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TRAINING-INDUCED CORTICAL PLASTICITY COMPARED BETWEEN THREE TONGUE-TRAINING PARADIGMS

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Abstract—The primary aim of this study was to investigate the effect of different training types and secondary to test gender differences on the training-related cortical plasticity induced by three different tongue-training paradigms: (1) therapeutic tongue exercises (TTE), (2) playing computer games with the tongue using the Tongue Drive System (TDS) and (3) tongue-protrusion task (TPT). Forty-eight participants were randomized into three groups with 1 h of TTE, TDS, or TPT. Stimulus–response curves of motor evoked potentials (MEPs) and motor cortex mapping for tongue muscles and first dorsal interosseous (FDI) (control) were established using transcranial magnetic stimulation at three time-points: (1) before tongue-training, (2) immediately after training, (3) 1 h after training. Subject-based reports of motivation, fun, pain and fatigue were evaluated on 0–10 numerical rating scales after training. The resting motor thresholds of tongue MEPs were lowered by training with TDS and TPT ($P < 0.011$) but not by TTE ($P = 0.167$). Tongue MEP amplitudes increased after training with TDS and TPT ($P < 0.030$) but not with TTE ($P = 0.302$). Men had higher MEPs than women in the TDS group ($P < 0.045$) at all time-points. No significant effect of tongue-training on FDI MEPs was observed ($P > 0.335$). The tongue cortical motor map areas were not significantly increased by training ($P > 0.142$). Training with TDS was most motivating and fun ($P < 0.001$) and TTE was rated the most painful ($P < 0.001$). Fatigue level was not different between groups ($P > 0.071$). These findings suggest a differential effect of tongue-training paradigms on training-induced cortical plasticity and subject-based scores of fun, motivation and pain in healthy participants.

Key words: transcranial magnetic stimulation (TMS), tongue-training, motor learning, cortical plasticity, Tongue Drive System (TDS).

INTRODUCTION

The course of swallowing entails a complex and semi-automatic sequence of events involving extrinsic and intrinsic tongue muscles, leading to protection of the airways during food ingestion (Martin et al., 2004; Sessle et al., 2005). Dysphagia, dysarthria and cognitive-associated deficits are common tongue dysfunctions with acquired brain injury such as stroke, traumatic brain injury as well as congenital or neurological diseases and may have a serious negative impact on health and quality of life (Hori et al., 2005, 2006; Khedr et al., 2005; Anderson et al., 2011). Infantile swallowing and cerebral palsy are other types of tongue dysfunction with implications for dental occlusion and jaw growth pattern (Melsen et al., 1987; Rogers, 2004).

Transcranial magnetic stimulation (TMS) is a non-invasive, widely used and pain-free technique to measure the functional integrity of descending corticospinal and corticoneural pathways in the human motor cortex through the intact scalp (Rothwell, 1997; Muellbacher et al., 2001; Abbruzzese and Trompetto, 2002; Curra et al., 2002; Tyc and Boyadjian, 2006; Baad-Hansen et al., 2009; Rogasch and Fitzgerald, 2012). Numerous studies on corticomotor control with TMS have shown changes in motor evoked potentials (MEPs) in human limb muscles following the modulation of, for example, sensory afferent inputs (Ridding et al., 1995; Ziemann et al., 1996; Rothwell, 1997; Lotze et al., 2003; Perez et al., 2004; Blicher et al., 2009) but comparatively little is known about the regulation of the cranial nerve-innervated human tongue muscles (Muellbacher et al., 2001; Svensson et al., 2003, 2006; Halkjaer et al., 2006; Baad-Hansen et al., 2009).

A number of tongue-training studies have shown training-induced neuroplasticity in human corticomotor control of the tongue by demonstrating an increase in MEPs as well as an increase in the motor cortex tongue representation produced by TMS (Pascual-Leone et al., 1994; Svensson et al., 2003, 2006; Baad-Hansen et al.,

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Abbreviations: ANOVA, analysis of variance; COG, center of gravity; EMG, electromyographic; FDI, first dorsal interosseous; F.O.T.T., facio-oral tract therapy; MEPs, motor evoked potentials; NRS, numerical rating scales; RM, repeated measurement; rMT, resting motor threshold; *S–R*, stimulus–response; TDS, Tongue Drive System; TMS, transcranial magnetic stimulation; TPT, tongue-protrusion task; TTE, therapeutic tongue exercises.

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2009). These studies have all used a highly standardized tongue-protrusion task (TPT) with a constant target force and timing of the task (Svensson et al., 2003, 2006; Boudreau et al., 2007; Baad-Hansen et al., 2009; Ernberg et al., 2009). The TPT can be considered a quite simple one-dimensional type of tongue training. There is a need to study the effects of different training paradigms for patients with compromised tongue function. For example, the TPT could be speculated to prove less beneficial for patients with compromised tongue function because of its lack of variation during training.

The empirically based multidisciplinary approaches to clinical oral rehabilitation techniques, such as facio-oral tract therapy (F.O.T.T.), involve a combination of diet modification, position adjustment and effortful swallowing that enhances airway protection during swallowing (Hansen and Jakobsen, 2010). In the present study in healthy participants, we used a range of therapeutic tongue exercise (TTE) which was derived by F.O.T.T. therapists acknowledging that the entire concept of F.O.T.T. can only be studied in patients with, for example, dysphagia.

Another approach to tongue motor rehabilitation could be playing computer games with the tongue using the newly introduced Tongue Drive System (TDS) (Kothari et al., 2012). This approach has more emphasis on skill training than the simple TPT (Kothari et al., 2012). So far we have shown that force level, task complexity and different motivational factors influence behavioral aspect of tongue motor learning in healthy participants (Kothari et al., 2012). TDS is an unobtrusive, non-invasive and accurate tongue–computer interface. The TDS can wirelessly detect the tongue position inside the oral cavity and translate its motion into a set of specific user-defined computer commands (Ghovanloo, 2007; Huo et al., 2007). The tongue thereby can act as a computer mouse and tongue training can thereby consist of playing tongue-controlled computer games (Huo et al., 2007, 2008a,b). Playing a computer game may increase the subjects' level of motivation during training in comparison with simple repeated tasks. Computer and video games have become among the most popular leisure time activity. However, a substantial gender difference in computer game involvement has been observed. Many studies reported that women display less interest in digital games and have less game-related knowledge than men (Hartmann and Klimmt, 2006; Hartman, 2007). This may influence the baseline TDS performance level and the level of motor behavioral learning.

In order to prioritize the use of available resources for neurorehabilitation, more knowledge is required on examination and training methods in patients with compromised tongue function. A main objective of many motor rehabilitation regimes is to encourage neuroplasticity at the subcortical and cortical levels, such that long lasting and beneficial alteration in motor control strategies can be achieved (Gabriel et al., 2006).

We hypothesized that the magnitude and time course of changes in cortical excitability as measured by TMS is different between the three tongue-training paradigms TPT, TDS and TTE and between genders. The primary aim of this study was to investigate the effect of different training types and secondary to test gender differences on the training-related cortical plasticity induced by three different tongue-training paradigms: (TTE, playing computer games with the tongue using TDS and TPT).

EXPERIMENTAL PROCEDURES

Participants

Sixty-two healthy participants (32 men and 30 women) aged 23.6 ± 0.7 years (19–52 years) were recruited for the study at Section of Clinical Oral Physiology, Department of Dentistry, Aarhus University after approval from the Central Denmark Region, ethics committee. Exclusion criteria were: medical or psychological problems, metal implants in the head, epilepsy, pregnancy, prior experience with any of the tongue-training paradigms used in the present study, inability to finish 1 h of tongue-training, gag reflex caused by tongue electrodes. Also, the participant was excluded if they were feeling too uncomfortable with the TMS stimulation or if the examiner was not able to locate the tongue "hot-spot" within 30 min. Informed consent was obtained in accordance with the guidelines of the Helsinki declaration II. Four participants were excluded due to discomfort with TMS stimulation, one was excluded due to gag reflex caused by tongue electrodes, and nine were excluded due to difficulties in locating tongue hot-spot. Finally 48 participants completed the study with mean age 23.7 ± 0.7 of (24 men and 24 women). The 48 participants were equally and randomly divided between three groups, i.e. each group consisted of 16 healthy participants (eight men, eight women). All participants received financial compensation for their time.

Study design

The 48 healthy participants were randomly assigned to three groups with different 1 h tongue-training paradigms: (1) TTE, (2) playing computer games with the tongue using TDS, and (3) TPT. Corticomotor excitability was assessed as MEPs evoked by TMS before, immediately after and 1 h after of tongue-training in tongue muscles and first dorsal interosseous (FDI) muscle (control). The corticomotor representations of the tongue muscles were mapped on a 1×1 cm^2 scalp grid. In addition, subject based report of motivation, fun, pain and fatigue were collected after training from all participants. The complete study lasted approximately 4.5–5 h.

Recording of MEPs

The participants were placed on a patient examination table in supine position with the head tilted toward the right side and supported by a headrest. A swimming cap was placed over the head and anatomical features were marked with a pen to secure a stable position of the cap. Electromyographic (EMG) activity was recorded from the right side of the tongue dorsum and FDI muscle. Disposable self-adhesive silver chloride electrodes (Alpine Biomed, Type 9013S0225, Skovelunde, Denmark) were placed on the right dorsal surface of the tongue (2–3 mm from midline, 10 mm from tongue tip) with an inter-electrode distance of 20 mm. Disposable surface electrodes (Ambu, Neuroline 720, Type 72001-k/12, Ballerup, Denmark) were placed over the FDI (muscle belly caput metatarsale I). The electrodes were connected to the amplifier to allow bipolar registration of contralateral MEPs. The EMG signals were amplified, filtered (20 Hz–1 kHz), and stored on Viking Select (Nicolet, CA, USA).

TMS (Magstim 200, The Magstim Co. Ltd., Whitland UK, peak magnetic field = 2 T) were delivered with a 5-cm diameter figure-of-eight coil to the left side of the scalp (Svensson et al., 2003, 2006; Halkjaer et al., 2006). The coil of the stimulator was oriented 45° obliquely to the sagittal midline so that the induced current flowed in a plane perpendicular to the estimated alignment of the central sulcus (Svensson et al., 2003, 2006; Halkjaer et al., 2006; Baad-Hansen et al., 2009). With constant stimulus intensity, the stimulator coil was moved over the left hemisphere to determine the optimal position to elicit maximal MEP peak-to-peak amplitudes in the tongue muscle. Three markings on the coil helped to identify the position in relation to the scalp sites. The scalp site at which EMG responses were evoked in the tongue at lowest stimuli strength (“hot-spot”) was determined and marked with a pen on the cap. In accordance with previous studies, MEPs in the right tongue musculature could be evoked by stimulation of discrete areas of the left scalp, approximately 2–3 cm anterior to the Cz and 7–8 cm lateral to the midsagittal plane (Svensson et al., 2003, 2006). The MEPs from the FDI (control) were evoked by stimulation of the scalp about 1 cm anterior to the Cz line and about 6 cm lateral to the midsagittal plane. The resting motor threshold (rMT) contralateral to stimulation was measured at all time-points in the relaxed muscles with the use of descending and ascending method of limits and was defined as the minimum stimulus intensity that produced five out of ten discrete MEPs clearly discernible on the monitor from background EMG activity (tongue MEP $\geqslant 5\ \mu v$ and FDI MEP $\geqslant 50\ \mu v$) (Svensson et al., 2003; Halkjaer et al., 2006; Baad-Hansen et al., 2009).

The peak-to-peak amplitudes of the MEPs were used to assess corticomotor stimulus–response (S–R) curves and to map the motor cortex for sites from which the MEPs could be evoked. S–R curves were constructed in steps of 10% of rMT, from $T - 20\%$ to $T + 60\%$ in a randomized order, where T was the rMT measured at the specific time of creating the S–R curve. Hence, if the rMT had changed after training, the post-training rMT was used as a reference for creation of the post-training S–R curve. Eight stimuli were given at each stimulus level.

For motor cortex mapping, magnetic stimuli were delivered at the sites over the scalp identified by the swimming cap marked with $1 \times 1\ cm^2$ grids in an anterior–posterior and lateral–medial coordinate system (Wilson et al., 1993). The anterior–posterior grid lines were related to the vertex (Cz) in accordance with the 10–20 electroencephalographic electrode placement system. The stimulator output was set at 20% above the rMT (T + 20%) and eight stimuli were delivered to each site (Svensson et al., 2003, 2006). The grid was stimulated in a regular pattern, beginning at the center of the motor representation, and then moving anterior then posterior at increasing and decreasing latitudes (sites typically covered 4–11 cm from the vertex and 4 cm anterior and posterior to the inter-aural line corresponding to at least 25 grids). The areas (cm^2) of the tongue with MEP amplitudes greater than 5 μV were determined on the $1 \times 1\ cm^2$ grid. Furthermore, the center of gravity (COG) was determined according to the description of Ridding et al. (2000): $X = \sum a_i X_i / \sum a_i$ where a_i is the amplitude at the scalp site with the coordinate X_i. In a similar way the Y-coordinate was determined (Svensson et al., 2003, 2006).

TTE

The examiner in the present study was a dentist, who had been carefully trained by two certified occupational therapists to use TTE in healthy participants. The following TTE elements were applied for 1 h with a main focus on sensory stimulation and tongue mobilization.

Preparation phase. The participants were seated upright and in a relaxed position on a chair with back support and bilateral equal hand support. The upright position secured a straight pelvis and 90° to the base of chair, which in turn helped the tongue to remain visible to the examiner. The examiner was seated in front of the participant as close as possible to a vertical level such that the examiner’s eyes were below the participant’s chin. This helped the examiner to visualize all the oral movements. Once the sitting position was secured, the examiner made the participants’ hands touch their own faces, as their own hands are likely to be tolerated best. The contact throughout performance of TTE was calm and firm (Seidl et al., 2007; Hansen and Jakobsen, 2010).

The oral cavity was divided into four quadrants [1 (right), 2 (left) for maxillary gingival sulcus area and 3 (right), 4 (left) mandibular gingival sulcus area]. The preparation phase was initiated by stabilizing the participant’s head and jaw using head and jaw control grip; during jaw support control the examiner’s middle finger was beneath the participant’s chin (to support the jaw during tongue and swallowing movement) and the thumb underneath their lower lip. The examiner’s left arm was placed around and behind the subject’s head. The back of the examiner’s hand was used to touch first one cheek and then the other cheek followed by above the upper lip and below the lower lip as a preparation phase (Fig. 1A). This pre-oral contact was a firm rather than stroking touch and can be considered as a preparation for entering the oral cavity.

Fig. 1. Tongue-training paradigms: therapeutic tongue exercises (TTE) – (A) preparation phase. (B) Gingival-sulcus massage. (C) Straw tongue movement. (D) Tongue-strengthening exercise.

Gingival sulcus and palate stimulation. Before entering into the oral cavity, the area around the outside of the oral cavity was relaxed (for example, the cheeks were brought forward and the nasio-labial lines were felt with the examiner's finger and thumb as necessary if the lips have been drawn upward or tense). The examiner wore latex gloves and used his index or little finger (depending on the size of finger, making sure that the participant felt comfortable) to slide it on the gum underneath the lip slightly to one side of the central incisor till the last molar of each quadrant (Fig. 1B). The finger was always moistened by water before entering into the oral cavity. The movement was firm and slow along the gum. All movements were repeated three times, starting from the central incisor toward the last molar of quadrant 1 and then the examiner's finger was taken out of the oral cavity by pushing out the cheek (Buccal-pad area) a little. After the finger was taken out, the mouth was kept as calm as possible allowing a short pause giving the participant an opportunity to swallow and relax. The rest time was of 10 s. The same movement was then performed in quadrant 3 (same side but opposite jaw), quadrant 2 and quadrant 4, respectively followed by a rest of 10 s between every quadrant movement. After finishing, control of the head and jaw was maintained by jaw control support and after a rest of 10 s, the examiner moved his wet gloved finger along the tongue, touching first the front of the tongue and then a little further back, until the third step when the center of the tongue was touched. The finger was removed to allow the participant to relax and swallow for 10 s. Next, the examiner's wet finger touched the palatal rugae (anterior palate) and pressed firmly on the ridge behind the two central incisors. The goal was to produce a clear, firm contact on this part where the tongue would normally make contact to make an '*N*' sound. The finger was removed and allowed the participant to relax and swallow for 10 s. Stages (a) and (b) were only performed once.

Straw–tongue movement. The end of a drinking straw was brought close to the center of the mouth and the participant was instructed to touch the straw with the tongue and then relax for 10 s. The straw was again placed near to the center of mouth and this time the participant was instructed to push the straw as far as possible outside by the tongue (Fig. 1C). This was performed three times continuously followed by a 10-s rest. Next, the straw was placed on the center of the philtrum (upper lip), chin, and corners of the lip (right and left), respectively. The participant was instructed to touch the straw with the tongue in all these positions. The straw placement was performed three times for every position followed by a 10-s rest. Before the start of any tongue movement, the end of the straw was brought close to the participant's center of mouth to feel the straw with the tongue and the participant was instructed to push the straw with the tongue as far as possible outside the mouth followed by 10-s relaxation.

Tongue stretching exercise/passive tongue movement. After maintaining control of the head and jaw by jaw control grip, the examiner's wet gloved finger was brought along the tongue, touched first at the front of the tongue and then a little further back, until the third step when the center of the tongue was touched. Then the finger was removed and the participant was allowed to relax and swallow for 10 s. The examiner instructed the participants to protrude the tongue and then the tongue was placed between thumb and index finger of the examiner using a piece of gauze (Fig. 1D). The examiner pulled the tongue very gently out until he felt a clear resistance to the movement from the participant. Then the tongue was released back into normal position followed by 10 s of rest and swallowing. The tongue stretching was followed by examiner-controlled (passive) movement of the tongue as low as possible to the chin area, as far as possible toward the corners of the lips (right and left), as close as possible to the tip of the nose, respectively. Tongue stretching was repeated three times continuously for every position followed by a pause of 10 s to swallow and rest.

Tongue sensory stimulation. After maintaining control of the head and jaw by jaw control support, the examiner used a tongue depressor for sensory stimulation of the tongue. The tongue depressor was used for the application of pressure to the dorsum of the tongue. The participant was instructed to protrude the tongue out of the mouth and then the tongue was placed between the examiner's thumb and index finger using a gauze piece without causing any discomfort to participants. Then the tongue depressor was placed on the dorsum of the tongue with light pressure. This was repeated thrice. Then the tongue was released back into normal position followed by 10 s of rest and swallowing. Tongue sensory stimulation was performed three times with 10-s pauses to relax and swallow in between.

Active tongue movement. The examiner demonstrated the next TTE element on a jaw model cast, where the examiner moved his finger from the last molar on the right side along the dental arch toward the last molar on the left side. The participant was instructed to similarly move the tongue from the last molar on the right side to the last molar on the left side, touching all the other teeth on the way. This tongue exercise was performed in both jaws buccally and lingually three times. This element was done first on the upper and then on the lower jaw. The mouth was secured as relaxed as possible by allowing a 10-s pause after every procedure, which gave the participant an opportunity to swallow and relax.

Tongue strength training. After maintaining control of the head and jaw by jaw control grip, the examiner put his index finger on one side of the participant's cheek and the participant was instructed to find the finger with his tongue through the cheek from inside the mouth. Once the finger was located by the participant's tongue, he was instructed to apply pressure as hard as possible to the examiner's finger. Meanwhile the examiner also applied pressure by his finger inward to the participant's cheek. This was done three times separately for both the cheeks. Later the finger was removed allowing a 10-s pause after every procedure, which gave the participant an opportunity to swallow and relax.

The performance of TTE training (stages straw–tongue movement, tongue-stretching exercise/passive tongue movement, tongue sensory stimulation, active tongue movement, and tongue strength training) was repeated until 1 h had been spent.

TDS

In this study, playing computer games with the tongue using TDS was used as three-dimensional tongue training (Kothari et al., 2012, 2013). To perform with TDS, a small disc-shaped rare earth permanent magnet with the size of 5 mm × 1.3 mm (10800 Gauss strength) attached to interdental floss (Colgate Total, Colgate-Palmolive, Ireland) and embedded inside putty soft impression material (Coltene, President, Switzerland), was secured on the tongue as a magnetic tracer by using a tissue adhesive (Periacryl Purified Cyanoacrylate Dental Adhesive, GluStitch, Inc. Delta, Canada). A magnetic field was generated inside and around the mouth by this magnet. Changes in the magnetic field around the mouth were measured by an array of magnetic sensors mounted on a headgear, which was worn by the subject on the head while performing the task (Huo et al., 2008a; Huo and Ghovanloo, 2010; Kothari et al., 2012). The sensor outputs were transmitted wirelessly to a computer, and received by the help of a wireless USB receiver affixed on the computer. The USB receiver and headgear had a built-in wireless connection (2.4 MHz), which allowed the tongue to act as a computer mouse. A digital sensor signal processing (SSP) algorithm running on the computer classified the sensor signals and converted the tongue gestures into user control commands, which were then executed by the computer.

There was the first 20 min of preparation time, which included placement of the TDS headgear, calibration, and attachment of magnetic tracer to the tongue and setup procedure session (Kothari et al., 2012, 2013). To setup the TDS, subjects were required to define specific positions in their mouth where they could easily reach with the magnet attached to the tip of their tongues, and associate them to each "tongue command", i.e. the subjects were instructed to consistently place their tongues at three recommended positions (tooth 14 for "up" command, tooth 24 for "down" command and tongue resting position) ten times in a row, such that TDS could collect enough data to be able to recognize those specific commands based on the recorded data (Kothari et al., 2012, 2013). Later on, when subjects placed their tongue at those specific positions, the TDS could correctly associate the positions to the commands practiced during the setup session (Huo et al., 2007, 2008c; Kothari et al., 2012). This setup procedure was then followed by 40 min of continuous training, in which the participants were instructed to play a tongue-controlled computer game called "Scuba Diver" (http://www.icq.com/greetings/cards/142/). In the Scuba Diver game, the participants were given three lives and were instructed to collect as many coins and wealth (number of game points achieved) as possible while swimming. In addition, they had to escape from obstacles like fish, bottles, and rocks coming their way. The performance (number of game points) was noted manually every time they lost their three lives. They were instructed to play the game several times, until the total Scuba Diver game time reached 1 h (Kothari et al., 2012). The performance was averaged in blocks of 5 min.

TPT

The participants performed a 1 h TPT in accordance with our previous description (Murray et al., 1991; Svensson et al., 2003, 2006; Baad-Hansen et al., 2009; Ernberg et al., 2009). In brief, the participants were asked to protrude the tongue with a force of 1 N onto a force transducer that was affixed rigidly to a beam on the chair in front of the participants; the force plate was located in the midline, 2 cm anterior to the most anterior portion of the upper lip. A horizontal beam to secure a constant distance to the force transducer supported the forehead. The transducer output controlled the vertical position of a cursor on a computer monitor located in front of the subject. During each tongue-protrusion trial, a computer-controlled baseline window appeared initially at the bottom of the computer screen and, after a pretrial period, it was displaced to a preset target-window level (equivalent to a force of 1.0 N) on the computer screen. The subjects were asked to keep the curser in the moving target window (1 ± 0.15 N) at all times. The following periods were defined for the TPT: a 10-s pretrial resting period during which the baseline window remained at the bottom of the screen and the subject sat relaxed in the chair; a dynamic phase (ramp up), which was the period from the onset of the rise of the target window from the bottom of the screen to the moment that the target window reached the 1 N level (0.5 s); a holding phase of 1.5 s, in which the target window stayed at the 1 N level, and finally a ramp down phase (0.5 s) (Murray et al., 1991). A total of 288 trials were performed during the 1 h trial. The performance success rate was determined for each individual tongue protrusion trial as the proportion of time (%), in which the cursor was placed inside the target window (Murray et al., 1991; Pascual-Leone et al., 1994; Svensson et al., 2006; Baad-Hansen et al., 2009; Ernberg et al., 2009; Kothari et al., 2011). The TPT success rate was averaged in blocks of 5 min (Svensson et al., 2003, 2006; Baad-Hansen et al., 2009; Kothari et al., 2011, 2012). The subjects were not allowed to rest during the 1 h trial, except for the 10 s between each tongue protrusion trial.

The participants were asked to report their perceived motivation, fun, pain and fatigue on four separate 0–10 numerical rating scales (NRS) after finishing any kind of tongue training (Kothari et al., 2012, 2013). On the scale, '0' indicated no motivation/fun/pain/fatigue at all and '10' indicated the highest level of motivation/fun/pain/ and fatigue imaginable. Before training all participants were encouraged to perform as well as possible.

Statistics

The MEP amplitudes were analyzed with three way-ANOVAs (analysis of variance) with gender as independent factor and stimulus intensity ($T-20$ to $T+60\%$) and time (baseline, post-training, 1 h after training) as repeated measures for all three tongue-training paradigms. rMTs, COG coordinates and MEP areas were analyzed with one-way ANOVAs between time-points (baseline, post-training, 1 h after training). In the TDS and TPT groups, training performance was averaged in blocks of 5 min. Analysis of performance over time was done by repeated measurement (RM) ANOVA with Gender as an independent factor and Time as the RM factor. When appropriate, the ANOVAs were followed by post hoc Tukey tests with correction for multiple comparisons. Relative improvement in performance, relative increase in MEPs at $T+20\%$ and relative increase in rMT over time were calculated for each participant and *t*-tests were performed to compare between the groups in TDS and TPT groups. Relative increase in performance (%) was calculated as ((last time block value − first time block value)/first time block value) $*$ 100%. Relative increase in MEPs at $T+20\%$ was calculated twice as ((immediately after training MEPS at $T+20\%$ − baseline MEPs at $T+20\%$)/Baseline MEPs at $T+20\%$) $*$ 100% and ((1 h after training MEPS at $T+20\%$ − baseline MEPs at $T+20\%$)/baseline MEPs at $T+20\%$) $*$ 100%, respectively. Also, relative change in rMT was calculated twice as ((rMT immediately after training − baseline rMT)/baseline rMT) $*$ 100% and ((rMT 1 h after training − Baseline rMT)/baseline rMT) $*$ 100%, respectively. Spearman correlation analyses were performed between relative increase in performance (%), relative increase in MEPs at $T+20\%$ and relative change in rMT (%) in TDS and TPT groups but not in the TTE group, since there was no measure of performance in this group. The subject-based reports of motivation, fun, pain and fatigue were compared between groups and genders with ANOVAs. Another Spearman correlation analysis was performed between relative increase in performance (%) and subject-based report of motivation, fun, pain and fatigue in all three groups. All data are presented as mean values and standard errors of mean (±SEM). The level of significance was set at $P < 0.05$.

RESULTS

rMTs

The rMT for the TTE group tongue MEPs were not significantly different between the three time-points ($P = 0.167$; Table 1).

The rMTs for the TDS group tongue MEPs were significantly different between the three time-points ($P = 0.005$; Table 1). Post hoc test showed that there was no significant difference between immediately post-training (42.8 ± 2.2) and baseline (44.7 ± 2.0) ($P = 0.102$) but there was a significant reduction in rMT 1 h after training (41.6 ± 2.1) compared with the baseline ($P = 0.003$).

The rMTs for the TPT group tongue MEPs were significantly different between the three time-points ($P = 0.011$; Table 1). A post hoc test showed that there was a significant reduction in rMT immediately after training (43.8 ± 2.0) ($P = 0.023$) and 1 h after training

Table 1. Resting motor thresholds (rMTs) of three different tongue training paradigm

Training paradigm	rMT	*P*-Value
TTE		$P = 0.167$
Baseline	47.5 ± 2.0	
Immediately after	46.6 ± 1.9	
1 h after	46.6 ± 2.1	
TDS		$P = 0.005$
Baseline	44.7 ± 1.9	
Immediately after	42.8 ± 2.2	
1 h after	41.6. ± 2.1*	
TPT		$P = 0.011$
Baseline	45.3 ± 2.0	
Immediately after	43.8 ± 2.0*	
1 h after	43.8 ± 2.0*	

TTE: therapeutic tongue exercise; TDS: Tongue Drive System; TPT: tongue protrusion task.

* Indicates significant different from baseline.

(43.8 ± 2.0) (P = 0.023) compared with the baseline (45.3 ± 2.0).

There were no significant differences in rMTs of the FDI muscle between the three time-points in any of the training paradigm groups (P > 0.166).

S–R Curves

The tongue MEPs for TTE group were significantly dependent on stimulus intensity (P < 0.001) but not on time (P = 0.302) or gender (P = 0.622) (Fig. 2A). The post hoc test showed that MEPs increased with increasing stimulus intensity (intensities of T + 30% compared with T) (P < 0.002).

The tongue MEPs in the TDS group was significantly influenced by stimulus intensity (P < 0.001), time (P = 0.030) as well as by gender (P = 0.045) (Fig. 2B). There was a significant interaction between time and stimulus intensity (P < 0.001) and between gender and stimulus intensity (P < 0.001). A post hoc test showed that MEPs increased with increasing stimulus intensity (intensities of T + 30% compared with T) (P < 0.002). Furthermore, a post hoc test showed that tongue MEPs were higher immediately after post-training (P = 0.029) but not 1 h after training (P = 0.131) compared with the baseline. Another post hoc test demonstrated that men had higher tongue MEPs compared to women (P = 0.045). The post hoc test of the time × stimulus intensity interaction showed that MEPs were higher immediately post-training and 1 h after training compared with baseline for stimulus intensities of T + 50% and T + 60% (P < 0.017) (Fig. 2B). The post hoc test of the gender × stimulus intensity interaction showed that men had higher MEPs at T + 40% and above compared with women (P < 0.035).

The tongue MEPs for TPT were significantly influenced by stimulus intensity (P < 0.001), time (P = 0.006) but not by gender (P = 0.200) (Fig. 2C). There were significant interactions between time and stimulus intensity (P < 0.001) and between gender and stimulus intensity (P = 0.034). A post hoc test showed that MEPs increased with increasing stimulus intensity (intensities of T + 30% compared with T) (P < 0.001). Furthermore, a post hoc test showed that tongue MEPs were higher immediately post-training (P = 0.005) but not 1 h after training (P = 0.336) compared with the baseline. Post hoc test of the time × stimulus intensity interaction demonstrated that for stimulus intensities of T + 30% and above (P < 0.001), MEPs were higher immediately after training compared with the baseline

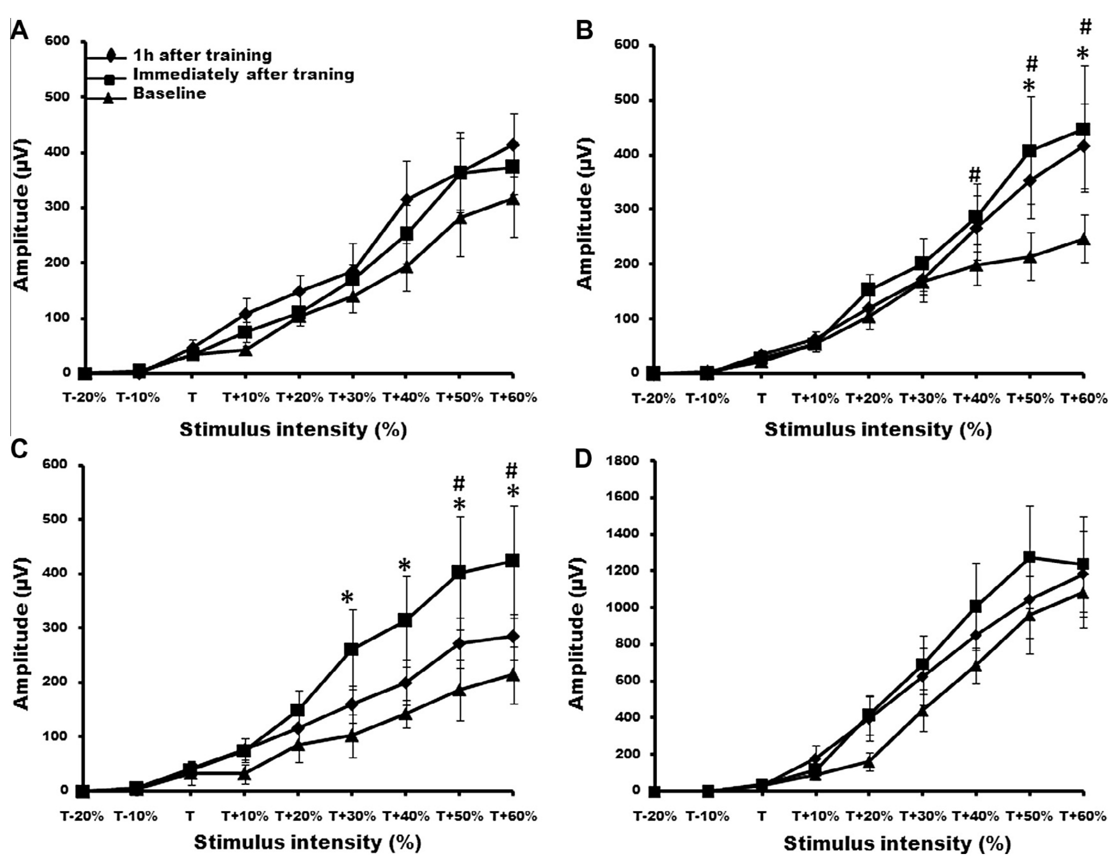

Fig. 2. Stimulus–response (*S–R*) curves of peak-to-peak amplitude of averaged motor evoked potentials (MEPs) obtained from transcranial magnetic stimulation of the tongue motor cortex on 48 subjects (means ± SEM). Stimulus intensity expressed in percentage of resting motor threshold (T). (A) Therapeutic tongue exercise (TTE) group (N = 16). (B) Tongue Drive System (TDS) group (N = 16). *Indicates significantly higher MEP amplitudes immediately after training compared with baseline (P < 0.029). #Denotes higher MEPs in men compared to women (P < 0.035). (C) Tongue protrusion task (TPT) group (N = 16). *Indicates significantly higher MEP amplitude immediately after training compared with baseline (P < 0.005). #Denotes higher MEPs in men compared with women (P < 0.040). (D) FDI motor cortex (all groups combined (N = 48).

(Fig. 2C). Post-hoc test of the gender × stimulus intensity interaction demonstrated that men had higher MEPs at $T + 50\%$ and above compared with women ($P < 0.040$).

The MEPs in the FDI muscle were significantly influenced by stimulus intensity ($P < 0.001$) but not by time ($P > 0.320$) or gender ($P > 0.120$) in any of the three training paradigm groups (Fig. 2D). There were no significant interactions between stimulus intensity, time or gender in any of three training paradigm groups ($P > 0.163$). The post hoc test showed that MEPs increased with increasing stimulus intensity (intensities of $T + 30\%$ compared with T) ($P < 0.047$).

Cortical motor map areas and COG

The areas of the tongue cortical motor maps (MEP amplitude > 5 μV) were not significantly different between the three time-points in any of the three training groups compared with baseline ($P > 0.142$; Table 2; Fig. 3A–C).

The COG analyses revealed no significant shifts in COG coordinates after training compared with baseline in any of the three training paradigms (Table 3; Fig. 3A–C).

Performance

For TDS training, there was a main effect of Gender ($P = 0.040$) as well as of Time ($P < 0.001$) on performance. The mean tongue-training performance improved from 30,459 ± 2623 to 138,667 ± 42,638 points for 1 h TDS training. A post hoc test revealed that there was a higher performance in men compared with women ($P = 0.046$). Performance in all time-blocks was significantly higher than at baseline ($P < 0.001$) and highest in the last time-block.

For TPT training, there was a main effect of Time ($P < 0.001$) on performance but there was no significant effect of Gender ($P = 0.850$). The mean TPT performance improved from 13.5 ± 0.7% to 37.2 ± 2.8% during 1 h of training. Performance in all time-blocks was significantly higher than at baseline ($P < 0.001$) and highest in the last time-block. There was no performance measure possible for TTE.

There were no significant correlations observed between relative improvement in performance (%) and relative increase in MEPs measured at $T + 20\%$ ($-0.165 < \delta < -0.044$; $P > 0.542$). Likewise, there were no significant correlations between relative improvement in performance (%) and relative change in rMT ($0.035 < \delta < 0.167$; $P > 0.538$).

Table 2. Areas (cm^2) of tongue motor cortical maps (motor evoked potentials > 5 μV)

Training paradigm	Area	*P*-Value
TTE		$P = 0.142$
Baseline	20.1 ± 0.8	
Immediately after	21.8 ± 0.7	
1 h after	21.9 ± 0.8	
TDS		$P = 0.171$
Baseline	20.6 ± 1.52	
Immediately after	21.3 ± 1.01	
1 h after	22.3 ± 0.70	
TPT		$P = 0.746$
Baseline	22.5 ± 0.6	
Immediately after	21.9 ± 0.8	
1 h after	22.2 ± 0.7	

TTE: therapeutic tongue exercise; TDS: Tongue Drive System; TPT: tongue protrusion task.

Subject-based report forms

The subject-based reports revealed that training with the TDS was rated as more motivating and fun compared with TPT and TTE (motivation: TDS: 6.7 ± 0.5, TPT: 3.6 ± 0.5, TTE: 4.6 ± 0.8, $P < 0.001$; Fun: TDS: 6.0 ± 0.5, TPT: 1.5 ± 0.4, TTE: 2.6 ± 0.6, $P < 0.001$). Also, training with TTE induced more pain than TDS and TPT (pain: TTE: 2.4 ± 0.3, TDS: 0.3 ± 0.2, TPT: 0.1 ± 0.1, $P < 0.001$). There was no significant difference in fatigue between groups (fatigue: TDS: 1.1 ± 0.3, TPT: 2.3 ± 0.4, TTE: 2.2 ± 0.5, $P = 0.071$). There were no significant correlations observed between relative improvement in performance (%) and subject based-reports for motivation, fun, pain and fatigue in TDS and TPT groups ($-0.467 < \delta < 0.203$; $P > 0.070$).

DISCUSSION

The present MEP findings are consistent with other studies on the *S–R* functions of the MEPs elicited by TMS in the tongue musculature (Muellbacher et al., 1994, 2001; Meyer et al., 1997; Fadiga et al., 2002; Svensson et al., 2003, 2006; Baad-Hansen et al., 2009).

The first main finding of the study was that the tongue MEP amplitudes were significantly increased after training with TDS and TPT but not with TTE in healthy participants. This finding can be important because it has been shown that skill training induces neuroplastic changes more efficiently than strength training and exercise training (Remple et al., 2001). The healthy participants in this study had no trouble performing the different elements of the TTE paradigm and as such, this can for healthy participants be considered as a type of "training", where the possibility for learning a new tongue motor skill is limited. This, of course, may be quite different in a population of patients with tongue motor disabilities, which should be subject to further investigations. In addition, other functional outcome measures like swallowing events, eating habits (diet modification) should be taken into consideration with tongue-disabled patients for future studies (Martin, 2009; Speyer et al., 2010). Training with a computer game may prove beneficial and keep the subject more actively involved in comparison with more simple and less fun training paradigms. Virtual reality and interactive video gaming have emerged as new treatment approaches in stroke rehabilitation (Laver et al., 2011). They may have some benefits over conventional therapy approaches as interactive video gaming may give people a prospect to practice

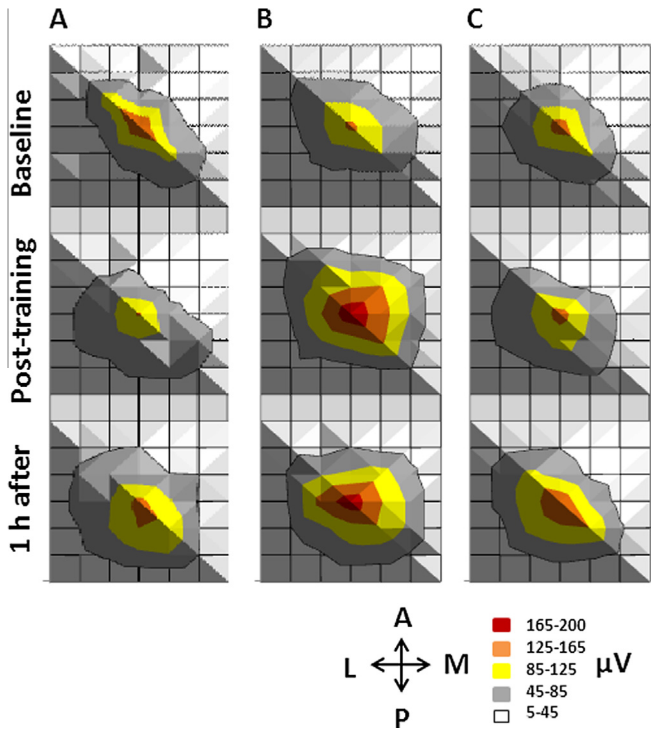

Fig. 3. Tongue cortical motor maps generated in 48 subjects (mean amplitudes) by transcranial magnetic stimulation of multiple scalp sites arranged in 1×1 cm^2 grid at baseline, immediately after and 1 h after training. Arrows indicates directions (*A* anterior; *P* posterior; *M* medial; *L* lateral). (A) Cortical motor maps with therapeutic tongue exercise (TTE). (B) Cortical motor maps with Tongue Drive System (TDS). (C) Cortical motor maps with tongue protrusion task (TPT).

Table 3. Center of gravity (COG) coordinates (cm) from the tongue motor cortical maps

Training paradigm	COGx	COGy
TTE		
Baseline	3.3 ± 0.1	6.9 ± 0.1
Immediately after	3.3 ± 0.1	7.0 ± 0.1
1 h after	3.4 ± 0.1	7.0 ± 0.1
P-Value	*P* = 0.438	*P* = 0.641
TDS		
Baseline	3.2 ± 0.1	7.0 ± 0.2
Immediately after	2.9 ± 0.1	7.0 ± 0.1
1 h after	3.2 ± 0.1	7.0 ± 0.1
P-Value	*P* = 0.086	*P* = 0.954
TPT		
Baseline	3.2 ± 0.1	7.0 ± 0.1
Immediately after	3.2 ± 0.1	7.1 ± 0.1
1 h after	3.3 ± 0.1	7.1 ± 0.1
P-Value	*P* = 0.548	*P* = 0.591

TTE: therapeutic tongue exercise; TDS: Tongue Drive System; TPT: tongue protrusion task.

everyday activities that are not or cannot be practiced in a hospital environment (Laver et al., 2011). Furthermore, there are numerous features of virtual reality and interactive video gaming that may motivate the patients to devote more time in therapy (Laver et al., 2011). Computerized training programs could offer a more flexible, personalized approach to conventional cognitive training programs, allowing for easier access and dissemination to persons with access to technology (Kueider et al., 2012). The socioeconomic and health consequences of dysphagia and dysarthria are vast and demand more research into rehabilitation strategies (Kirshner, 1989; Martin et al., 1993; Mari et al., 1997). Moreover, motor skill training coupled with strength training does not promote greater cortical neuroplastic changes in the motor cortex than motor skill training alone (Remple et al., 2001; Perez et al., 2004; Jull et al., 2009; Boudreau et al., 2010a). The present findings extend our recent observations in humans that both a standardized tongue-protrusion training (TPT) and a novel training with TDS are associated with muscle-specific changes in the corticomotor control of tongue musculature. In addition, a comparison of the relative training-induced changes in MEPs at the highest intensities ($T + 50$ and $T + 60\%$ respectively) between TDS (154.3 ± 62.7% and 122.4 ± 68.5%) and TPT (140.1 ± 49.2% and 106.0 ± 26.8%) showed no significant difference between groups ($P > 0.825$).

Another important finding was that the rMTs were significantly decreased after training with TDS and TPT but not with TTE. It has been suggested that changes in motor thresholds and MEPs provide information on different aspects of cortical excitability (Hallett et al., 1999). A decrease in motor thresholds may indicate increased excitability of a neuronal central core region, whereas increases in MEPs at higher TMS intensities suggest the involvement of neurons in addition to the core region (Hallett et al., 1999; Svensson et al., 2003, 2006). With TDS, there was a tendency toward a significant reduction in rMT already immediately after training and a significant reduction in rMT 1 h after training (there was no difference between immediately after and 1 h after training). This indicates a similar effect on rMT between TDS and TPT, for which rMT was reduced both immediately after and 1 h after training, although the changes were more prominent after TPT than after TDS. The finding of reduction in rMT for TPT is in accordance with previous studies on TPT for tongue motor learning showing decreased motor thresholds and increase in MEP amplitudes at higher TMS intensities indicating changes in cortical excitability after training (Svensson et al., 2003, 2006; Baad-Hansen et al., 2009).

Development of motor skills is supported by changes in cortical motor map topography (Kleim et al., 2004). However, we did not observe an expansion of the tongue motor maps and there was no subtle shift in COG coordinates for any of the three training paradigms, which was in contrast to previous tongue-training studies (Svensson et al., 2003, 2006). Kleim et al. (2004) hypothesized that motor map reorganization occurs during the late slower phase of motor learning and demonstrated a significant increase in motor performance after 3 days training and a further increase after 7 and 10 days of training; however significant motor map reorganization did not occur until 10 days of training.

The functional significance of training-associated plasticity in the corticomotor control of the tongue muscles is not known but is likely related to mechanisms underlying the acquisition of oral motor skills such as those associated with manipulation of food by the tongue, chewing, swallowing and speech (Smith, 1992; Sawczuk and Mosier, 2001; Hiiemae and Palmer, 2003). Similarly, it could be important to the understanding of tongue dysfunctional behaviors like, dysphagia and dysarthria but this remains to be investigated in future studies.

Another finding was that gender also influenced the outcome in motor performance and learning for the tongue-controlled computer game task: men performed better than women. The higher performance in men compared with women may be due to a confounding factor that women generally do not play computer games to the same degree as men (Hartmann and Klimmt, 2006; Hartman, 2007; Kothari et al., 2013). We also noted that men had higher MEPs compared to women. This gender difference was present at all time-points, which suggests that it was not a training-induced phenomenon. The clinical implication of gender differences in performance could be that different approaches to this kind of training (for e.g., different level of computer games) between genders could be beneficial in patients undergoing neurorehabilitation programs involving tongue disability.

The analyses of subject-based reports showed that participants were feeling significantly more motivated and experienced more fun while playing computer games with the tongue using TDS compared with the TPT and TTE tongue-training. In addition, the TTE training was more painful compared with TDS and TPT. Fatigue and pain have been shown to negatively influence motor learning (Boudreau et al., 2010b) and are therefore important confounding factors. However, it should be recognized that the general motivation to participate in experimental studies like the present may be highly individual and variable. In contrast, the motivation in patients suffering from impaired tongue function with potential physical and psychosocial consequences may prove quite different. The motivational function of feedback (like, for example, the number of game points in a computer game) is thought to energize the task interest and encourage continued effort, persistence, and attention to goal accomplishment through evidence of performance progress (Lewthwaite and Wulf, 2010). Within the motor-learning literature, the role of feedback has played an important role and garnered research attention (Wulf et al., 2010). The role of feedback not only has an informational function, but also has motivational properties that have an important influence on motor learning. Feedback indicating better than average performance has been shown to have a beneficial effect on learning (Wulf et al., 2010). In the present study no significant correlation was found between relative increases in performance and subject-based reports of motivation, fun, pain and fatigue in TPT and TDS training. A possible limitation may be the uni-dimensional NRS applied in the present study, as more aspects of motivation and other feedback measures, such as observational feedback, focus of attention, and self-controlled practice, can also play a major role in behavioral learning and it will be valuable to take these into consideration for future studies (Lewthwaite and Wulf, 2010; Wulf et al., 2010).

CONCLUSION

In conclusion, the present findings demonstrated that a specific plasticity of the corticomotor excitability related to the tongue motor control could be induced by TDS and TPT tongue-training but not by performing TTE in healthy participants. Playing computer games with the tongue using TDS may after further studies be considered as a new adjunctive neurorehabilitation regime in patients with reduced tongue functions. Future tongue-training studies need more focus on the consequences of the training task on improvement of tongue disabilities like dysphagia and dysarthria in addition to the training-induced cortical plasticity.

COMPETING INTEREST

No conflicts of interest.

ETHICAL APPROVAL

Local ethics committee, Central Denmark Region.

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