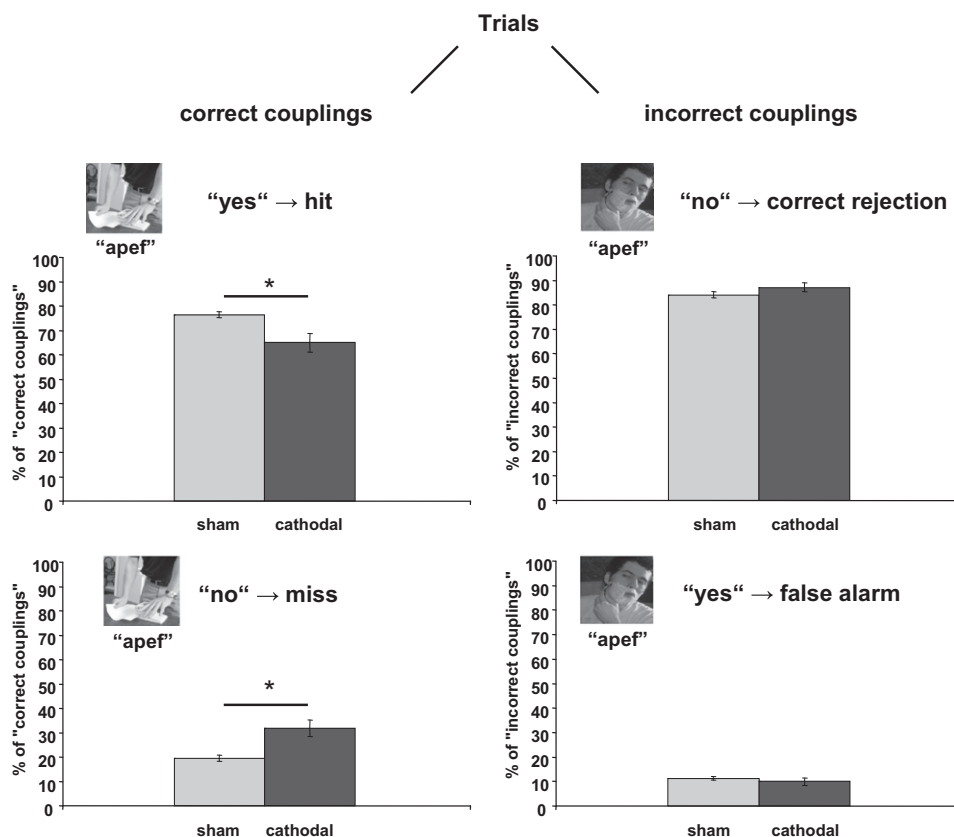
**Trials**



Figure 3. Effect of tDCS over the Left Motor Cortex on Response Types during Action Word Training

tDCS had a significant effect on associative learning behavior. Responses to correct couplings were different between cathodal and sham tDCS. No such difference was found for incorrect couplings. Stars above lines indicate significant differences (p < 0.05). Data are represented as mean ± standard error.
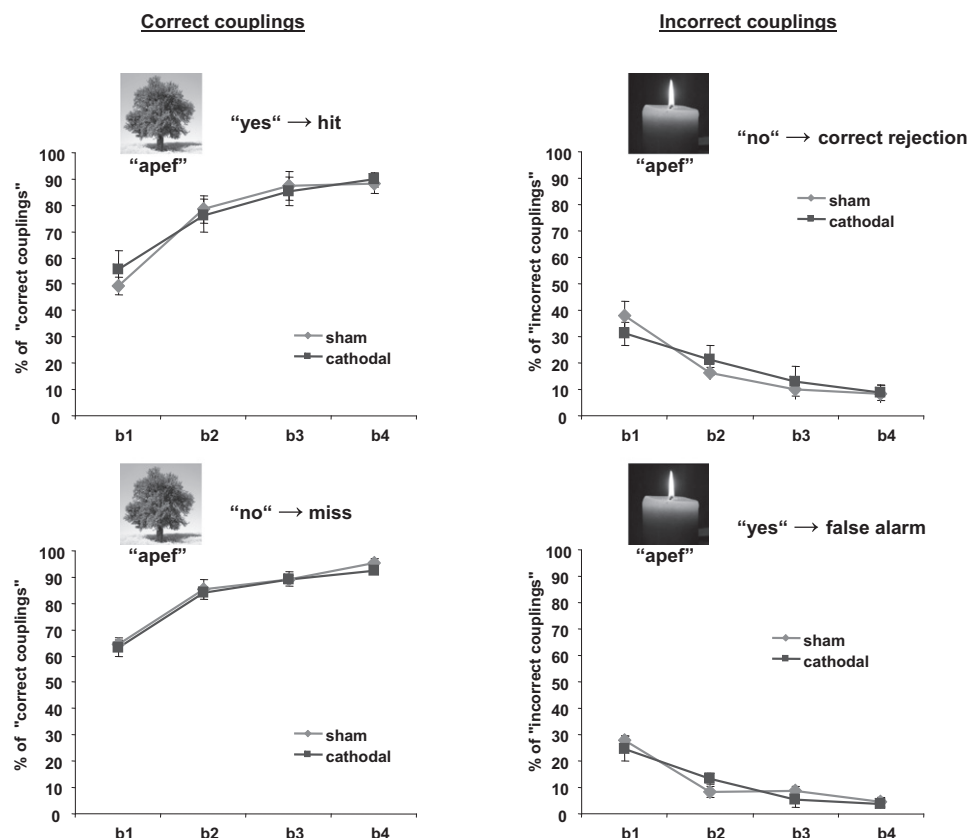
**Figure 4. Effect of tDCS over the Left Motor Cortex on Response Types during Object-Word Training**

Learning curves during acquisition of novel object words were not affected by cathodal tDCS as compared with sham tDCS (all Mann-Whitney U tests p > 0.1). b1–b4: block 1–block 4.

was not observed after stimulation to DLPFC (response type × stimulation: $F_{6,72} = 0.75$, $\varepsilon = 0.55$, p = 0.54) or during OWL (all Mann-Whitney U tests p > 0.1), but learning behavior independent of stimulation was comparable to the MC experiment (*DLPFC experiment:* time × response type: $F_{18,432} = 58.62$, $\varepsilon = 0.13$, p < 0.001; Figure S1, learning curves for OWL in Figure 4).

Although a general influence of tDCS on behavior and cognition cannot be excluded with certainty, we would like to argue that some obvious confounds can be ruled out by the present pattern of results. Discomfort, mood ratings, and reaction times failed to indicate differences between stimulation conditions (Supplemental Results). Furthermore, inadvertent remote stimulation (such as prefrontal cortex, ventral premotor cortex, or Broca's area) would predict effects related to DLPFC stimulation or to MC stimulation during OWL (control experiment). Moreover, matched subject samples in the MC and DLPFC experiments showed no differences in the number of fluently spoken foreign languages and cognitive abilities including verbal learning and memory [28], as the results of an extensive neuropsychological evaluation demonstrated (Supplemental Results).

## Discussion

### Motor Cortex and Language

Recent theories about "embodied" brain representations of semantic concepts put forward that semantic memory draws upon sensorimotor circuits that are also involved in perception and action [1, 14]. However, these theories leave open how such a system of embodied action semantics is acquired when novel action words are learned. One proposition is that repeated co-occurrence of motor information, for example observation of an action, together with phonological information generates coactivation of perisylvian language areas and the MC [2, 3]. By virtue of the Hebbian learning [5], connections between neurons processing the sensorimotor properties of an action and neurons coding the word form are reenforced. After learning, transmodal connections establish functional cell assemblies and provide convergent information on the meaning of an action-related word [2, 3]. In a laboratory setting, the language paradigm employed in the present study mimics Hebbian assumptions of associative learning. Subjects that received cathodal tDCS to the left MC showed less robust associations of novel words with action meaning. Cathodal tDCS to the left MC particularly reduced the number of correctly identified couplings of novel words with the appropriate action-related information. It is conceivable that synaptic strengthening between motor and language areas operates during the presentation of correct couplings. Hence, correct couplings may be particularly susceptible to downregulation of excitability and especially of cortical N-methyl-D-aspartate (NMDA)-receptor-dependent activity, which is regarded as an important prerequisite for synaptic strengthening and learning [29]. tDCS effects <u>after</u> stimulation are especially NMDA-receptor dependent [7, 29] and share similarities with plastic processes such as long-term potentiation and long-term depression [25]. Hence, it can be

speculated that depression of NMDA-receptor-dependent synaptic strengthening might have weakened the re-enforcement of functional cell assemblies after cathodal tDCS to the MC. In contrast, anodal stimulation is interpretable in the sense of upregulation of the left MC similar to long-term potentiation [6, 7]. Anodal tDCS did not have the opposite effect of increasing learning success. In healthy subjects, paradoxical effects of anodal tDCS, especially with 10 to 15 min latency after stimulation, have been reported [30]. One alternative explanation could be that tDCS prior to learning slightly influences homeostatic mechanisms involved in neuroplasticity [31]. It has been put forward that homeostatic rules might apply differently to anodal and to cathodal tDCS with regard to learning [32].

The finding that the left MC is specifically involved in specific aspects of language learning may open new perspectives to the rehabilitation of aphasia and other linguistic deficits. Pharmacological NMDA-receptor antagonism has proven enhanced training effects of action-based language therapy in poststroke aphasia [33]. Hence, it could well be that cathodal tDCS may have a positive effect on language learning in poststroke aphasia by regulating glutamatergic overactivation.

## Local Specificity of Motor Cortical Involvement during Language Learning

As with every stimulation technique, inadvertent effects may occur in remote cortical or less likely subcortical areas [34]. However, considering the pattern of the present results, it is very unlikely that the effects observed in the MC experiments were influenced by inadvertent remote stimulation. If this were the case, tDCS to the left DLPFC or to the left MC during OWL should also have an effect on language learning. It has to be pointed out that the present study did not have the scope to specifically probe the involvement of DLPFC in specific aspects of learning. The stimulation protocol differs in important methodological aspects, e.g., stimulation time, duration, intensity, and position of the reference electrode, from previous studies that applied tDCS to the left DLPFC in combination with linguistic tasks [27]. Hence, we cannot draw conclusions regarding the involvement of the left DLPFC in associative language learning. Neither do we attempt to reject any related hypothesis, given that modulating activity in this region led to a null result in the present research.

The present study does not allow firm conclusions about which exact subregion of the left MC contributed to the observed effect on action-related words. However, it can be assumed that the interference was highest in primary motor and adjacent premotor areas, but less so in the mirror neuron region of the inferior frontal gyrus [34]. Moreover, our results do not exclude the possibility that other brain areas will also contribute generally to learning of word meanings and semantic processing. Previous studies have demonstrated that processing of action words engages several additional brain regions, for example the temporal, inferior frontal, and parietal cortex [4, 16, 17, 35]. Moreover, it has been demonstrated that associative learning of word meanings engages limbic structures, in particular the hippocampus [36]. The language-learning paradigm employed in the present study entails not only associative coupling of word form with an action concept, but also phonological processing and encoding to establish a phonological input lexicon for novel words involving classical language areas in the perisylvian regions [37, 38]. We cannot rule out with certainty that the electric current might have reached classical language areas,

especially the inferior frontal regions. However, if one of the processes beyond association of word form with action concepts were sufficiently affected by tDCS, we would expect this to happen for both action- and object-word learning. We would also expect correct and incorrect couplings to be similarly influenced by tDCS.

Taken together, the results here demonstrate that the MC plays a specific role in associative language learning. To the best of our knowledge, this finding is the first experimental evidence that supports the longstanding hypothesis about the left MC causally participating in the process of associatively learning words for actions. Apart from addressing a critical issue at the forefront of cognitive neuroscience research, this result may have important neurobiological implications for the relearning of language after language impairments due to diseases of the brain, such as poststroke aphasia.

### Experimental Procedures

#### Subjects

A total of 63 young, healthy subjects completed the study protocol (*MC experiment*: n = 30 [cathodal n = 10, anodal n = 10, sham n = 10], 18 female, mean age: 24.97 ± 0.56 yrs, age range 21–34; *DLPFC experiment*: n = 27 [cathodal n = 9, anodal n = 9, sham n = 9], 15 female, mean age: 24.96 ± 0.43 yrs, age range 22–31; *control experiment OWL*: n = 6 [cathodal n = 6, sham n = 6; crossover design], 3 female, mean age: 24.50 ± 0.50 yrs, age range 23–26). According to the Edinburgh inventory of handedness [39], all subjects were right-handed (*MC*: mean score 94 ± 2, range 63–100; *DLPFC*: mean score 88 ± 3, range 60–100; *OWL*: mean score 86 ± 5). They were native German speakers and spoke 1–4 foreign languages (*MC*: mean 2.4 ± 0.17; *DLPFC*: 2.26 ± 0.21; *OWL*: 2.0 ± 0.26); had received a diploma from a German secondary school, qualifying for university admission; and were currently registered at the University of Hamburg, Germany (*MC*: n = 27 at medical school, n = 3 at business school; *DLPFC*: n = 26 at medical school, n = 1 at law school; *OWL*: n = 5 at medical school, n = 1 in health studies). Exclusion criteria encompassed bilingualism; a history of serious medical, neurological, or psychiatric illnesses, especially severe head traumas, seizures, metal implants in the head/neck region, or pacemaker implantation; pregnancy; and the use of illegal, neuroactive (e.g., antidepressants, anticonvulsants, etc.), or recreational drugs (> 15 cigarettes/day, > 6 cups of coffee/day, > 50 g of alcohol/day), as probed by a standardized questionnaire. Subjects in the MC and DLPFC experiments, respectively, were subdivided into triplet groups matched according to gender, age, formal years and type of education, as well as proficiency in previously learned foreign languages. After assignment to triplets, subjects were randomized into three different stimulation groups: anodal verum stimulation, cathodal verum stimulation, and sham stimulation. For the control experiment, we designed a crossover study. Subjects learned two separate object word lexicons in two sessions separated by 5–7 days. In one of the two sessions, subjects received cathodal tDCS, and in the other session, they received sham tDCS. The type of stimulation was counterbalanced across sessions. All subjects gave written informed consent to participate in the study protocol. The study protocol was approved by the local ethics committee and was in accord with The Code of Ethics of the World Medical Association (Declaration of Helsinki; http://www.wma.net/e/policy/b3.htm). All subjects were naive to the experimental purpose of the study.

#### Action Word Learning Paradigm
For details of the action-word learning paradigm, please see Figure 1 and Supplemental Experimental Procedures.

#### Object Word Learning Paradigm
For details of the object-word learning paradigm, please see Supplemental Experimental Procedures.

#### Transcranial Direct Current Stimulation
##### MC Experiment
Prior to tDCS application, the "hot spot" of each participant's cortical hand motor area was determined with transcranial magnetic stimulation (TMS). TMS was delivered by a Magstim 200 stimulator connected to a figure-8-shaped coil (7 cm in diameter). tDCS was delivered through two sponge

electrodes (Eldith; surface area 25 cm$^2$) embedded in a saline-soaked solution. The stimulating electrode (anode or cathode) was then positioned over the left-hemispheric hotspot of the primary hand MC, and the reference electrode was placed on the skin overlying the right supraorbital region.

*DLPFC Experiment*
The stimulating electrode (anode or cathode) was fixed over F3 according to the international 10–20 system of electrode placement, and the reference electrode was placed contralaterally above the right orbit, the same location that was used for placement of the reference electrode in the MC experiment.

*Control Experiment OWL*
Size and position of electrodes were identical to the MC experiment.

*All Experiments*
In all experiments (MC, DLPFC, OWL), tDCS was applied at 1 mA for 20 min in the anodal and cathodal group and for 30 s in the sham condition with the use of a DC-Stimulator (Eldith; serial no. 0006). At the onset of the stimulation (anodal, cathodal, and sham), the current was increased in a ramp-like fashion over 8 s, eliciting a transient tingling sensation on the scalp that faded over seconds [6, 8]. The current (1 mA) remained on for 20 min in the anodal and cathodal group, whereas in the sham group the current was turned off after 30 s. At the end of all interventions, the current was turned off slowly over 8 s, a procedure that does not elicit perceptions and was preprogrammed in the stimulator software. This is an established and validated method of stimulating the hand MC with tDCS and reliably blinding the subjects toward verum and sham stimulation [40]. Besides the subjects, the investigator testing and analyzing the language learning was blind to the intervention (verum or sham), which was administered by a separate investigator who did not participate in language testing or data analysis. Moreover, subjects were not informed about different groups or stimulation types of the study protocol.

**Data Analysis**
Please see Supplemental Experimental Procedures.

**Supplemental Information**

Supplemental Information includes Supplemental Experimental Procedures, Supplemental Results, three figures, and two tables and can be found with this article online at doi:10.1016/j.cub.2010.08.034.

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